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The potential effects and mechanisms of traditional Chinese non-pharmacological therapy for nero-musculoskeletal disorders

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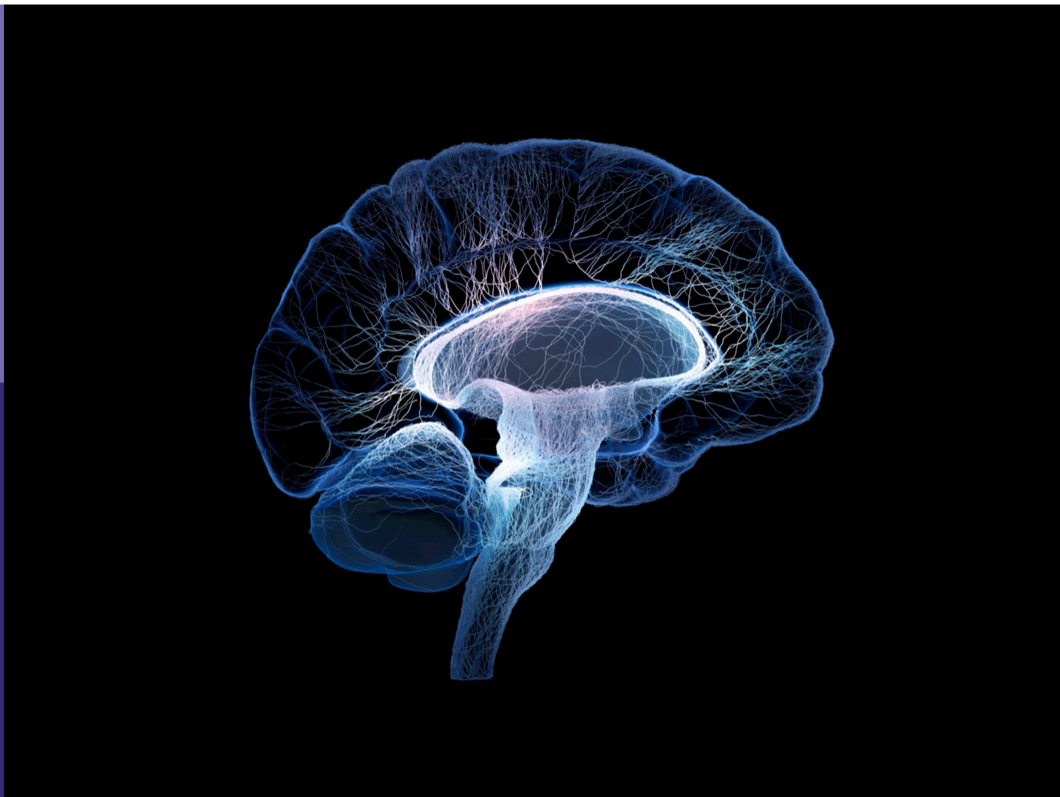

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The potential effects and mechanisms of traditional Chinese non-pharmacological therapy for nero-musculoskeletal disorders

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The effect of hip abductor fatigue on knee kinematics and kinetics during normal gait

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Objective: To investigate the effect of hip abductor fatigue on the kinematics and kinetics of the knee joint during walking in healthy people to provide a new approach for the prevention and treatment of knee-related injuries and diseases.

Methods: Twenty healthy participants, ten females, and ten males, with a mean age of 25.10 ± 1.2 years, were recruited. Isometric muscle strength testing equipment was used to measure the changes in muscle strength before and after fatigue, and the surface electromyography (SEMG) data during fatigue were recorded synchronously. The Vicon system and an AMTI© force platform were used to record the kinematic parameters and ground reaction force (GRF) of twenty participants walking at a self-selected speed before and after fatigue. Visual 3D software was used to calculate the angles and torques of the hip and knee joints.

Results: After fatigue, the muscle strength, median frequency (MF) and mean frequency (MNF) of participants decreased significantly ($P < 0.001$). The sagittal plane range of motion (ROM) of the knee ($P < 0.0001$) and hip joint ($P < 0.01$) on the fatigue side was significantly smaller than before fatigue. After fatigue, the first and second peaks of the external knee adduction moment (EKAM) in participants were greater than before fatigue ($P < 0.0001$), and the peak values of the knee abduction moment were also higher than those before fatigue ($P < 0.05$). On the horizontal plane, there is also a larger peak of internal moment during walking after fatigue ($P < 0.01$).

Conclusion: Hip abductor fatigue affects knee kinematics and kinetics during normal gait. Therefore, evaluating hip abductor strength and providing intensive training for patients with muscle weakness may be an important part of preventing knee-related injuries.

KEYWORDS
hip abductor, fatigue, knee joint, kinematics, kinetics

Introduction

Knee injuries, such as anterior cruciate ligament (ACL) injuries and patellofemoral pain syndrome (PFPS) (Hutchinson and Ireland, 1995; Laprade et al., 2019), are the most common sports-related injuries. Knee osteoarthritis (KOA) is the most common knee disease in persons 60 years of age or older, seriously affecting the mobility of the elderly (Sharma, 2021). During weight-bearing activities, the knee joint carries the greatest load and therefore has the potential for injury to the joint (Kumar et al., 2013). Although the occurrence and development of ACL injury, PFPS, and KOA are caused by a combination of multiple, abnormal knee biomechanics in the coronal plane appears to be a common risk factor for disease factors (Moyer et al., 2014; Montalvo et al., 2019; Neal et al., 2019). The focus of the current studies was on the external knee adduction moment (EKAM), which is determinative of medial knee joint loads (Landry et al., 2007; Foroughi et al., 2009; Duffell et al., 2014). Previous studies have shown that the higher EKAM seen in females compared to males may suggest an increased risk for the development of KOA in females with ACL-reconstruction (Webster et al., 2012). Patients with medial compartment knee osteoarthritis (MC-KOA) or PFPS usually have a higher EKAM (Bolgla et al., 2008; O'Connell et al., 2016), and the peak EKAM is positively correlated with disease progression and increased pain (Birmingham et al., 2019; Rees et al., 2019). However, recent studies have shown that hip abductor also play an important role in those diseases (Willy and Davis, 2011; Bell et al., 2016).

As the proximal joint of the lower limbs, the hip joint plays an integral role in maintaining balance and providing stability (Pel et al., 2008). However, this function depends on the hip muscles providing dynamic stability during exercise (Williams et al., 2001). As a result, hip muscle weakness may lead to certain movement dysfunctions, putting certain muscles and joints, especially the knee joint, at high risk of injury. In recent years, some scholars have reported that the weakness of hip abductor (such as gluteus medius) may be an important reason for the increase in EKAM (Kean et al., 2015; Bennett et al., 2018). The hip abductor mainly stabilize the femur in the frontal plane of the lower limb movement (Mcleish and Charnley, 1970). The weakness of hip abductor makes the hip more prone to adduction or rotation during weight-bearing activities (such as jumping or landing). Abnormal hip movements increase the abduction angles and moments of the knee joint and affect the muscle activation of the hip abductor and quadriceps femoris. The shearing force exerted on the tibia by the quadriceps during jumping or landing can increase the abduction angle of the knee or abduction moment of the knee and abnormal muscle activation, which further increases the tension of the ACL and increases the risk of ACL injury (Hewett et al., 2005). Studies have shown that most patients with PFPS have decreased strength in the hip abductor muscles (gluteus maximus and gluteus medius) (Magalhaes et al., 2013; Rathleff et al., 2014; Neal et al., 2019). Contralateral pelvic drop and internal rotation of the femur are the most common methods for improving defects in the abductor muscle of the hip, which presumably would result in higher peak EKAM to further affect the occurrence and generation of PFPS (Bolgla et al., 2008; Baldon et al., 2009; Powers, 2010).

Patellofemoral pain syndrome patients experience decreased activity and delayed start time in the hip abductor muscles (Gluteus medius, gluteus maximus) when performing tasks such as standing on one leg, squatting, or running (Willson et al., 2011, 2012; Mirzaie et al., 2019). Fukuda et al. (2010) and Lack et al. (2015) demonstrated that hip abductor strength training can relieve pain and improve the function of patients with PFPS, supporting the theory that hip abductor have an effect on PFPS to some extent. Deasy et al. (2016) showed that the strength of hip abductor muscles in symptomatic KOA patients was significantly weaker than that in healthy controls. Greater external hip abduction moments while walking have been shown to reduce the risk of KOA progression (Chang et al., 2005). Therefore, we hypothesized that decreased hip abductor strength may lead to an increased load in the medial compartment of the knee joint.

However, it leaves doubt whether the weakness, insufficiency and activation pattern changes of the hip abductor existed before injury or became evident secondary to the injury. Previous studies used fatigue protocols to simulate hip abductor deficiency and then measured the effects of knee kinematics and kinetics to identify a cause-and-effect relationship. However, because the fatigue degree of patients has not been strictly quantified and the effect of fatigue recovery has not been considered, the conclusion of the study on the effect of hip abductor fatigue on the knee joint is disunified. Patrek et al. (2011) studied the influence of hip abductor fatigue on the single-leg landing biomechanics of female athletes but found no change in the kinematics and kinetics of the knee joint. However, Geiser et al. (2010) found that hip abductor fatigue increased peak EKAM during cutting, jumping, and running. Based on this, we made three attempts to quantify the level of fatigue over the fatigue protocol. (1) Ratings of the Borg perceived exertion scale (on a 6–20 scale) were recorded every 10 s during the exertion protocol; (2) peak hip-abductor strength immediately after the exertion protocol was compared with hip-abductor strength values before the protocol; and (3) muscle activity patterns were

Abbreviations: ACL Injuries, anterior cruciate ligament injuries; CV, conduction velocity; EHAM, external Hip adduction moment; EKAM, external Knee adduction moment; GM, gluteus medius; GRF, ground reaction force; KOA, knee osteoarthritis; MC-KOA, medial compartment knee osteoarthritis; MF, median frequency; MNF, mean frequency; MVIC, maximum voluntary isometric contraction; PFPS, patellofemoral pain syndrome; ROM, range of motion; sEMG, surface electromyography; WA, weight acceptance.

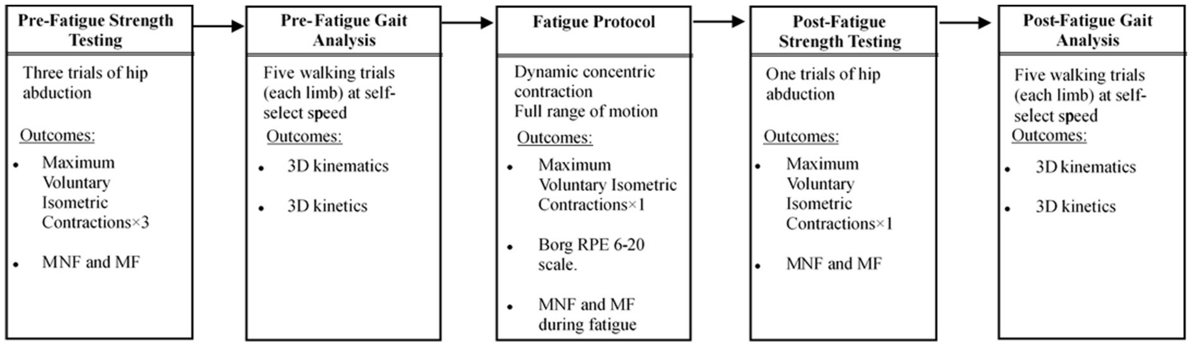

FIGURE 1
Experimental protocol.

measured by surface electromyography (SEMG) over the fatigue protocol.

The purpose of this study was to determine the effects of weakness induced by isolated hip abductor fatigue on lower limb kinematics and kinetics in healthy participants. Specifically, we hypothesized that knee kinematics and kinetics would change after an isolated hip abductor fatigue protocol.

Materials and methods

Participants

Twenty healthy participants, 10 females and 10 males, 21–35 years old, were recruited. The sample size was based on previous studies (Geiser et al., 2010; Patrek et al., 2011). Participants were free from any lower limb joint or muscle pain or injury that limited activity in the past 6 months, any neuromuscular condition that precluded exercise training, and any past injury requiring surgery to the lower extremity. All participants provided written informed consent, and the study was reviewed and approved by the ethics committee of Huadong Hospital (No. 2020K079).

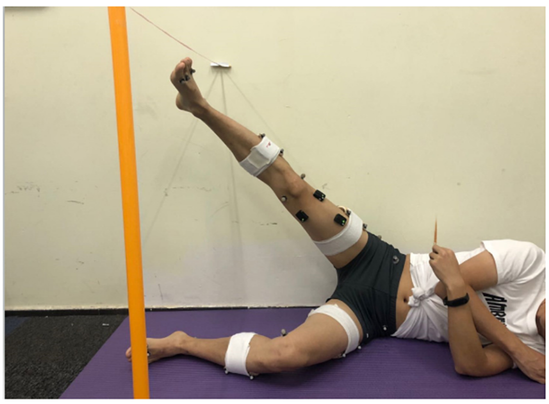

FIGURE 2
Participant positioning for the hip abductor fatigue protocol.

Instrumentation

The kinematics of the hip and knee joints were recorded at a sampling rate of 100 Hz using an 8-camera motion capture system (Vicon® T40, Oxford Metrics, Oxford, UK). One force platform (model OR6-7; Advanced Mechanical Technology, Inc., Watertown, MA, USA) embedded on the laboratory floor captured the ground reaction force (GRF) at 1,000 Hz. A wireless EMG recording system (Telemyo 2400T G2, Noraxon, Scottsdale, AZ, USA) operated at 2,000 Hz was used to synchronously record the EMG of the gluteus medius (GM) muscle. A HYGJTL-002 handheld dynamometer was used to test the maximum isometric strength of the hip abductor.

Experimental protocol

The study protocol is illustrated in **Figure 1**. The first thing is to familiarize participants with the experimental procedure. Before the test, the dominant leg (leg to be fatigued) was selected for each participant by asking which leg was preferred for kicking the ball. Participants underwent hip abductor strength testing and biomechanical gait analysis before and after unilateral hip abductor fatigue (prefatigue and postfatigue, respectively). Hip abductor strength tests were conducted before gait analysis in the pre-fatigue and post-fatigue condition. After the postfatigue gait, hip abductor strength was collected immediately to determine the level of recovery from fatigue during the gait test.

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TABLE 1 Mean (SD) maximum voluntary isometric contractions, median frequency, and mean frequency values before and after fatigue.

Variable	Women (n = 10)				Men (n = 5)				P-value (Group)	
	Pre-fatigue	Post-fatigue	P-value	Effect size (d), 95% confidence interval	Pre-fatigue	Post-fatigue	P-value	Effect size (d), 95% confidence interval	Pre-fatigue	Post-fatigue
Maximum Voluntary Isometric Contractions (%BW)	0.480 ± 0.088	0.255 ± 0.065	0.000****	2.908 (0.182,0.267)	0.573 ± 0.049	0.328 ± 0.038	0.000****	5.58 (0.182,0.267)	0.047*	0.040*
mean frequency, (Hz)	97.093 ± 13.047	84.750 ± 11.985	0.000****	0.985 (7.619,17.067)	97.656 ± 12.009	84.750 ± 11.985	0.019*	1.076 (4.840,31.090)	0.594	0.502
median frequency, (Hz)	71.880 ± 11.136	56.460 ± 10.834	0.001***	1.404 (7.955,22.885)	67.000 ± 16.045	53.600 ± 8.837	0.035*	1.035 (1.540,25.260)	0.2541	0.619

BW, Body weight. Effect size (d) is based on standardized differences; $P > 0.05$, $*P < 0.05$, $***P < 0.001$, $****P < 0.0001$.

Strength testing

The participants completed three series of maximum voluntary isometric contractions (MVIC) of the study limbs on the handheld dynamometer (HYGJTL-002). The position of each participant was as follows: they lie on the side of the non-dominant leg, the dominant leg knee was straight, and the dominant hip flexion, abduction and rotation were 0°. To maintain the consistent placement of the hand-held dynamometer in all strength tests, a marker was placed on the skin near 2.5 cm of the lateral femoral epicondyle of the dominant leg. The handheld dynamometer was placed on this mark in all strength tests. Participants first warmed up with a perceptual maximum of approximately 50% and then performed three maximal effort contractions. Each MVIC trial lasted for 5 s, with a 2-min break between the tests. In each MVIC trial, participants were told not to flex their knees and to keep the toes at the top of their thighs pointing forward to help prevent changes in muscle recruitment and compensation during the test. After the fatigue protocol, the MVIC trial was measured repeatedly using the same scheme, and the MVIC was measured after post-fatigue gait analysis, but only one maximum effort contraction was carried out.

Surface electromyography

Electromyography activity of the GM muscle was recorded during the first and last 30 s of the fatigue protocol. The skin was wiped and cleaned with 70% alcohol before placing the sensor. Wireless bipolar EMG sensors (Delsys Inc, Natick, MA, USA) were placed on the midpoint of the line between the most cranial and lateral point of the iliac crest and the greater trochantor. We chose the GM to place the sensor because although most studies measure the overall strength of the abductor muscle of the hip joint, reduced strength is usually interpreted as weakness of the GM (Sogaard et al., 2006; Decorte et al., 2012). In addition, the lower limb kinematics related to hip abductor weakness, such as the weight acceptance (WA) portion of the stance phase, hip adduction, internal rotation and knee abduction (Kluger et al., 2013), are consistent with the decrease in activity of the posterior GM muscle (Sogaard et al., 2006; Muotri et al., 2107). Signals use a Trigno TM wireless system with analog-to-digital conversion at 2000 Hz.

Gait biomechanics procedures

Kinematic data were collected using an 8-camera motion capture system (Vicon® T40, Oxford Metrics, Oxford, UK) sampling at 100 Hz. GRF data were collected at 1000 Hz from one force platform (model OR6-7; Advanced Mechanical

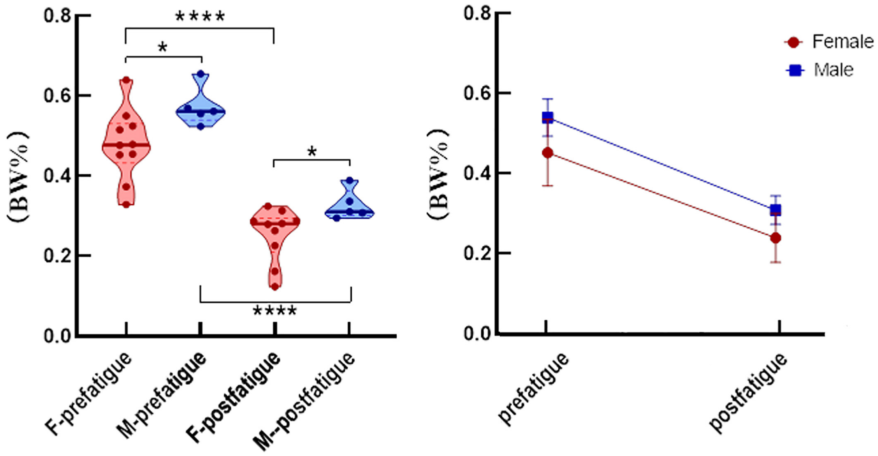

FIGURE 3
After weight normalization, the average isometric hip strength (mean and standard error) was significantly different after fatigue in men (blue) and women (red). *$P < 0.05$, ****$P < 0.0001$.

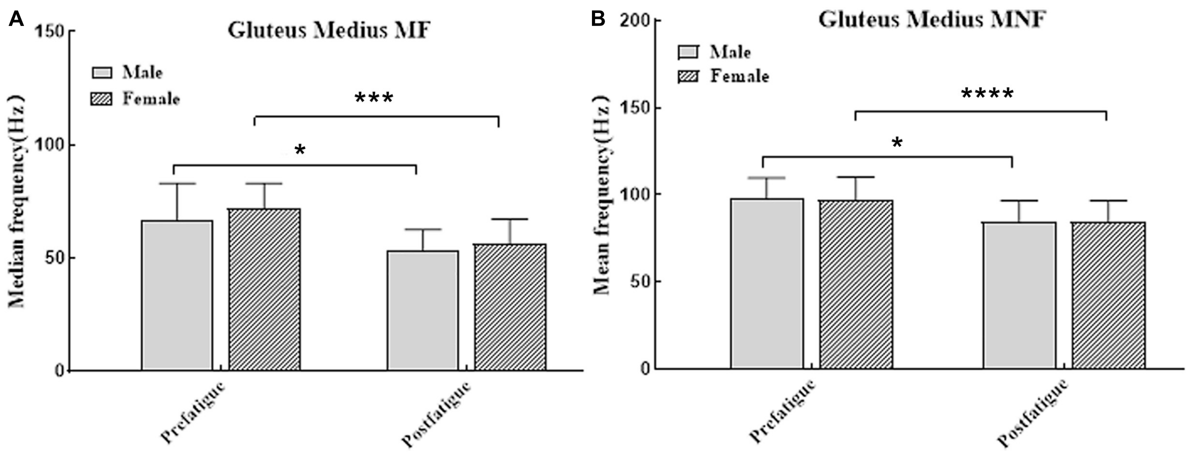

FIGURE 4
(A) The median frequency (mean and standard error) were significantly different after fatigue in men (dark bars) and women (bar with oblique line). **(B)** The mean frequency (mean and standard error) were significantly different after fatigue in men (dark bars) and women (bar with oblique line). *$P < 0.05$, ***$P < 0.001$, and ****$P < 0.0001$.

Technology, Inc., Watertown, MA, USA) along a 10 m walkway. To monitor joint and segment motion over the ground, 22 reflective markers (14 mm in diameter) were placed on the participant's anatomical landmarks: the anterior-superior iliac spine (ASIS), posterior-superior iliac spine (PSIS), greater trochanter, lateral and medial femoral condyles, lateral and medial malleoli, posterior portion of the calcaneus, and head of the first, second, and fifth metatarsals. The four anatomical frames were rigid clusters of four on orthogonal markers and were placed on the lateral sides of the bilateral thighs and shank. A static trial was conducted as a reference to determine the body mass and the positions of the joint centers. After the static neutral standing test, the kinematic and kinetic gait data of five lower limb ground and barefoot walking trials were collected. Previous studies have shown that the average fatigue time of abduction fatigue tests is approximately 2∼3 min, so the five walking trials after fatigue were completed within 3 min (Patrek et al., 2011). Walking velocity was monitored using the TC Timing System (Brower Timing System, Salt Lake City, UT, USA) and was maintained within ± 5% of the self-selected speed of the participant.

Fatigue protocol

The hip abductor fatigue protocol used in this study is based on previous studies (Patrek et al., 2011; Soriano-Maldonado et al., 2014). Participants were positioned side-lying on the floor in a starting position of full knee extension and neutral hip position. Participants slowly abducted the hip of the top (dominant) limb while keeping the knee in extension, the tibia and femur in a neutral transverse plane position, with the bottom limb stationary. Participants stopped at 30° of hip abduction and returned to the starting position (the side-lying hip abduction exercises led to the greatest activation of the GM; Distefano et al., 2009). The height of the participants' hip abduction was marked by a plastic bar at the height of 30° of hip abduction, and the hip abduction angle was measured by a standard goniometer. The bar provided the participant with a fixed goal of hip abduction of 30° and provided tactile feedback for achieving the goal (**Figure 2**). Each participant was asked to perform hip abductions at a rate of 60 beats per minute (provided by a digital metronome) until she reported a Borg perceived exertion scale rating of 19 or greater (on a 6–20 scale) and failed to reach the plastic bar at the required tempo on two consecutive days. The hip-abduction strength was tested again when the two fatigue criteria were met.

Our study used three methods to quantify fatigue. First, ratings of the Borg perceived exertion scale (on a 6–20 scale) are recorded every 10 s in the fatigue protocol. RPE scores correlate well with both physiological measures of stress and arousal threshold (e.g., HR, ventilatory, blood lactate and creatinine concentration) as well as psychological measures of exhaustion (Soriano-Maldonado et al., 2014). Second, the peak hip abductor strength before and after the exertion protocol was compared because fatigue was defined as a decrease in the ability of the neuromuscular system to produce force during continuous activity. Previous studies have reported that there is a 33–55% decrease in muscle strength in MVIC during fatigue, and a 33% reduction in muscle strength as the fatigue criterion of muscle strength (Thomas et al., 2015). Third, the mean frequency (MNF) and median frequency (MF) of the first and last 30 s of the hip abduction fatigue protocol were calculated to ensure fatigue. Previous authors have reported that the decrease in MNF and MF during fatigue are related to isotonic and dynamic muscle contraction. The MFs of different muscles decreased by 4 and 20% in different fatigue tasks (Gayda et al., 2005; Mcmullen et al., 2011; Zaman et al., 2011). The last 30 s MF of the fatigue scheme reduced the MF by more than 4% compared with the first 30 s as the fatigue criterion in our study.

Data analysis

Electromyography data during the fatigue protocol were processed using custom MATLABTM programs (The Mathworks Inc, Natick, MA, USA). We calculated the MF and MNF during the first and last 30 s of the hip-abduction fatigue protocol to examine this isolated fatigue protocol. First, all signals were filtered using a 20 Hz high-pass and 450 Hz low-pass Butterworth filter design. The 30-s filtered EMG

TABLE 2 Study limb mean (SD) peak kinematic and joint kinetic outcomes from the before and after fatigue gait analyses.

Variable	Women (n = 10)				Men (n = 5)				P-value (Group)	
	Pre-fatigue	Post-fatigue	P-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue	P-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue
The sagittal plane ROM of hip (°)	38.235 ± 2.273	35.418 ± 3.115	0.041**	1.033 (0.151,5.482)	30.556 ± 3.798	27.894 ± 2.751	0.033*	0.803 (0.344,4.980)	0.000***	0.001**
Hip adduction moments (N·m·kg^{-1})	1.056 ± 0.215	0.977 ± 0.199	0.006**	0.381, (0.029,0.128)	0.815 ± 0.096	0.934 ± 0.238	0.328	−0.656 (−0.416,0.178)	0.035*	0.716

ROM, Range of motion. Effect size (d) is based on standardized differences; $P > 0.05$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

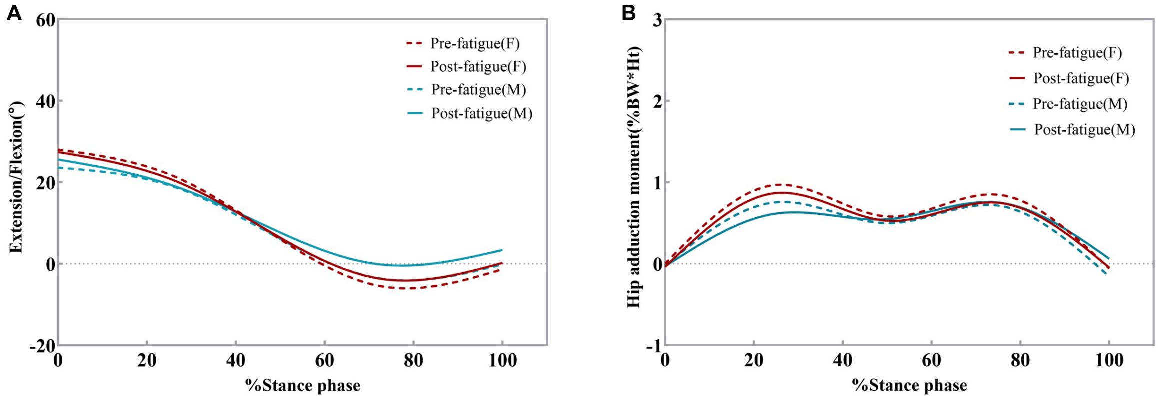

FIGURE 5
Ensemble average hip kinematics and kinetics for the dominant limb for all male and female participants. Changes in hip flexion angles **(A)** and hip adduction moments **(B)** pre-fatigue and post-fatigue. Moments are given in% bodyweight times height (Ht).

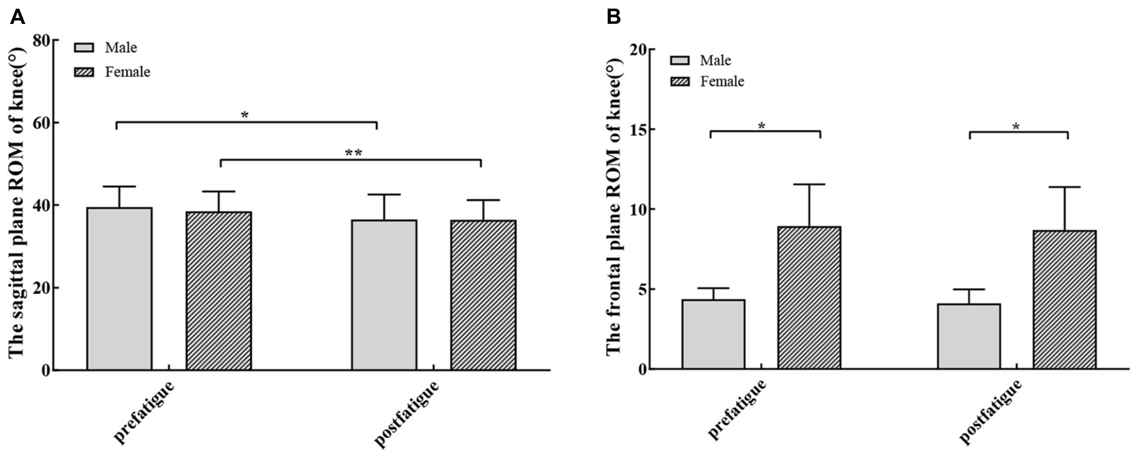

FIGURE 6
(A) The knee sagittal plane range of motion (mean and standard error) were significantly different after fatigue in men (dark bars) and women (bar with oblique line). **(B)** There were no significant differences in frontal plane range of motion (mean and standard error) after fatigue. There were significant differences in the frontal plane range of motion among different sexes before and after fatigue. *$P < 0.05$, **$P < 0.01$.

data were divided into six 5-s sections. The power spectra of each section were calculated using a fast Fourier transform (Wang et al., 2019), and then the MF and MNF for the spectrum were identified.

All kinematic and kinetic data of the hip and knee joint were processed using Visual3D software (Visual 3D, C-motion Inc., Germantown, MD, USA). Ankle, knee and hip joint centers were calculated using the coordinates of the static neutral standing trial. The midpoints between the medial and lateral joint markers were defined as the ankle and knee joint centers. The hip joint center was calculated from the ASIS and PSIS markers, which was defined according to a previous study (Bell et al., 1990). All 3D joint angles were referenced as the distal segment relative to the proximal segment with the Cardan sequence of rotations using an X-Y-Z (Greuel et al., 2017) (x = flexion/extension, y = abduction/adduction, z = internal/external rotation). An inverse dynamics approach was used to calculate the joint kinetic data of the hip and knee joint from the GRF and kinematic data (Kadaba et al., 1990). The joint moments were normalized to body mass. We analyzed joint kinematics and moments for the stance phase and normalized them to 101 data points.

Statistical analyses were performed with SPSS Statistics 22.0 to analyze the intergroup and intragroup differences in gait parameters and surface EMG. Demographic data were collected for descriptive statistics and are described as the mean ± standard deviation (SD). The Shapiro–Wilks test was used to check whether the gait parameters and surface EMG data in the non-fatigue and fatigue states were in accordance

TABLE 3 Study limb mean (SD) knee joint kinematic outcomes from the before and after fatigue gait analyses.

Variable	Women (n = 10)				Men (n = 5)				*P*-value (Group)	
	Pre-fatigue	Post-fatigue	*P*-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue	*P*-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue
Peak knee flexion angle (°)	45.742 ± 5.748	43.944 ± 5.567	0.170	0.318, (−0.930,4.526)	39.412 ± 3.586	42.029 ± 7.305	0.427	0.455, (−10.839,5.605)	0.044*	0.580
Peak knee adduction angle (°)	4.952 ± 3.624	4.410 ± 4.109	0.255	0.140, (−0.467,1.551)	5.223 ± 1.733	4.592 ± 1.177	0.159	0.426, (−0.382,1.644)	0.878	0.925
The sagittal plane ROM of knee (°)	38.963 ± 4.886	36.051 ± 4.530	0.009**	0.618, (0.939,4.885)	39.516 ± 5.009	36.522 ± 6.060	0.037*	0.539, (0.305,5.683)	0.841	0.868
The frontal plane ROM of knee (°)	8.935 ± 2.617	8.696 ± 2.688	0.959	0.090, (Wilcoxon signed rank test)	4.365 ± 0.690	4.103 ± 0.875	0.121	0.333, (−0.109,0.634)	0.002**	0.003**

ROM, Range of motion. Effect size (d) is based on standardized differences; $P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$.

with the normal distribution. If the differences were normally distributed, we used a paired t test to determine whether hip abductor fatigue significantly affected knee kinematics and kinetics. The Wilcoxon signed rank test was used for the resulting variables whose differences were not normally distributed. We also used an independent sample t test to compare gender differences in all data before and after fatigue. The Mann–Whitney *U* test was used if the difference values did not conform to homogeneity of variance. The significance level for each test was set *a priori* at 0.05.

Results

In this study, only 15 people met our standard of hip abductor fatigue (10 females, 5 males; age = 24.80 ± 0.79 years, 25.40 ± 1.67 years; height = 161.70 ± 5.85 cm, 172.20 ± 2.39 cm; body mass = 51.20 ± 4.21 kg, 62.60 ± 3.71 kg; body mass index = 19.57 ± 1.06 kg/m^2, 21.13 ± 1.43 kg/m^2), providing data for analysis (**Supplementary Table 1**). All participants were right leg dominant. At the end of fatigue protocols, all participants reported a score of 19 or higher on the Borg RPE 6–20 scale.

Hip fatigue

The average time for participants to fatigue was 684.867 ± 382.422 (s), compared to 689.9 ± 372.453 (s) for men and 684.8 ± 446.922 (s) for women. There was no significant difference between the two groups ($P > 0.05$). Peak isometric hip-abduction strength and median muscle frequency and mean muscle frequency data before and after the strength testing are summarized in **Table 1**. At the end of the fatigue test, the muscle strength of the participants decreased (95% CI: 10.93–14.57; P = 0.000). Peak isometric hip abduction strength decreased by 43% (95% CI: 38.50–47.11; P = 0.000) in men and 46% (95% CI: 39.96–54.21; P = 0.000) in women. After weight normalization, the hip abductor strength of male participants was significantly higher than that of female participants either before or after fatigue ($P < 0.05$, **Figure 3**). SEMG data demonstrated that over the course of the fatigue protocol, MF decreased by 21% (95% CI: 9.29–20.20; P = 0.000, **Figure 4**), and MNF (95% CI: 9.67–18.77; P = 0.000, **Figure 4**) decreased by 15%. However, SEMG data of the GM muscle were not different for men or women ($P > 0.05$, **Table 1**).

Changes at the hip

The *post hoc* analysis showed that after fatigue, the hip range of motion (ROM) of participants ($P < 0.01$, **Table 2**) decreased from flexion to extension (**Figure 5**). There were significant

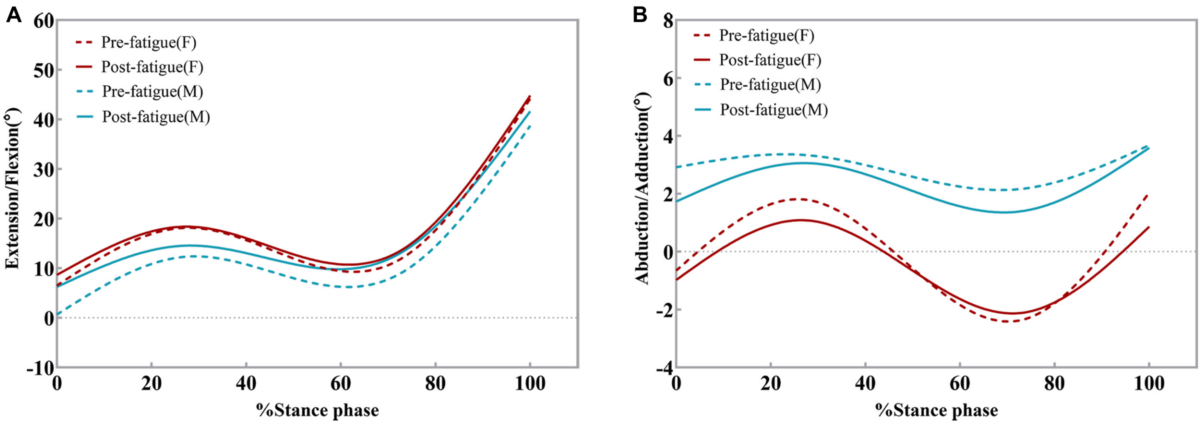

FIGURE 7
Ensemble average knee kinematics for the dominant limb for all male and female participants. Changes in knee flexion angles **(A)** and knee adduction angles **(B)** pre-fatigue and post-fatigue.

differences in hip flexion and extension between the sexes before (95% CI: 4.329–11.029; $P = 0.000$, Table 2) and after fatigue (95% CI: 3.965–11.083; $P = 0.001$, Table 2).

Figure 5 shows the external hip adduction moments (EHAM) during the stance phase. The EHAM had two peaks at the early and late stance phases. There was no significant difference in the peak value of EHAM before and after fatigue. In female participants, the peak value of EHAM was smaller than that before fatigue (95% CI: 0.029–0.128; $P = 0.006$, Table 2), but no significant difference was found in male participants. This may be due to the small sample size of male participants affecting the test results. There were no significant differences in the peak EHAM between the sexes after fatigue.

Knee kinematics

Post hoc analysis showed that the range of flexion and extension of the knee joint decreased significantly after fatigue ($P < 0.0001$). The average decrease after fatigue was 2.912° (95% CI: 0.939–4.885; $P = 0.009$, Figure 6) for women and 2.994° (95% CI: 0.305–5.683; $P = 0.037$, Figure 6) for men. The peak knee flexion angles were similar during the pre-fatigue and post-fatigue walking conditions ($P > 0.05$, Table 3 and Figure 7). There were significant differences in the peak knee flexion angle between the sexes before fatigue. The peak flexion angle before fatigue of female participants was significantly greater than that of male participants (95% CI: 1.332–15.530; $P = 0.044$, Table 3).

After the hip abductor fatigue protocol, no significant difference was found in the frontal plane knee ROM ($P > 0.05$, Table 3 and Figure 7). There were significant differences in the frontal plane ROM between the sexes before fatigue (95% CI: 1.954–7.187; $P = 0.002$, Table 3) and after fatigue (95% CI: 1.884–7.302; $P = 0.003$, Table 3). Both before and after fatigue, the frontal plane ROM of female participants was significantly greater than that of male participants. Participants displayed no differences in the peak knee adduction angle before and after fatigue, and there was no difference between the sexes ($P > 0.05$, Table 3).

Knee kinetics

Both male and female participants displayed no differences in the peak external knee extension moment after fatigue. However, there was a significant difference between the sexes before ($P = 0.043$, Table 3) and after fatigue ($P = 0.037$, Table 3). Regardless of before or after fatigue, the peak knee extension moment of female participants was higher than that of male participants. Figure 8 shows the external knee adduction and extension moments during the stance phase. The EKAM had two peaks at the early and late stance phases, and the maximum EKAM was observed at the early stance phase. On the coronal plane, the peak values of the first (95% CI: −0.165, −0.077; $P = 0.000$) and second (95% CI: −0.114, −0.043; $P = 0.000$) adduction moments of the knee were significantly increased after fatigue. Female participants demonstrated 22.7% (0.101 N·m/kg) greater first knee-adduction moments peak (95% CI: −0.134, −0.067; $P = 0.000$, Table 4 and Figure 9) and 21.1% (0.056 N·m/kg) greater second knee-adduction moments peak (95% CI: −0.086, −0.028; $P = 0.002$, Table 4 and Figure 9) in the post-fatigue condition. Male participants demonstrated 47.4% (0.161 N·m/kg) greater first knee-adduction moments peak (95% CI: −0.308, −0.014; $P = 0.039$, Table 4 and Figure 9) and 53.0% (0.123 N·m/kg) greater second knee-adduction moments peak (95% CI: −0.226, −0.019; $P = 0.030$, **Table 4** and **Figure 9**) in the post-fatigue condition.

The peak value of the knee abduction moment after fatigue was also higher than that before fatigue ($P < 0.05$). Peak external knee abduction moments were 26.3% (0.035 N·m/kg) greater in male participants after the fatigue protocol ($P = 0.017$, **Table 4** and **Figure 9**). Female participants demonstrated 36.0% (0.073 N·m/kg) greater peak knee-abduction moments in the post-fatigue condition ($P = 0.043$, **Table 4** and **Figure 9**). On the horizontal plane, the peak value of the internal rotation moment is also larger while walking after fatigue ($P < 0.001$, **Figure 9**).

Discussion

Hip-muscle weakness has been implicated as a risk factor for ACL injuries, PFPS, and KOA (Hewett et al., 2005; Baldon et al., 2009). There is a growing amount of evidence supporting the influence of hip muscle weakness, as well as changes in lower limb mechanics on the knee joint, which may lead to injuries. The aim of our study was to induce hip abductor weakness through prolonged exertion and then to test injury-related changes in knee kinematics and kinetics. After the fatigue protocol, the peak hip abduction strength of healthy male and female participants decreased by 43 and 46%, respectively. The effect size for the change in strength after the protocol suggests the validity of the isolated fatigue protocol for this study. We observed that after the fatigue protocol of the hip abductor, the decreased hip abductor strength led to a decrease in the sagittal plane ROM of the knee and hip joint and an increase in the external adduction moment at the knee.

Hip abductor fatigue

The simplest way to determine muscle fatigue is to measure individual load changes during the completion of an exercise task, such as the maximum level of voluntary isometric contraction. This is a visual manifestation of muscle fatigue, the "failure to maintain required or expected force" (Edwards, 1981). Previous studies have reported a 46% (Pohl et al., 2015) and 43% (Patrek et al., 2011) decrease in hip abductor strength, respectively, after the hip abductor fatigue protocol. We observed that the peak hip abduction strength of participants decreased by 44%. After body weight standardization, the hip abductor strength of male participants was significantly higher than that of female participants before and after fatigue. The risk of KOA, PFPS, and ACL injuries in women is significantly higher than that in men (Boling et al., 2010; Frank et al., 2017). Previous studies have shown that the weaker abductor muscles in females may be related to the increase in knee coronal movement and the risk of knee joint injury (Ro et al., 2017). Our research may prove this point to some extent.

Gluteal medius EMG data were recorded during the first 30 and 30 s after the fatigue protocol, providing further objective evidence for hip abductor fatigue caused by the protocol. Most of the literature on the objective performance of muscle fatigue has reported that the variation in muscle fiber propagation velocity will affect the power spectrum of EMG signals (Molinari et al., 2006). During fatiguing isometric contractions, MF mainly reflects the change in conduction velocity (CV) of the active motor units (Mus). From the beginning to the end of muscle fatigue, the high-frequency components of CV are reduced due to the tissue low-pass filtering effect causing the sEMG spectrum to shift to lower frequencies (Zhang et al., 2018). Decreases in MNF and MF are reliable electromyographic indications of local muscle fatigue (Molinari et al., 2006; Zhang et al., 2018). In previous studies, the same hip abduction fatigue protocol recorded 8.6% (Patrek et al., 2011) and 10% (Kogi and Hakamada, 1962) decreases in MF. In our study, we recorded a decrease of 13.4% (female) and 18% (male) in MNF and 21% (female) and 20% (male) decreases in MF. We believe that these EMG changes, coupled with a 43% reduction in peak hip abductor strength and a Borg rating of perceived exertion values of 19/20 for the last 30 s of the fatigue protocol, provide sufficient evidence of hip abductor fatigue.

Kinematic and kinetic data

Studies have shown that hip abductor weakness is associated with increased hip adduction during dynamic weight-bearing activities in female athletes (Dierks et al., 2008; Willson and Davis, 2008). However, we did not find a difference between the peak hip abduction angle and coronal plane hip ROM. This may be because a decrease in hip abductor strength appears to have little effect on lower limb kinematics: GM has only 20–70% activation during the stand phase of normal walking (Zacharias et al., 2019). Therefore, the requirements of this task may not be sufficient to cause changes in the kinematics of the coronal plane. Tasks that place greater demands on hip abductor may yield greater GM activation and larger kinematic effects than those shown in this investigation. Henriksen et al. (2009) reported that reduced function of the hip abductor resulted in a decrease in peak hip and knee extension angles during gait. In our study, there was no significant difference in the peak flexion angle of the hip and knee joint during walking after fatigue. We observed that the sagittal plane ROM of the hip and knee joint was smaller than that before fatigue.

In our study, there were no associated changes in EHAM after experimentally reducing hip abductor strength. This result is consistent with the results of regression analyses by Rutherford and Hubley-Kozey (2009), who found that posterior abductor strength did not explain variability in

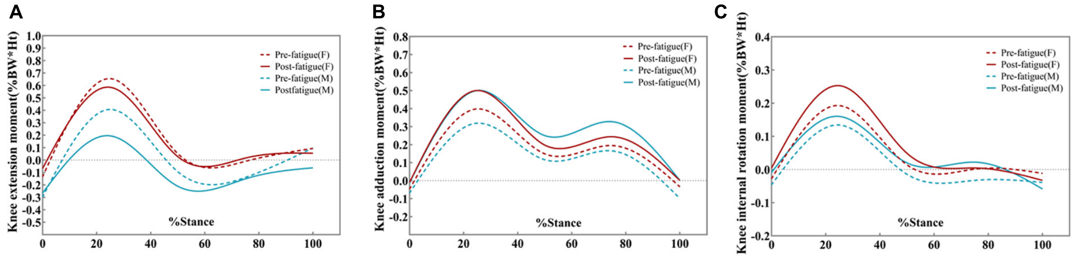

FIGURE 8
Ensemble average knee kinetics for the dominant limb for all male and female participants. Changes in knee extension moments **(A)**, knee adduction moments **(B)**, and knee internal rotation moments **(C)** during pre-fatigue and post-fatigue. Moments are given in % bodyweight times height (Ht).

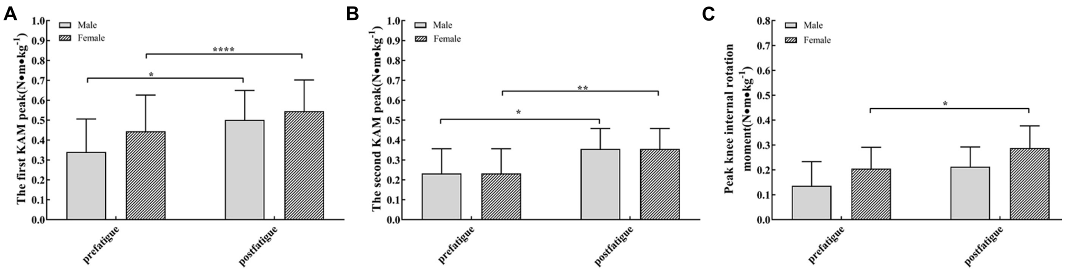

FIGURE 9
(A) The first peak of external knee adduction moment in female (bar with oblique line) and male participants (dark bars) was significantly different after fatigue. **(B)** The second peak of external knee adduction moment was significantly different after fatigue in men (dark bars) and women (bar with oblique line). **(C)** The peak knee internal rotation moments (mean and standard error) were significantly different after fatigue in men (dark bars). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

EHAM. In contrast to our results, Henriksen (Gayda et al., 2005) observed that after intramuscular injection of hypertonic saline, reduced hip-abductor function was accompanied by a decrease in EHAM during walking. The difference in results may be attributed to the type of intervention. The biomechanical changes they observed after injection could stem from analgesic gait adaptation. Chang et al.'s (2005) study found that a greater baseline hip adduction moment protected against ipsilateral medial OA progression from baseline to 18 months. Chang et al. (2005) postulated that the lower EHAM was due to the decrease in hip abductor strength, resulting in greater contralateral pelvic drop and EKAM. In our study, there was no significant difference in EHAM after fatigue. However, the reduction in hip-abductor strength results in greater EKAM.

One previous study adopted a probabilistic modeling approach to explore the effect of hip abductor weakness on normal gait (Valente et al., 2013). This model demonstrated that weakness of the hip abductor muscles mainly affected hip and knee contact forces during normal walking. There were greater increases in the peak knee joint loads than in loads at the hip. One possible explanation for the lack of changes in hip kinematics is that the magnitude of the induced hip-abductor weakness in our study was insufficient to evoke changes. According to the authors, the greater increase in peak knee load is due to compensation for the hip abductor by the muscular system. Unfortunately, we did not measure the EMG activity in the knee-spanning muscle (rectus femoris and biceps femoris) to support or oppose this. This is a limitation of our study design.

The EKAM based on inverse dynamics analysis is the most commonly used dynamic parameter to reflect the medial load of the knee joint. There is evidence that the peak EKAM is positively correlated with disease progression and knee joint pain (Rutherford and Hubley-Kozey, 2009; O'Connell et al., 2016), and a higher peak EKAM is related to radiographic changes in the knee joint structure and cartilage degeneration (Chehab et al., 2014). In asymptomatic people, the presence and severity of medial meniscus tears were also positively correlated with the peak EKAM (Davies-Tuck et al., 2008). The results of our study indicate that hip abductor fatigue leads to an increase in EKAM, which is consistent with the observations of Geiser et al. (2010). However, some studies have come to different conclusions. Pohl et al. (2015) showed that a reduction in the force output of the hip abductor muscles by superior gluteal nerve block injection did not result in a subsequent increase in EKAM. They reduced hip-abductor function *via* superior gluteal nerve block injection. Nevertheless, the proximity of the

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TABLE 4 Study limb mean (SD) knee joint kinetics outcomes from the before and after fatigue gait analyses.

Variable	Women (n = 10)				Men (n = 5)				P-value (Group)	
	Pre-fatigue	Post-fatigue	P-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue	P-value	Effect size, 95% confidence interval	Pre-fatigue	Post-fatigue
The first KAM peak ($N \cdot m \cdot kg^{-1}$)	0.444 ± 0.182	0.545 ± 0.157	0.000****	−0.594, (−0.134, −0.067)	0.340 ± 0.166	0.501 ± 0.148	0.039*	−1.024, (−0.308, −0.014)	0.302	0.612
The second KAM peak ($N \cdot m \cdot kg^{-1}$)	0.265 ± 0.113	0.321 ± 0.106	0.002**	−0.511, (−0.086, −0.028)	0.232 ± 0.124	0.355 ± 0.103	0.030*	−1.079, (−0.226, −0.019)	0.620	0.567
Peak external knee extension moment ($N \cdot m \cdot kg^{-1}$)	0.779 ± 0.221	0.800 ± 0.232	0.733	−0.092, (−0.160,0.117)	0.519 ± 0.190	0.542 ± 0.115	0.838	−0.146, (−0.317,0.271)	0.043*	0.037*
Peak external knee abduction moment ($N \cdot m \cdot kg^{-1}$)	−0.133 ± 0.106	−0.098 ± 0.062	0.017*	−0.403, (Wilcoxon signed rank test)	−0.203 ± 0.145	−0.130 ± 0.133	0.043*	−0.525, (Wilcoxon signed rank test)	0.221	0.528
Peak external knee internal rotation moment ($N \cdot m \cdot kg^{-1}$)	0.205 ± 0.086	0.288 ± 0.089	0.010*	−0.948, (−0.140,−0.026)	0.136 ± 0.097	0.213 ± 0.079	0.288	−0.870, (−0.252,0.098)	0.178	0.136

ROM, range of motion. Effect size (d) is based on standardized differences; $P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

injection to the superior gluteal nerve and the duration of the drug effect are difficult to control. This may have contributed to the difference in results. Henriksen et al. (2009) observed a decrease in the EKAM peak after a pain-induced decrease in hip abductor function. It is important that Henriksen's study reduced hip abductor function by inducing a pain response. It is unclear whether the gait adaptation they observed after injection stems from the analgesic gait pattern.

Inevitably, our study has several limitations. First, these results should be viewed with respect to the characteristics of the participants. As this study was conducted on healthy participants, the current results cannot be directly translated to joint dynamics in patients with knee joint diseases. Therefore, we will further expand the sample size and enrich the sample composition in future studies. Second, the reduction in strength associated with fatigue in this study was used to represent hip abductor muscle weakness. It is important that the kinematic and kinetic changes caused by muscle fatigue may be different from those caused by muscle weakness. Muscle weakness occurs over a long period of time, and compensation patterns can be developed to address this weakness. This adaptive gait change cannot be detected in our study design. It is necessary to further study the effect of hip abductor weakness on knee joint mechanics. Third, we should record EMG activity in more knee and hip muscles to confirm the fatigue compensation strategy.

Conclusion

We examined knee kinematics and kinetics and hip abductor EMG response to a hip-abduction fatigue protocol in healthy people. Our results revealed that after the fatigue protocol, the sagittal plane knee ROM decreased, and the EKAM increased. From a clinical perspective, significant weakness of the hip abductor muscles exists in people with KOA, PFPS, and ACL injury. The hip abductor muscle plays an important role in gait control and step-to-step symmetry in normal people. Therefore, evaluating hip abductor strength and providing intensive training for patients with muscle weakness is an important part of preventing knee-related injuries.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The study was reviewed and approved by the Ethics Committee of Huadong Hospital (No. 2020K079).

The patients/participants provided their written informed consent to participate in this study.

Author contributions

JZ and BA conceived and designed the experiments. YT and XZ acquired and analyzed the data. YT wrote this manuscript. YL and MY checked the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1003023/full#supplementary-material

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Exploring the mechanism of immediate analgesic effect of 1-time tuina intervention in minor chronic constriction injury rats using RNA-seq

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Previous studies have proved and investigated the mechanism of the analgesic effect of tuina treatment on neuropathic pain. The purpose of this study was to analyze changes in gene expression in the dorsal root ganglia (DRG) and spinal dorsal horn (SDH) after 1-time tuina intervention to investigate the immediate analgesic mechanism by tuina. An improvement in nociceptive behavior in minor chronic constriction injury (CCI) rats after 1-time tuina was observed. 1-time tuina was more effective in the amelioration of thermal hyperalgesia, but no changes were found in the ultrastructure of DRG and SDH. Sixty-five differentially expressed genes (DEGs) modulated by tuina were detected in the DRG and 123 DEGs were detected in the SDH. Potential immediate analgesic mechanisms of tuina were analyzed by the Kyoto Encyclopedia of Genes and Genomes. DEGs were enriched in 75 pathways in DRG, and 107 pathways in SDH. The immediate analgesic mechanism of tuina is related to the calcium signaling pathway, thermogenesis, and regulation of lipolysis in adipocytes.

KEYWORDS
neuropathic pain, tuina, RNA sequencing, dorsal root ganglia, spinal dorsal horn, analgesia

Introduction

Neuropathic pain (NP) is a syndrome caused by injury or disease of the somatosensory nervous system, either in the periphery or central, and is characterized by spontaneous pain, hyperalgesia, allodynia, and paresthesia (Baron et al., 2010). NP has a significant influence on the physical and psychological health of patients, and the prevalence in the whole population is approximately 10%, which varies by disease. Due to the complicated pathogenesis, current treatments such as medication did not show obvious effects (Schaefer et al., 2014; Fayaz et al., 2016; Scholz et al., 2019; Zheng et al., 2020).

Tuina is an alternative medical therapy which is safe and has virtually no side effects (Field, 2016). Clinical studies have proved that tuina has either immediate or cumulative analgesic effects, which can ameliorate the symptoms of NP (Gok Metin et al., 2017; Izgu et al., 2019). Its cumulative analgesic mechanism is based on the down-regulation of inflammatory cytokines (such as tumor necrosis factor-α, interleukin-1, and interleukin-1β) and the inhibition of microglial activation (Liu et al., 2021). Our previous studies confirmed the effectiveness of tuina analgesia, and found differentially expressed genes (DEGs) in DRG and SDH of rats with sciatic nerve injury after 20-time tuina treatment, which were mainly related to regulation of protein binding, response to pressure, and neuron projection (Lv, 2020; Lv et al., 2020a). However, the immediate analgesic mechanism of tuina is unknown. Clinically, 1 or 2 time tuina treatment can effectively relieve pain, achieve immediate analgesia and prevent disease progression in patients (Li et al., 2004; Qing et al., 2022). Therefore, searching for immediate effective targets and exploring mechanisms of tuina analgesia can provide new evidence and methods for the therapeutic targets of NP, as well as help tuina to be accepted and applied in more countries and regions.

As the sensory neurons of the first and second levels, the dorsal root ganglia (DRG) and the spinal dorsal horn (SDH) are the primary portals for nerve afferents and integration of pain information. They are important for both inducing central sensitization and processing NP development (Simeoli et al., 2017; Inoue and Tsuda, 2018; Shepherd et al., 2018). Here, we investigate the immediate analgesic mechanism of 1-time tuina and changes in RNA expression in DRG and SDH using the minor chronic constriction injury (CCI) model, which is a recognized model for simulating clinical peripheral neuropathic pain (Jaggi et al., 2011). To this end, we behaviorally assessed mechanical and thermal allodynia changes after the tuina treatment and non-treatment conditions in the CCI rat model. We also analyzed the gene expression differences and functions before and after intervention in the DRG and SDH of the surgical side by RNA-Seq.

Results

Changes in symptoms of hyperalgesia and allodynia in minor chronic constriction injury rats

The rats were in good condition and recovered well from the surgical incision. The posture of rats in the sham group was normal when walking and resting. Rats in the model and tuina group had curled hind paws on the surgical side, limping when walking, and mostly lying on the left side when resting. There was no statistical difference in behavior tests between groups before modeling, and before intervention. Mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL) were decreased in both the model ($P = 0.00$, $P = 0.00$) and tuina groups ($P = 0.00$, $P = 0.00$) compared with the sham group. After a 1-time tuina intervention, MWT and TWL increased in the tuina group ($P = 0.014$, $P = 0.00$) compared with the model group (**Figure 1** and **Table 1**).

Changes in the ultrastructure of dorsal root ganglia and spinal dorsal horn

The electron microscopy results of DRG in the sham group showed that the mitochondrial morphology was intact, and the mitochondrial matrix was homogeneous (**Figure 2A**). The results of the model and tuina groups showed mitochondrial swelling, disorganized mitochondrial cristae arrangement with matrix dissolution and dilated mitochondria with occasional vacuolization (**Figures 2B,C**). The electron microscopic results of SDH in the sham group showed the nuclear membrane was smooth and intact, the perinuclear gap was not significantly widened, and the chromatin was sparse (**Figure 2D**). The images of the model and tuina groups showed that the nucleus was irregular in shape, the double-layered nuclear membrane was intact, the perinuclear gap was not significantly widened, and the chromatin was aggregated (**Figures 2E,F**).

Bioinformatic analysis of dorsal root ganglia and spinal dorsal horn on the surgical side of rats

Results of the sample quality control

The results of performing quality control on the raw data indicated that the data were qualified and ready for subsequent analysis. We obtained a total of 920 million reads, including an average of 49.84 million reads per DRG sample and 53.32 million reads per SDH sample. The results of the error rate, Q20 and Q30 met the quality control standards, which showed that the sequencing results were reliable and credible (**Table 2**).

Changes of differentially expressed genes after tuina intervention

The results of principal component analysis (PCA) showed good intragroup aggregation in each group, indicating a high degree of similarity between the samples within the group. It also showed that there was good intergroup dispersion, which indicated significant differences between all groups. The results confirmed that the model was established successfully and tuina treatment was effective (**Figure 3**). Changes of DEGs in DRG and SDH on the surgical side were detected by RNA sequencing. A total of 964 DEGs were detected in the DRG of the three

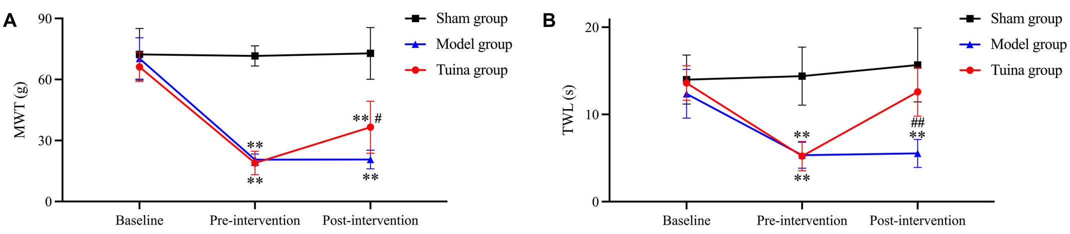

FIGURE 1
Results of behavioral tests of rats in each group. **(A)** MWT; **(B)** TWL. Sham group (*n* = 6); model group (*n* = 6); tuina group (*n* = 6). $^{**}P < 0.01$, *vs.* the sham group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, *vs.* the model group.

TABLE 1 Results of behavioral tests of rats in each group.

	MWT			TWL		
	Baseline	**Pre-intervention**	**Post-intervention**	**Baseline**	**Pre-intervention**	**Post-intervention**
Sham group	72.36 ± 12.7	71.61 ± 4.95	72.83 ± 12.7	14 ± 2.81	14.39 ± 3.33	15.68 ± 4.24
Model group	70.33 ± 10.17	20.56 ± 2.84	20.64 ± 4.56	12.37 ± 2.79	5.33 ± 1.49	5.53 ± 1.6
Tuina group	66.18 ± 7.19	18.91 ± 5.78	36.53 ± 12.78	13.61 ± 1.98	5.22 ± 1.68	12.58 ± 2.78

groups. There were 65 up-regulated DEGs and 277 down-regulated DEGs in the model *vs.* sham (**Figure 4A**), and 106 up-regulated DEGs and 129 down-regulated DEGs in the model *vs.* tuina (**Figure 4B**). Venn analysis showed a total of 122 DEGs between the model *vs.* sham and the model *vs.* tuina (**Figure 5A**). A total of 65 DEGs showed opposite expression trends between the model group and the tuina group. A total of 674 DEGs were detected in the SDH of the three groups. There were 80 up-regulated DEGs and 308 down-regulated DEGs in the model *vs.* sham (**Figure 4C**), and 52 up-regulated DEGs and 198 down-regulated DEGs in the model *vs.* tuina (**Figure 4D**). Venn analysis showed a total of 127 DEG between the model *vs.* sham and the model *vs.* tuina (**Figure 5B**). 123 DEGs showed opposite expression trends between the model and tuina group.

Pathways analysis of differentially expressed genes regulated by tuina in dorsal root ganglia and spinal dorsal horn

To understand the function and role of DEGs in detail, we performed Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses (**Figure 6**). DEGs in DRG were enriched in 75 pathways, including the calcium signaling pathway, vascular smooth muscle contraction, leukocyte transendothelial migration, regulation of lipolysis in adipocytes, gonadotropin-releasing hormone (GnRH) secretion, cGMP-protein kinase G (cGMP-PKG) signaling pathway, apelin signaling pathway, and thermogenesis pathways. DEGs in SDH were enriched in 107 pathways, including the hypoxia-inducible factor (HIF) -1 signaling pathway, interleukin-17 signaling pathway, Toll-like receptor signaling pathway, GnRH signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathway, and T helper (Th) 17 cell differentiation pathways.

Discussion

Tuina analgesia is effective and rapid, with practically no side effects (Wang et al., 2020; Rivaz et al., 2021; Liu et al., 2022). The goal of this study was to investigate the potential mechanisms in the induction of immediate analgesia by tuina. We assessed the immediate analgesic effect of tuina treatment by evaluating the changes in MWT and TWL before and after the treatment and screened DEGs using RNA-Seq. KEGG analysis was used to further explore the mechanisms.

Minor CCI model was used for simulating clinical NP. The minor CCI model causes nerve edema through ligation, producing chronic constriction and compression resulting in degeneration and necrosis of some nerve fibers which manifests as neuropathic pain with inflammatory pain after modeling, forming stable chronic pain in 3–5 days (Grace et al., 2011; MacDonald et al., 2021). In our preliminary study, consistent with the literature, we found that the model was stable at day 7 after modeling, so we chose that time point to give tuina intervention. The "Three-Manipulation and Three-Acupoint" is a combination of manipulations and acupoints that we have studied and proven to be effective (Li et al., 2019; Lv et al., 2020a). We found that after 20-time intervention, the MWT and TWL of rats with sciatic nerve injury were significantly improved, and demonstrated significant cumulative analgesic effects of the "Three-Manipulation and Three-Acupoint".

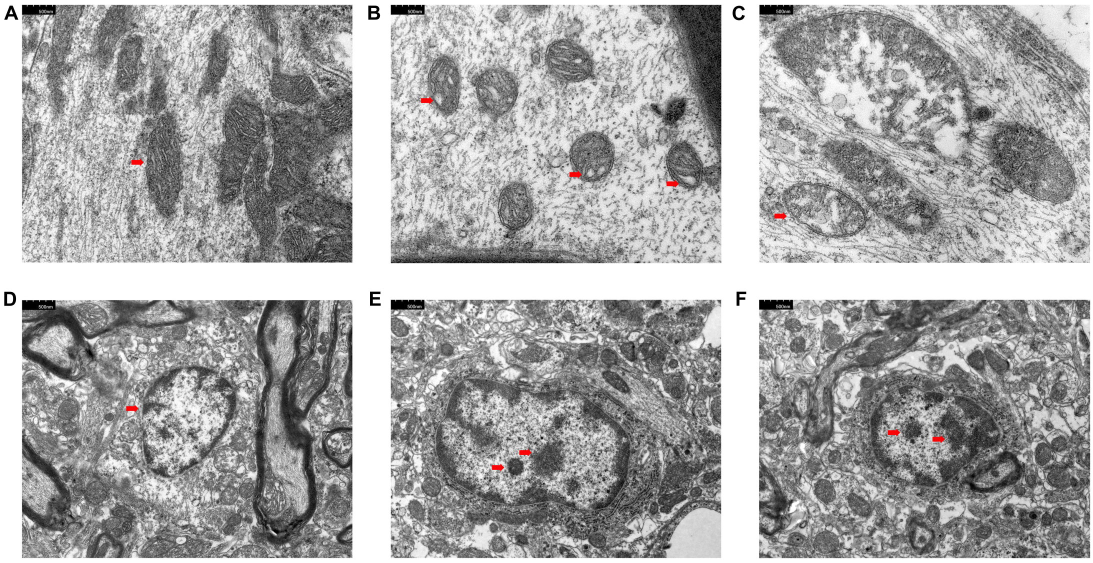

FIGURE 2
Electron microscopy results of DRG and SDH. Sham group (n = 3); model group (n = 3); tuina group (n = 3). Panels **(A–C)** were DRG; the arrow showed the mitochondrial vacuoles; panels **(D–F)** were SDH; the arrow shows the chromatin aggregation. **(A,D)** Sham group; **(B,E)** Model group; **(C,F)** Tuina group.

TABLE 2 Sample sequencing information and quality control results.

Sample	Raw reads	Clean reads	Error rate (%)	Q20 (%)	Q30 (%)
DRG_Sham_1	48158012	47760586	0.0243	98.31	94.9
DRG_Sham_2	56223240	55863814	0.0237	98.52	95.44
DRG_Sham_3	46544026	46183596	0.0241	98.36	95.02
DRG_Model_1	47859852	47517974	0.0236	98.56	95.58
DRG_Model_2	45210228	44920418	0.0238	98.51	95.42
DRG_Model_3	54200106	53876928	0.0236	98.56	95.57
DRG_Tuina_1	49908500	49592802	0.024	98.44	95.21
DRG_Tuina_2	57265050	56877106	0.0239	98.47	95.32
DRG_Tuina_3	43214794	42957848	0.0235	98.59	95.66
SDH_Sham_1	52341804	51731738	0.0261	97.5	93.17
SDH_Sham_2	51960712	51356472	0.026	97.53	93.26
SDH_Sham_3	50816528	50241342	0.0262	97.48	93.11
SDH_Model_1	50957220	50388816	0.0259	97.6	93.36
SDH_Model_2	53375656	52715726	0.0261	97.5	93.19
SDH_Model_3	53827014	53217702	0.026	97.57	93.3
SDH_Tuina_1	45437160	44443632	0.0282	96.68	91.41
SDH_Tuina_2	61969304	61269358	0.026	97.57	93.32
SDH_Tuina_3	59304792	58595522	0.0263	97.44	93.03

(1) Sample: sample name, 18 Cdna libraries are sham group, model group, tuina group. (2) Raw reads and clean reads: the number of original sequence data and the data after filtering. (3) Error rate: average error rate of the sequencing base, generally below 0.1%. (4) Q20 and Q30: percentage of bases with sequencing quality above 99 and 99.9% of total bases, generally above 85 and 80%.

In this experiment, we found that rats in the model and tuina groups showed significant allodynia, thermal hyperalgesia, and limp positions after modeling. The electron microscopy results of DRG and SDH in the model group also confirmed the difference in ultrastructure from the sham group. This suggests that the model replication was successful and consistent with the literature (Grace et al., 2010). While in previous experiments, we tested the therapeutic effect after a 20-time tuina intervention, the present study focuses on the immediate analgesic effect of tuina (Lv et al., 2020b). Behavioral tests were performed immediately after 1-time tuina treatment. Compared to the model group, the results of MWT and TWL in the tuina group were statistically significant. This result showed that 1-time tuina treatment can effectively alleviate

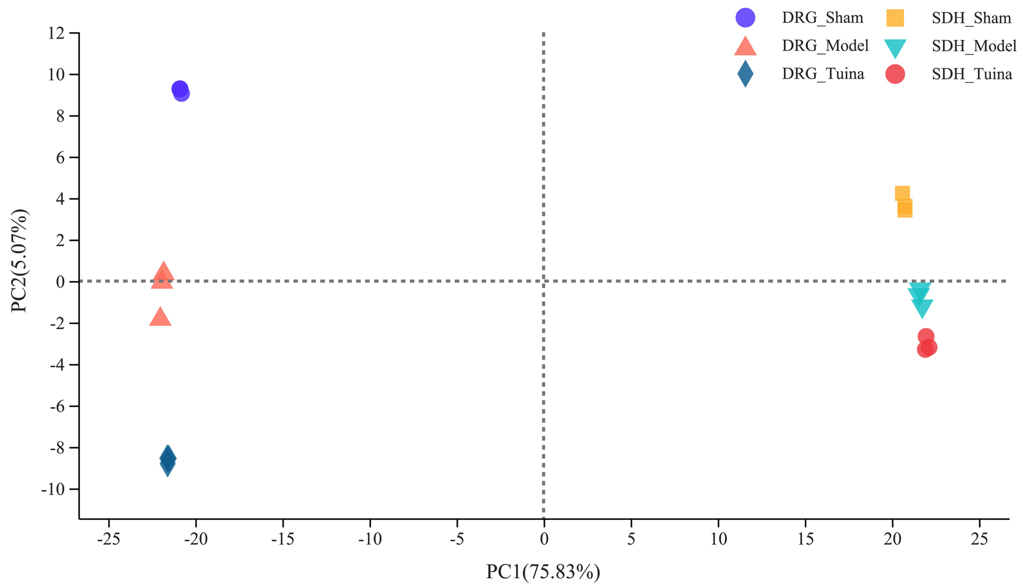

FIGURE 3
PCA analysis of DRG and SDH samples. Sham group (n = 3); model group (n = 3); tuina group (n = 3). PC1 = 75.83%, PC2 = 5.07%, a higher percentage means that this principal component is more capable of differentiating the samples. The distance between graphs represents how far the results of samples showed, and the farther distance indicates the lower similarity between samples.

hyperalgesia. Compared with mechanical hyperalgesia, the improvement in thermal hyperalgesia was more noticeable. The electron microscopic results of DRG and SDH revealed no difference in ultrastructure between the model and tuina groups, implying that short-term tuina intervention did not restore the morphology.

The calcium signaling pathway of DRG is a key factor in the immediate analgesic effect of tuina. Many of the pathways enriched in this study were associated with cascade activation of the calcium signaling pathway, which is critical to initiate and maintain peripheral sensitization of NP (Cui et al., 2021). Peripheral injurious stimuli increase intracellular $Ca2^{+}$ through calcium signaling pathways, *N*-methyl-D-aspartic acid receptors, and other metabolic-like receptors in response to each other, and it can further activate calcium/calmodulin-dependent protein kinase II, and protein kinase A, which enhances postsynaptic excitability and triggers NP, resulting in peripheral and central sensitization (Yang et al., 2004; Latremoliere and Woolf, 2009; Incontro et al., 2018; Liu et al., 2018). The study proved that the mechanical stimulation administered to the body by tuina could initiate the skeletal muscle calcium signaling pathway, regulate the uptake and release of $Ca2^{+}$, and adjust the intracellular $Ca2^{+}$ concentration, thus repairing the damaged cells (Lin et al., 2013). The 1-time tuina intervention was able to modulate the calcium signaling pathway, which was beneficial in reducing nerve damage, local inflammatory microenvironment-induced nociceptive hypersensitivity, and reducing the hyperexcitability of injury-sensing neurons (Luo et al., 2008; Chen et al., 2009).

Thermogenesis/regulation of lipolysis in adipocytes in DRG and SDH is associated with the immediate analgesic mechanism of tuina. The results of behavioral tests indicated that tuina was more effective for thermal nociceptive sensitization. Tuina is considered to have a warming effect in Chinese medical theory. In the KEGG enriched pathways, we have found that the expression of thermogenesis/regulation of lipolysis in adipocytes, and uncoupling of protein-1 mediates the dissipation of energetic chemicals then induces adaptive thermogenesis through brown fat tissue. The binding to beta-adrenergic receptors increases lipolysis and regulates local energy metabolism of nerve injury at the genetic level, thereby increasing TWL (Kissig et al., 2016; Mills et al., 2018). The immediate mechanism of tuina analgesia will continue to be validated in future research. Furthermore, the KEGG enrichment results revealed that the 1-time tuina intervention was able to activate the apelin signaling pathway. Apelin is expressed in fat tissue and skeletal muscle. It can induce skeletal muscle cell proliferation and inhibit skeletal muscle atrophy, suggesting that tuina exerts immediate analgesic effects while preventing possible motor dysfunction of NP in the long term (Vinel et al., 2018).

The main limitation of this study is the lack of verification for the target genes and pathways to further confirm that the results were reliable. We will further verify the calcium signaling pathway and differential genes, focus on the gene expression changes of DRG after different times of tuina (1, 2, 3 times) in the future, and explore gene expression patterns through different

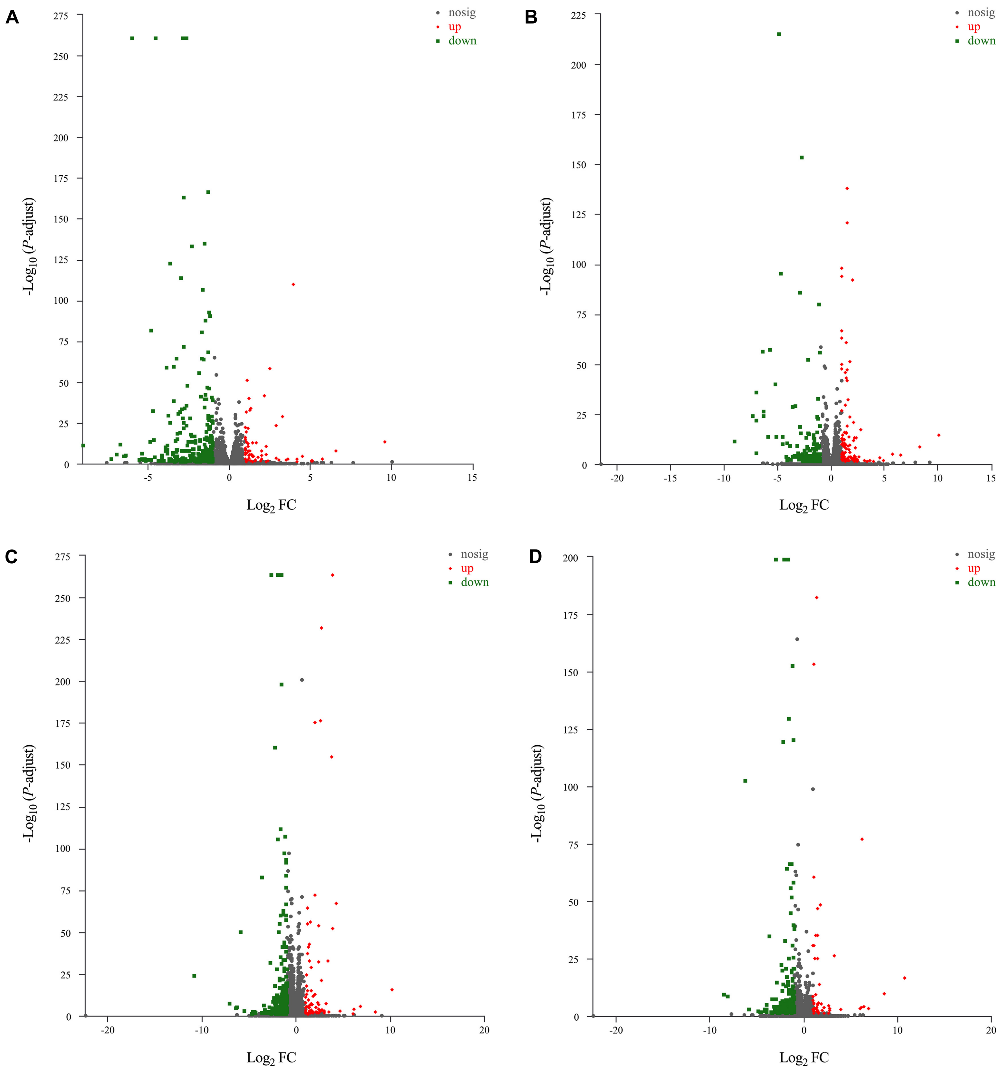

FIGURE 4
Volcano map results, the abscissa is the Log_2 FC and the ordinate is the -LOG_{10}, *P*-adjust <0.05. Results of DRG sequencing, **(A)** model *vs.* sham; **(B)** model *vs.* tuina; Results of SDH sequencing, **(C)** model *vs.* sham; **(D)** model *vs.* tuina. Gray are genes with no differential expression, red are genes with up-regulated expression, and green are genes with down-regulated expression.

therapeutic styles combined with multiple omics approaches to clarify the unique mechanism of tuina analgesia.

Materials and methods

Animals and ethical approval

Eighteen male Sprague-Dawley (SD) rats of 8-week-old, weighing 200 ± 10 g, were obtained from SPF Biotechnology Co., LTD. (Beijing, China), and the certificate number is SCXK (JING) 2019-0010. Rats can drink and feed freely and are cultured in an environment with the appropriate temperature (25 ± 0.5°C), humidity (45 ± 5%), and light cycle (12/12 h). All animal experimental procedures followed the local principles of the Animal Ethics Committee of the Beijing University of Chinese Medicine (BUCM-4-2020111103-4087). We strive to reduce the number of animals used and ensure their welfare in the design of our experiments.

Modeling methods and study design

Pathological modeling started after 7 days of acclimatization. The method of modeling the minor CCI was as described in previous studies (Bennett and Xie, 1988; Grace et al., 2010). Briefly, rats were anesthetized with pentobarbital (1%, Sigma-Aldrich LLC., Germany). The sciatic nerve of the right side was exposed in front of the nerve branch by blunt dissection. A chromic intestinal suture (4-0, Shandong Boda

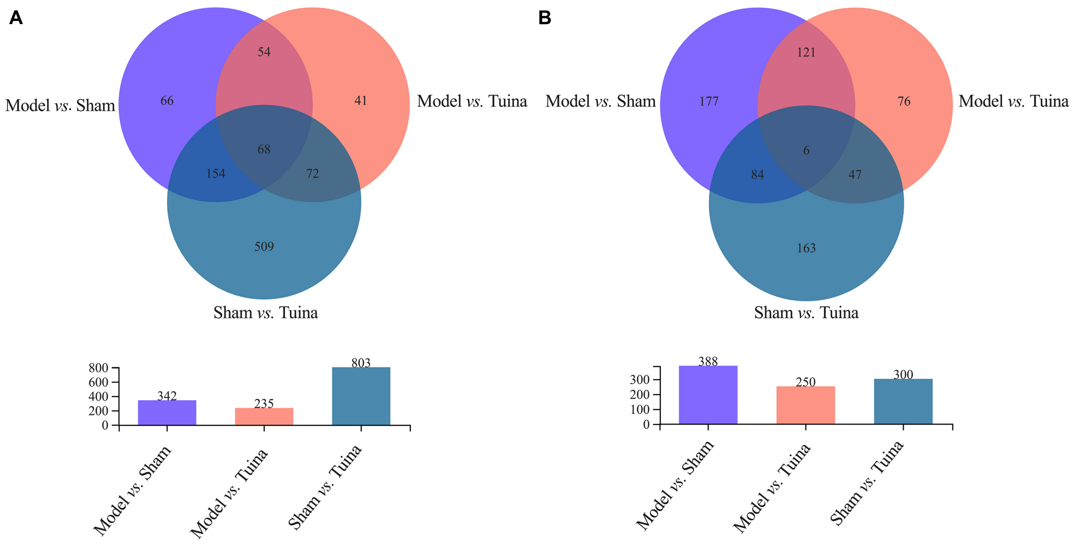

FIGURE 5
Results of the Venn analysis, the abscissa is the group, and the ordinate is the number of DEGs. **(A)** DRG sequencing; **(B)** SDH sequencing. The overlapping regions are identically expressed genes, and genes in the overlapping regions of model *vs.* sham and model *vs.* tuina are associated with the therapeutic effects of tuina.

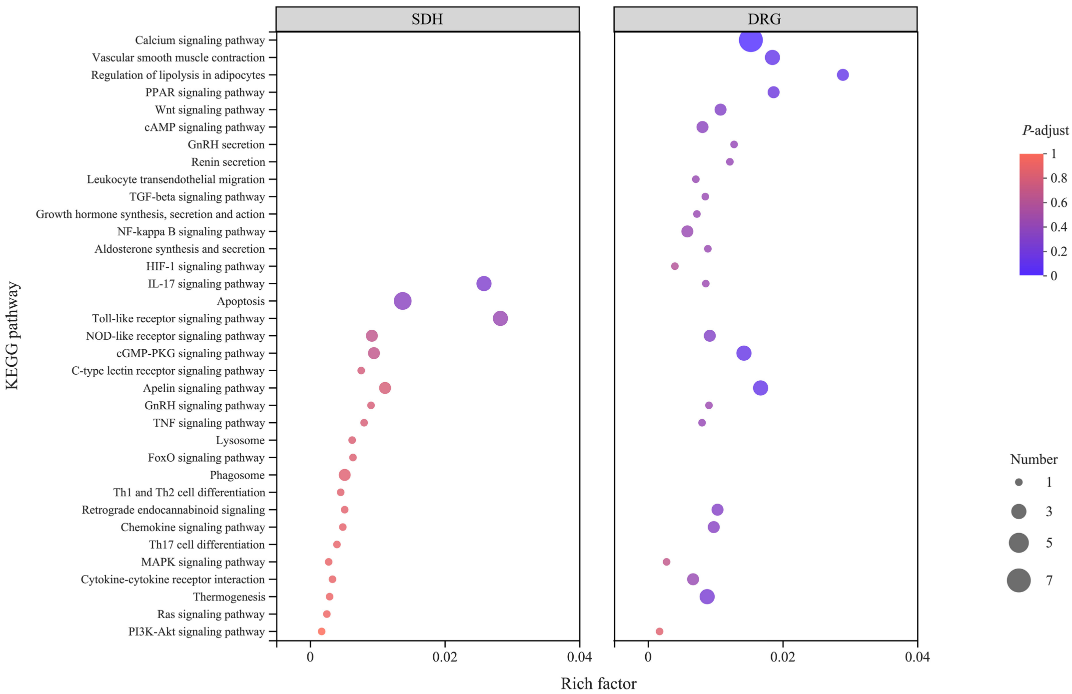

FIGURE 6
KEGG analysis results of DRG samples. SDH on the left and DRG on the right, the abscissa is the KEGG pathway, and the ordinate is the rich factor. The higher the rich factor, the greater the degree of enrichment, and the size of the dots indicates the number of genes in the pathway, while the color of the dots corresponds to the different *P*-adjust ranges.

Medical Products Co., Ltd., Shandong, China) was loosely tied around the nerve and did not interrupt the blood circulation of the epineural vasculature. The sciatic nerve was exposed for 3 min without any ligation in the sham group. The skin was then sewn together with two sutures. Seven days of acclimatization after operation, the 18 rats, which had similar levels of pain sensation, were randomly divided into the sham group ($n = 6$), model group ($n = 6$), and tuina group ($n = 6$).

Intervention methods

The intervention was performed after the model was stably established (7th day after modeling) according to the literature and previous studies (Ma et al., 2017; Lv et al., 2020b; Talaei et al., 2022). The tuina group received a 1-time tuina intervention. The procedure for the "Three-Manipulation and Three-Acupoint" treatment was performed as follows: Firstly, a rat was fixed on the message platform of the Tuina Manipulation Simulator (Self-developed machine, China invention patent number ZL200710187403.1). Secondly, the machine parameters were set to stimulate with a force of 4 N, 60 times per minute. Third, the stimulus rod was placed on BL 37, GB 34, and BL 57 of the surgical side, then finger pressing, plucking, and kneading manipulation were stimulated, respectively. Each acupoint and manipulation were operated for 1 min consecutively for 9 min in total (Lv et al., 2020a). The grip restraint intervention was performed in the sham and model groups.

Behavior tests

Behavioral tests were performed three times—baseline (before modeling), pre-intervention, and post-intervention. MWT and TWL were operated on the right hind paw as in the previous description (Bennett and Xie, 1988). The measurement was repeated three times with a 10-min interval between each measurement.

MWT: Measurement started when exploratory and grooming behaviors stopped, and the rats were motionless and relaxed. An electronic Von Frey instrument (BIO-EVF5; Bioseb, USA) was used, avoiding the metal grid, and the same position on the plantar surface of the hind paws was stimulated with the disposable measurement tip. The intensity of the applied force was adapted, recording the animal's response (e.g., curling hind paws, licking hind paws) and the maximum value automatically was recorded by the system.

TWL: Using a thermal analgesia device (PL-200; Chengdu Techman Software Co., Ltd., China), the heat intensity was set to 50%, and the latency was cut off at 30 seconds to prevent skin damage. The infrared source beneath the plantar surface of the hind paws was put in the right position. The recording of the animal's response and the time was taken automatically by the system.

Electron microscopy

After the last behavioral test, three rats in each group were randomly selected and deeply anesthetized with pentobarbital (1%), then fixed with 4% paraformaldehyde. The DRGs and SDHs of the fourth to sixth lumbar (L_{4-6}) on the right side were removed and fixed for 2 h in 0.1 M PB with 1% osmic acid. The SDH was then subjected to gradient dehydration in ethyl alcohol and acetone, with concentrations of 30, 50, 70, 80, 95, 100, 100, 100 (acetone), 100 (acetone), for 15∼20 min each. After being embedded overnight in the resin, the spinal dorsal horn was sectioned at a thickness of approximately 70 nm. Ultrathin sections were stained for 8 min with 2% uranyl acetate followed by 2.6% lead citrate for 8 min, and dehydrated overnight at room temperature. Transmission electron microscopy (Hitachi TEM system, Japan) was used for observation.

RNA-seq

Three rats were rapidly sacrificed using the same anesthetic method. The RNA-Seq experimental procedure consists of 5 parts: (1) RNA extraction, (2) transcriptome library preparation and sequencing, (3) read mapping of raw data, (4) differential expression analysis and (5) analysis of functional enrichment and alternative splice events identification. The DRG and SDH of L4-6 segments on the right side were removed and separated from the cauda equina (stored at −80℃). Total RNA was extracted from DRG and SDH with TRIzol reagent according to the manufacturer's protocol (Invitrogen, CA, USA), then RNA was determined in quality and quantity. Only high-quality RNA samples were selected for the next experiment. The cDNA transcriptome library was constructed following a TruSeq RNA sample preparation kit (Illumina, CA, USA) according to the protocol of the manufacturer (Chomczynski and Sacchi, 2006). The final double-stranded cDNA samples were synthesized with a SuperScript double-stranded cDNA synthesis kit (Invitrogen, CA, USA). After end-repair, phosphorylation, 'A' base addition, and amplification, sequencing was performed on an HiSeq X Ten platform (Illumina, CA, USA). The raw paired-end reads were trimmed, and quality controlled using SeqPrep and Sickle. The differential expression genes (DEGs) can be identified and considered statistically significant with the P-adjust ≤ 0.05 and fold change >2.0. Finally, all the alternative splice events that occurred in the samples were identified using rMATS (Shen et al., 2014).

Statistical analysis

Data analysis was performed with SPSS Statistics software (version 26.0). MWT and TWL results were presented as mean ± SD. One-way ANOVA was used for comparisons between groups, and the LSD multiple comparison test was used for multiple comparisons. $P < 0.05$ was treated as statistically significant. The KEGG enrichment analysis of DEGs was performed with KOBAS.[1]

1 http://kobas.cbi.pku.edu.cn/home.do

Conclusion

In this study, we found that 1-time tuina intervention could alleviate the hyperalgesia of minor CCI rats, and especially ease thermal hyperalgesia more effectively. However, 1-time tuina treatment did not change the ultrastructure in DRG and SDH when observed using electron microscopy technology. The immediate analgesic mechanism of tuina is mainly related to the calcium signaling pathway, thermogenesis, and regulation of lipolysis in adipocytes.

Data availability statement

The original contributions presented in this study are publicly available. The raw data of RNA-Seq can be found on NCBI at the following link: https://www.ncbi.nlm.nih.gov/bioproject/884185 with accession number: PRJNA884185. Further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by Animal Ethics Committee of the Beijing University of Chinese Medicine.

Author contributions

TY and ZL: study conception and design of the work. HW, YZ, YX, YJ, QG, and DL: animal experiments and data acquisition. HW and ZL: analysis, data interpretation, and drafting of the manuscript. HW, ZL, and TY: approval of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Optimal modes of mind-body exercise for treating chronic non-specific low back pain: Systematic review and network meta-analysis

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Background: There were limited studies that directly compare the outcomes of various mind-body exercise (MBE) therapies on chronic non-specific low back pain (CNLBP).

Objectives: To compare the efficacy of the four most popular MBE modes [Pilates, Yoga, Tai Chi (TC), and Qigong] in clinically CNLBP patients, we conducted a systematic review and network meta-analysis (NMA).

Methods: We searched databases for eligible randomized controlled trials (RCTs) (from origin to July 2022). RCTs were eligible if they included adults with CNLBP, and implemented one or more MBE intervention arms using Pilates, yoga, TC, and qigong. In addition, pain intensity and physical function were evaluated using validated questionnaires.

Results: NMA was carried out on 36 eligible RCTs involving 3,050 participants. The effect of exercise therapy on pain was in the following rankings: Pilates [Surface under cumulative ranking (SUCRA) = 86.6%], TC (SUCRA = 77.2%), yoga (SUCRA = 67.6%), and qigong (SUCRA = 64.6%). The effect of exercise therapy on function: Pilates (SUCRA = 98.4%), qigong (SUCRA = 61.6%,), TC (SUCRA = 59.5%) and yoga (SUCRA = 59.0%).

Conclusion: Our NMA shows that Pilates might be the best MBE therapy for CNLBP in pain intensity and physical function. TC is second only to Pilates in improving pain in patients with CNLBP and has the value of promotion. In the future, we need more high-quality, long-term follow-up RCTs to confirm our findings.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=306905, identifier: CRD42022306905.

KEYWORDS

tai chi, yoga, qigong, Pilates, mind-body exercise, chronic low back pain, network meta-analysis

Introduction

Low back pain (LBP), which occurs below the costal border and above the buttock folds, is one of the most prevalent public health issues worldwide (Van Tulder et al., 2006). Non-specific LBP (NLBP) refers to LBP for which no clear cause has been found and accounts for approximately 80–90% of all cases of LBP (Casazza, 2012), and a significant proportion of patients (10–20%) develop chronic NLBP (CNLBP) lasting at least 12 weeks (Maher et al., 2017). LBP is a major risk factor for physical disability globally, thus affecting nearly 20–25% of the global population over the age of 65 (Vadalà et al., 2020). In the United States, the total annual fiscal effect of low back and neck pain is the third-highest proportion of health care expenditures (Dieleman et al., 2016) and it affects approximately 13.1% of adults from 20 to 69 years old (Shmagel et al., 2016). However, satisfice with treatment is low for CNLBP patients (Patrick et al., 2014). In addition, CNLBP patients usually have a high recurrence rate (Taylor et al., 2014) and were associated with an increased risk of comorbidities such as depression and anxiety (Taylor et al., 2014). Conventional drug therapy appears to provide a short-term benefit to the symptoms of patients with CNLBP; however, recent studies have questioned the effectiveness and safety of these interventions (Deyo et al., 2015b; Al-Qurain et al., 2020; Cashin et al., 2021). Meanwhile, long-term use of analgesics is associated with psychopathy-like depression (Maher et al., 2017) and may decrease bone mass and induce sexual dysfunction (Bishop and Wing, 2003). Pharmacotherapy is insufficient to resolve chronic pain symptoms and improve physical function for this population. Therefore, recently, various clinical guidelines have recommended that the treatment of CNLBP should focus on non-pharmacological interventions (Bernstein et al., 2017; Qaseem et al., 2017; Stochkendahl et al., 2018).

Over the past decades, the advantages of exercise therapy have been discovered in the literature (Miyamoto et al., 2019; Hayden et al., 2020, 2021a; Owen et al., 2020), and it has been used as a first-line option to treat CNLBP (Chiarotto and Koes, 2022). Mind-body exercise (MBE), is a mild to moderate intensity physical activity, such as tai chi (TC) (Qin et al., 2019), yoga (Zhu et al., 2020), qigong (Li et al., 2019) (e.g., Baduanjin and Wuqinxi), and Pilates (Miyamoto et al., 2013), has attracted researchers' wide attention (Zou et al., 2019; Wen et al., 2022). MBE underlines mind-body integration and has the advantages of both mind-body therapy and exercise therapy. It involves various slow body movements synchronized with musculoskeletal relaxation, breathing control, and a meditative state of mind (Bower and Irwin, 2016; Zou et al., 2018). In recent years, it has been successfully used worldwide for the treatment of CNLBP (Teut et al., 2016; Cruz-Díaz et al., 2018; Liu et al., 2019; Yao et al., 2020) and is recommended as a complementary and alternative medicine therapeutic intervention based on the guidelines of the American College of Physicians (Qaseem et al., 2017). Moreover, some meta-analyses indicated that MBE is beneficial for pain intensity and back-specific disability of patients with CNLBP (Li et al., 2019; Qin et al., 2019; Zou et al., 2019; Anheyer et al., 2022). Evidence for these results was also supplied in our previous study (Wen et al., 2022).

Although there is some evidence that MBE intervention is effective in treating the symptoms of patients with CNLBP, there are varying modes. The low efficacy of MBE intervention not only delays the CNLBP patients' condition but also increases unnecessary medical costs. It has become a critical task to further rank the efficacy of different forms of MBE to obtain more comprehensive evidence in terms of MBE for improving symptoms of CNLBP. However, there has been little effort to compare the curative effect of different MBE modes to obtain a deeper awareness. Most randomized controlled trials (RCTs) compare MBE interventions with no treatment or usual care groups, and direct comparisons between different MBE modes were very few. Based on our search results, only one RCT direct compared yoga with qigong in the treatment of patients with CNLBP (Teut et al., 2016). It is because, a head-to-head comparative study would be very expensive, and it would be impractical to use an RCT to examine the relative effects of all MBE modes. Meta-analyses provide a summary estimate of treatment effects by combining data from various studies. However, an important drawback is that standard meta-analyses can only compare two interventions at a time. Meanwhile, network meta-analysis (NMA) can indirectly compare multiple treatments by a common comparator to synthesize evidence across a network of RCTs. Therefore, researchers will be able to rank the effectiveness of multiple MBE modes by the use of NMA.

To date, limited reviews and NMA were done on exercise for patients with CNLBP (Owen et al., 2020; Hayden et al., 2021b; Fernández-Rodríguez et al., 2022). Owen et al. (2020) accomplished a sequential analysis and NMA to evaluate whether or not there was ample evidence to support the application of physical exercise for CNLBP patients and whether one exercise mode was better than another. But TC was included in "Other exercise" intervention group and Qigong-related studies were not included in their NMA. Similar classification appears in the studies of Hayden et al. (2021b) and Fernández-Rodríguez et al. (2022). We cannot find out which MBE mode is the most optimal for improving pain intensity and physical function of patients with CNLBP through current studies. Moreover, most NMA does not include Chinese RCTs because of language barriers and limited retrieval resources. Therefore, it is necessary to identify and assess the best MBE modes for CNLBP treatment by a new systematic review and NMA.

This review aimed to conduct a systematic review and NMA of current evidence from RCTs to compare the therapeutic effects of four common MBE modes (TC, yoga, qigong, and Pilates) in improving pain intensity and physical function for adults with CNLBP. The results of this review may help clinicians choose the ideal MBE modes for the treatment of CNLBP and enrich the theoretical basis for MBE selection. Meanwhile, for patients, the results of this study are assumed to provide evidence-based advice for treatment planning for them and to use optimal MBE intervention as the ideal form of self-care to relieve their symptoms and improve physical function.

Materials and methods

Protocol and registration

In the International Prospective Register of Systematic Reviews, the protocol was prospectively recorded (CRD42022306905) and was conducted by Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Network Meta-Analysis (PRISMA-NMA) (Hutton et al., 2015).

Literature search

This search strategy was designed using systematic reviews (Zou et al., 2019; Owen et al., 2020; Wen et al., 2022) that have already published and the Cochrane Back and Neck Group (Furlan et al., 2015). It was based on the following seven databases, including PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Chinese Scientific Journals Full-Text Database (VIP). Publication dates ranged from the first date available to July 2022 in all languages. Moreover, the following keywords are searched: "Mind-body exercise," "Tai chi", "Yoga", "Pilates", "Qigong", and "Chronic low back pain". The complete searching strategies of all databases are submitted in Supplementary material 1.

Eligibility criteria

Participants, Intervention, Comparison, Outcomes, and Study (PICOS) design was employed as a framework to enact eligibility criteria (Hutton et al., 2015).

Inclusion criteria

(1) adults (≥18 years) that were diagnosed with CNLBP at baseline based on the National Institutes of Health (NIH) definition (Deyo et al., 2015a).
(2) to assess the therapeutic impact of one or even more MBE arms, an RCT protocol was adopted.
(3) to avoid the influence of different positive background treatments between the MBE group and the control group on the final NMA results, MBE group only received TC, yoga, qigong, or Pilates intervention with no additional treatments (e.g., electrotherapy, manipulation). For the NMA, we need to include a common comparator across different MBE modes. The common comparator refers to the comparator which has been used by at least two studies for two different exercises (Li et al., 2011; Goh et al., 2016). The control group included no treatment control, usual care control, and conventional therapeutic exercise control.
(4) at least one of the outcome measures of interest were included in studies: subjective pain intensity and subjective physical function level.

Exclusion criteria

(1) conference abstracts, researcher protocols, and books all published studies.
(2) study data could not be obtained or converted.
(3) recruited patients suffering from acute, subacute LBP or LBP with unclear duration (e.g., recurrent LBP without a clear duration).
(4) LBP due to pregnancy, infections, tumors, osteoporosis, fractures, structural malformations (such as scoliosis), inflammatory disorders, radiculopathy, or cauda equina syndrome are excluded.
(5) trials were excluded if pain intensity and disability were not considered as primary or secondary outcomes.

Data extraction

Here, two evaluators (JS and HZZ) independently extracted data from each chosen study using a data extraction form, and then reviewed and revised by the corresponding author, including publication information (e.g., author, year, and country of origin), study design (e.g., parallel or crossover trail, two- or multi-arm parallel trial), subject characteristics (e.g., age, gender, pain duration, and sample size), interventions considered (e.g., TC, yoga, qigong, and Pilates), and outcome measures (e.g., pain intensity and physical function). Considering the determinate baseline similarities of pain intensity and physical function measures in included RCTs, post-intervention mean and standard deviation (SD) were directly extracted as outcome data from the published data. However, when the necessary information could not be adequately extracted, we got in touch with the study's authors to request it. When standard errors (SEs), confidence intervals (Cls), or interquartile ranges (IQRs) were provided in place of Means and SDs, RevMan 5.3 calculator was used to convert these to Means and SDs. In addition, if data were expressed only as a graph (rather than numerical data within the text), the software Engauge Digitizer 10.8 was used to extract it. Meanwhile, when there were multiple post-intervention measurement points where data could be extracted such as post-intervention and follow-up, only data immediately following the end of the intervention stage was used.

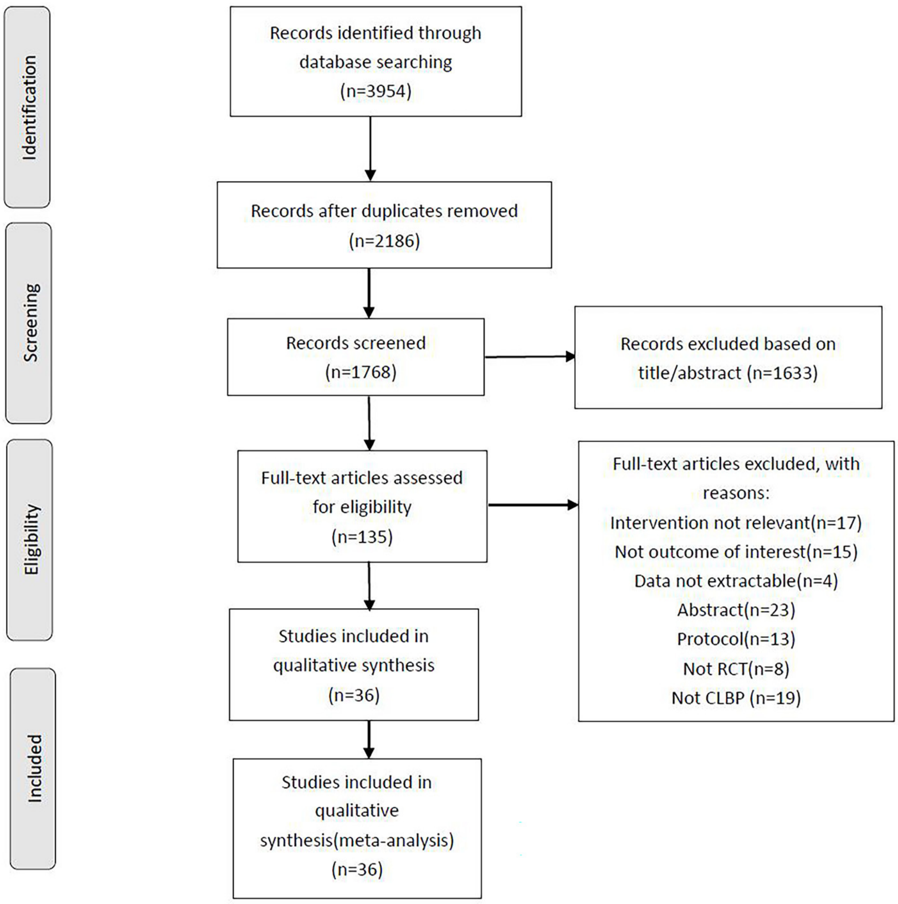

FIGURE 1
PRISMA flow diagram of the search process for studies examining the efficacy of mind-body exercise in patients with non-specific chronic low back pain.

Risk of bias

The Cochrane Risk of Bias Tool (Sterne et al., 2019) was used to independently assess the methodological quality and the risk of bias of these studies by two authors (ZYH and YRW). In order to analyze potential selection bias, performance bias, detection bias, attrition bias, reporting bias, and other relevant biases, the Cochrane tool split the quality risk into three categories: low, high, and uncertain. Two assessors will reach a consensus through a discussion if there are any discrepancies regarding the risk of bias in these studies. However, when a consensus cannot be reached between two assessors, the corresponding author will give his opinion and adopts the consensus of the majority.

Data synthesis and analysis

The NMA was performed using Stata v16.0 software (StataCorp, Texas, USA) based frequentist approach and in conformity with PRISMA-NMA guidelines (Shim et al., 2017). The crucial supposition underlying a network meta-analysis is that of network consistency, in other words, the therapeutic effects are equivalent on average, whether they are estimated by direct or indirect comparisons. Herein, the NMA's consistency was evaluated by fitting both the consistency and the inconsistency NMA and taking into account the outcomes of the Wald test for inconsistency. Moreover, the node-splitting technique was used to further evaluate inconsistency. Given the possibility of heterogeneity among studies, we choose the random effects model for the meta-analysis.

Standardized mean difference (SMD) was utilized as the summary measure to homogenize results from several scales and instruments into a single scale because all of the outcomes of interest were continuous or ordinal. When trails were inverted scaled (with higher values favoring outcomes instead of lower values), the mean in each group was multiplied by −1 as suggested by the Cochrane Handbook (Higgins et al., 2019) to guarantee all outcomes were illustrated with lower values, thereby suggesting improvements in pain intensity or physical function.

TABLE 1 Principal characteristics of included studies.

References	Country	Sample size (F/M)	Age, Mean (SD) years	Duration (weeks)	Follow-up weeks	Main pain/function outcome assessments	Experimental group intervention	Control group intervention
Liu et al. (2019)	China	11/32	59.0(4.6)	12	–	VAS	Tai Chi (60 min/36 sessions)	CTE/NT
Hall et al. (2011)	Australia	119/41	43.9(13.2)	10	–	NRS	Tai Chi (40 min/18 sessions)	NT
Liu et al. (2018)	China	37/8	57.2(3.3)	12	–	ODI	Tai Chi (60 min/36 sessions)	NT
Wang (2020)	China	29/16	31.8(9.7)	6	12	NRS/RMDQ	Tai Chi (45 min/18 sessions)	CTE/UC
Tong (2017)	China	40/31	41.9(4.2)	12	–	VAS	Tai Chi (30 min/36 sessions)	CTE
He (2013)	China	7/35	59.0(4.1)	12	–	VAS	Tai Chi (60 min/36 sessions)	CTE/NT
Wang et al. (2018)	China	45/32	45.2(15.0)	10	–	VAS/ODI	Qigong (5 min/50 sessions)	CTE
Chen (2020)	China	37/28	56(5.4)	4	–	VAS/ODI	Qigong (15 min/40 sessions)	CTE
Yao et al. (2020)	China	58/14	53.5(14.9)	24	–	VAS	Qigong (60 min/96 sessions)	CTE
Ding and Wang (2014)	China	20/20	61(4.7)	12	–	VAS	Qigong (40 min/60 sessions)	NT
Ning et al. (2015)	China	43/37	41.5(11.2)	12	–	VAS/ODI	Qigong (30 min/36 sessions)	CTE
Wu (2016)	China	42/36	39(7.6)	12	12	VAS/ODI	Qigong (30–40 min/36 sessions)	CTE
Phattharasupharerk et al. (2019)	Thailand	46/26	35.3(4.0)	6	–	VAS/RMDQ	Qigong (60 min/6 sessions)	NT
Teut et al. (2016)	Germany	156/20	72.7(5.7)	12	24	VAS	Qigong (90 min/12 sessions) Yoga (45 min/24 sessions)	NT
Blödt et al. (2015)	Germany	102/25	46.7(10.4)	12	24	VAS/RMDQ	Qigong (90 min/12 sessions)	CTE
Cruz-Díaz et al. (2018)	Spain	41/21	36.8(7.5)	12	–	VAS/RMDQ	Pilates (50 min/24 sessions)	NT
Valenza et al. (2017)	Spain	41/13	39(14)	8	–	VAS/RMDQ/ODI	Pilates (45 min/16 sessions)	UC
Kofotolis et al. (2016)	Spain	101/0	40.9(8.0)	8	–	RMDQ	Pilates (–/24 sessions)	UC/NT
Natour et al. (2015)	Brazil	47/13	47.9(12.1)	12	24	VAS/RMDQ	Pilates (50 min/24 sessions)	UC
Patti et al. (2016)	Italy	38	41.5(12.0)	14	28	ODI	Pilates (50 min/42 sessions)	CTE
Wajswelner et al. (2012)	Australia	48/39	49.1(15.2)	6	12–24	NRS	Pilates (60 min/12 sessions)	CTE
Mazloum et al. (2018)	Iran	47	39.6(9.3)	6	10	VAS/ODI	Pilates (50 min/18 sessions)	NT
Lee et al. (2014)	Korea	25	43.3(7.5)	12	–	VAS	Yoga (60 min/36 sessions)	NT
Kim et al. (2014)	Korea	30/0	Yoga group: 44.33/ Control group: 50.46	4	–	VAS/RMDQ/ODI	Yoga (30 min/12 sessions)	CTE
Neyaz et al. (2019)	India	35/35	35.5(12.4)	6	12	DVPRS/RMDQ	Yoga (35 min/6 sessions)	CTE
Tekur et al. (2012)	India	36/44	48.5(3.8)	1	–	VAS	Yoga (480 min/6 sessions)	CTE
Sherman et al. (2011)	USA	146/82	48.4(9.8)	12	26	RMDQ	Yoga (45–50 min/12 sessions)	UC
Cox et al. (2010)	UK	7/13	45	12	–	RMDQ	Yoga (75 min/12 sessions)	UC
Williams et al. (2009)	USA	69/21	48(11.1)	24	48	VAS/ODI	Yoga (90 min/48 sessions)	NT
Demirel et al. (2019)	Turkey	62/15	44.9(10.5)	6	–	VAS/ODI	Yoga (60 min/18 sessions)	CTE
Nambi et al. (2014)	India	32/28	44(9.0)	4	24	VAS	Yoga (60 min/4 sessions)	CTE
Bai et al. (2020)	China	60/0	33.3(2.5)	12	36	VAS	Yoga (75 min/36 sessions)	UC
Kuvačić et al. (2018)	Croatia	14/16	34.2(4.5)	8	–	NRS/ODI	Yoga (75 min/16 sessions)	UC

(Continued)

TABLE 1 (Continued)

References	Country	Sample size (F/M)	Age, Mean (SD) years	Duration (weeks)	Follow-up weeks	Main pain/function outcome assessments	Experimental group intervention	Control group intervention
Saper et al. (2017)	USA	204/116	46(10.7)	12	26/40/52	NRS/RMDQ	Yoga (75 min/12 sessions)	CTE/ UC
Williams et al. (2005)	USA	30/14	48.3(7.2)	16	–	VAS	Yoga (30 min/16 sessions)	UC
Michalsen et al. (2021)	Germany	187/87	54.6(11.3)	8	–	VAS/RMDQ	Yoga (75 min/8 sessions)	CTE

M, male; F, female; VAS, visual numerical scale; NRS, numerical pain scale; BPI, Brief Pain Inventory; DVPRS, Defense and Veterans Pain Rating Scale; RMDQ, Roland Morris Disability Questionnaire; ODI, Oswestry Disability Index; UC, Usual care; NT, No treatment; CTE, Conventional therapeutic exercises.

Herein, the interventions were ranked once their comparative effectiveness had been assessed to determine their superiority of the interventions. Surface under cumulative ranking (SUCRA) values, mean rank, and cumulative ranking plots for all outcomes were used to reflect the effects of different MBE to improve the values of pain intensity and physical function. The value of SUCRA ranges from 0 to 100% and a higher value indicates a greater possibility given that MBE mode is in the top rank or highly effective (Page et al., 2016). These data, which were averaged over the 10,000 replications, rank treatments according to their capacity to deliver the biggest treatment effects in each simulation. At least three studies on the same mode of MBE were required to rank the efficacy of interventions. Network funnel plots were generated and visually inspected using the symmetry criteria by us to examine for the presence of publication bias caused by small-scale studies that could contribute to publication bias in NMA. We also performed pairwise meta-analysis to compare the two interventions with pooled effect sizes. The value of the I^2 statistic (I^2 statistic whose values were 25, 50, and 75% indicated mild, moderate, and high heterogeneity) was used to assess the heterogeneity.

Results

Search results

A preliminary search of seven databases identified a total of 3,954 records. In the preliminary search results, there were 2,186 duplicate records excluded, and 1,633 records that did not match the review's inclusion criteria were eliminated based on the title and abstract. Then, through the evaluation of the full text of the remaining 135 studies, we found that 99 studies of them for several reasons, including intervention not relevant MBE ($n = 17$), not the outcome of interest ($n = 15$), data not extractable ($n = 4$), conference abstracts ($n = 23$), study protocol ($n = 13$), not RCT ($n = 8$), not CNLBP ($n = 19$). Ultimately, 36 studies were included in NMA. The systematic review process is shown in Figure 1.

Study characteristics

The fundamental characteristics of all articles were summarized in Table 1. The considered studies were published from 2005 to 2021. Among the included studies, most of them were carried out in China (12/36) and the others were conducted in the USA (4/36), India (3/36), Germany (3/36), Spain (3/36), Korea (2/36), Australia (2/36), Brazil (1/36), Turkey (1/36), Iran (1/36), Thailand (1/36), Croatia (1/36), UK (1/36), and Italy (1/36). A total of 36 eligible RCTs with 3,050 subjects diagnosed with CNLBP were included in this NMA. Meanwhile, three studies (Kim et al., 2014; Kofotolis et al., 2016; Bai et al., 2020) included only females, and all others included both sexes. Furthermore, three studies (Lee et al., 2014; Patti et al., 2016; Mazloum et al., 2018) did not present information on gender distribution. Thus, researchers carried out various MBE treatments, which included yoga (Williams et al., 2005, 2009; Cox et al., 2010; Sherman et al., 2011; Tekur et al., 2012; Kim et al., 2014; Lee et al., 2014; Nambi et al., 2014; Teut et al., 2016; Saper et al., 2017; Kuvačić et al., 2018; Demirel et al., 2019; Neyaz et al., 2019; Bai et al., 2020; Michalsen et al., 2021) (studies: $n = 15$, subjects, $n = 652$), TC (Hall et al., 2011; He, 2013; Tong, 2017; Liu et al., 2018, 2019; Wang, 2020) (studies: $n = 6$, subjects, $n = 183$), qigong (Ding and Wang, 2014; Blödt et al., 2015; Ning et al., 2015; Teut et al., 2016; Wu, 2016; Wang, 2018; Phattharasupharerk et al., 2019; Chen, 2020; Yao et al., 2020) (studies: $n = 9$, subjects, $n = 348$), and Pilates (Wajswelner et al., 2012; Natour et al., 2015; Kofotolis et al., 2016; Patti et al., 2016; Valenza et al., 2017; Cruz-Díaz et al., 2018; Mazloum et al., 2018) (studies: $n = 7$, subjects, $n = 205$). There were three control comparators including no treatment, usual care, and conventional therapeutic exercises. The intervention duration of all MBE was between 1 and 24 weeks and sessions ranged from 4 to 96. A total of 32 studies used pain intensity as an outcome measure and the assessment scales were the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), Defense and Veterans Pain Rating Scale (DVPRS), and Oswestry Disability Index (ODI)-pain. Meanwhile, 24 studies used physical function as an outcome measure and the assessment scales were ODI,

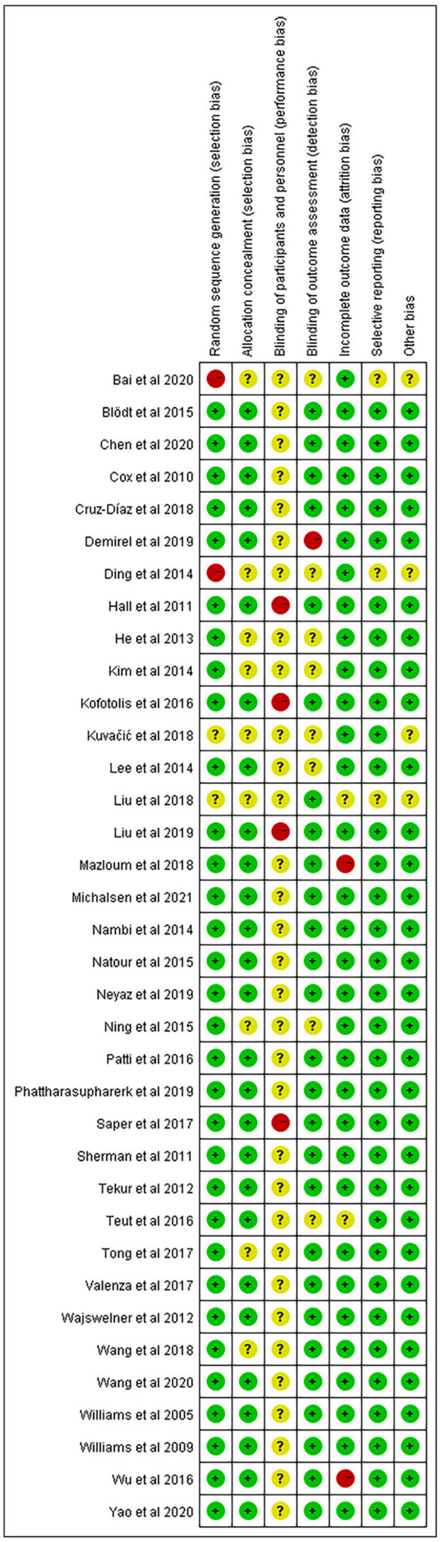

FIGURE 2
Percentage of studies examining the efficacy of mind-body exercise in patients with non-specific chronic low back pain with low, unclear and high risk of bias for each feature of the Cochrane Risk of Bias Tool.

Quebec Back Pain Disability Scale (QBPDS), and Roland Morris disability questionnaire (RMDQ).

Quality appraisal of literature

The results of the Cochrane risk of bias assessment for each study were shown in Figures 2, 3. Due to insufficient random sequence generation, such as randomly assigning participants to groups based on their birth dates or hospitalization dates, two studies were classified as high risk. Owing to the MBE training involved in this trial, it was simply not able to blind the subjects to the treatment allocation. Therefore, subjects' blindness was considered to be a higher risk of bias in all studies. All studies were defined as unclear risk of bias, except those that explicitly stated that the subjects were not successfully blinded. One study was classified as high risk of bias because it did not utilize the appropriate blinding method for the evaluator. Meanwhile, two trials were defined as high-risk bias because of incomplete outcome data because of the high dropout rate of subjects or the number of subjects who left the group greatly varied between groups.

Pairwise meta-analysis

We performed pairwise meta-analysis to compare the two interventions with pooled effect sizes. In terms of pain intensity, thirteen direct comparisons were performed to use a random effect model. TC was more efficacious than usual care (three RCTs; SMD: −1.29, 95% CI: −2.16 to −0.41; $I^2 \geq 50\%$), and no treatment (two RCTs; SMD: −2.86, 95% CI: −3.65 to −2.07; $I^2 < 50\%$). Compared with usual care, yoga (five RCTs; SMD: −0.9, 95% CI: −1.51 to −0.28; $I^2 \geq 50\%$) was more effective in decreasing pain intensity scores but Pilates (three RCTs; SMD: −1.85, 95% CI: −3.87 to 0.18; $I^2 \geq 50\%$) and qigong (one RCTs; SMD: −0.32, 95% CI: −0.69 to 0.04) did not show a significant difference.

In terms of physical function, ten direct comparisons were constructed. Yoga was more efficacious than usual care (five RCTs; SMD: −1.45, 95% CI: −0.75 to −0.15; $I^2 < 50\%$), and no treatment (two RCTs; SMD: −1, 95% CI: −1.45 to −0.54; $I^2 < 50\%$). There were no differences in physical function score between usual care and Pilates, and TC. Supplementary Table 1 showed additional results of the pairwise meta-analysis and heterogeneity estimates.

Network meta-analysis

Figures 4, 5 showed the NMA figure for different interventions.

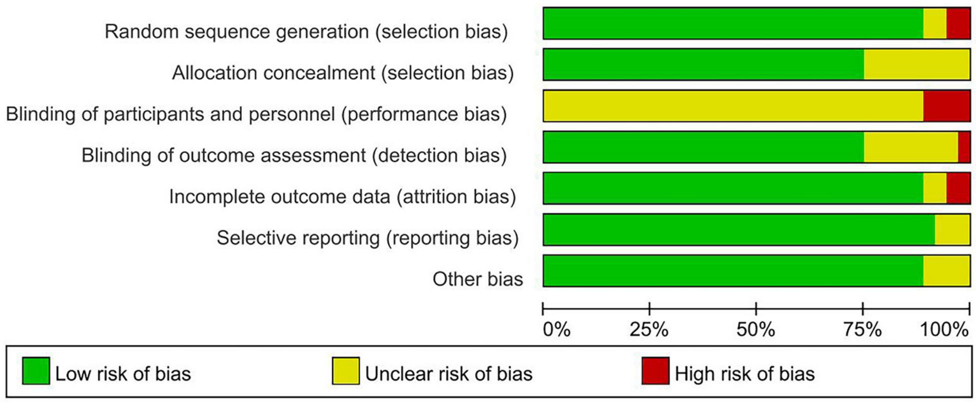

FIGURE 3
Methodological quality summary: Review authors' judgments about each methodological quality item for each included study.

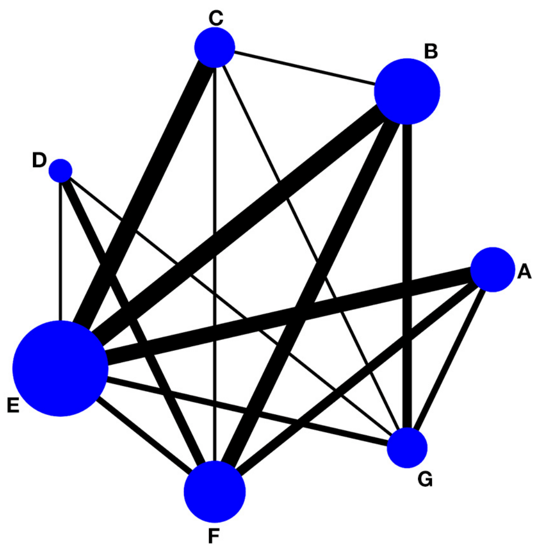

FIGURE 4
Network of evidence of pain intensity and the size of the nodes relates to the number of participants in that intervention type and the thickness of lines between interventions relates to the number of studies for that comparison. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

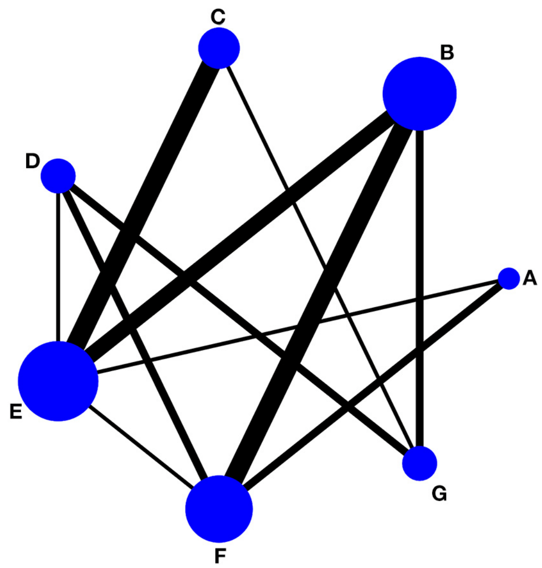

FIGURE 5
Network of evidence of physical function and the size of the nodes relates to the number of participants in that intervention type and the thickness of lines between interventions relates to the number of studies for that comparison. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

Pain intensity

There are a total of 32 included studies that evaluated pain intensity as presented in Figure 4 (The size of the circle represents the number of participants, and the thickness of the edge corresponds to the number of studies). The results of the node-splitting method reported that indirect and direct comparisons between each segmentation node were not statistically significantly different ($P > 0.05$), which indicated that the effect of consistency between studies was acceptable (see Supplementary Table 2). In terms of pain intensity improvement, the results of consistency NMA showed that compared to the control group with usual care (no exercise), Pilates intervention (SMD: −1.57, 95% CI: −2.44 to −0.71), TC intervention (SMD: −1.34, 95% CI: −2.15 to −0.53), yoga intervention (SMD: −1.18, 95% CI: −1.82 to −0.54),

TABLE 2 League table on pain intensity.

_D_	_A_	_B_	_C_	_E_	_F_	_G_
D	0.23 (−0.84, 1.31)	0.39 (−0.57, 1.35)	0.44 (−0.63, 1.52)	0.85 (−0.09, 1.79)	1.57 (0.71, 2.44)	2.37 (1.32, 3.41)
−0.23 (−1.31, 0.84)	A	0.16 (−0.67, 0.99)	0.21 (−0.71, 1.13)	0.62 (−0.11, 1.35)	1.34 (0.53, 2.15)	2.13 (1.21, 3.06)
−0.39 (−1.35, 0.57)	−0.16 (−0.99, 0.67)	B	0.05 (−0.71, 0.82)	0.46 (−0.11, 1.02)	1.18 (0.54, 1.82)	1.97 (1.21, 2.74)
−0.44 (−1.52, 0.63)	−0.21 (−1.13, 0.71)	−0.05 (−0.82, 0.71)	C	0.41 (−0.22, 1.03)	1.13 (0.29, 1.97)	1.92 (1.03, 2.81)
−0.85 (−1.79, 0.09)	−0.62 (−1.35, 0.11)	−0.46 (−1.02, 0.11)	−0.41 (−1.03, 0.22)	E	0.72 (0.05, 1.40)	1.52 (0.75, 2.29)
−1.57 (−2.44, −0.71)	**−1.34 (−2.15, −0.53)**	**−1.18 (−1.82, −0.54)**	**−1.13 (−1.97, −0.29)**	**−0.72 (−1.40, −0.05)**	F	0.79 (−0.08, 1.66)
−2.37 (−3.41, −1.32)	**−2.13 (−3.06, −1.21)**	**−1.97 (−2.74, −1.21)**	**−1.92 (−2.81, −1.03)**	**−1.52 (−2.29, −0.75)**	−0.79 (−1.66, 0.08)	G

A, tai chi; B, yoga; C, qigong; D, Pilates; E, control group (conventional therapeutic exercises); F, control group (usual care); G, control group (no treatment). The bold font indicates a statistical difference.

and qigong (SMD: −1.13, 95% CI: −1.97 to −0.29) were superior to the control group, the details of which are presented in Table 2. The ranking probability results of different MBE modes in terms of improving pain intensity indicated that Pilates (SUCRA = 86.6%) and TC (SUCRA = 77.2%) were among the best MBE interventions for pain. The control group with no treatment was most probably going to be the most ineffective (SUCRA = 0.6%). See Figure 6 for further details.

Physical function

A total of 24 included studies evaluated physical function outcomes, as shown in Figure 5. There was no evidence of inconsistency in the network ($P > 0.05$, see also Supplementary Table 3). In terms of physical function improvement, the results of consistency NMA showed that compared to the control group with usual care (no exercise), Pilates intervention (SMD: −1.68, 95% CI: −2.50 to −0.86), and yoga intervention (SMD: −0.63, 95% CI: −1.21 to −0.05) were superior to the control group; relative to the Qigong intervention group, Pilates intervention (SMD: −1.05, 95% CI: −1.89 to −0.21) was better than the qigong group in improving physical function, the details are shown in Table 3. The ranking probability results of different MBE modes in terms of improving physical function were initially positioned in the SUCRA for Pilates (SUCRA = 98.4%). The control group with no treatment was most probably going to be the most ineffective (SUCRA = 12.9%). See Figure 7 for further details.

Sensitivity analysis

We tested the sensitivity analysis of the results of NMA by comparing the results of the random effect model with the fixed effect model, and found no significant difference between the results obtained using the two models, which indicated that our results were robust.

Publication bias

We built and assessed a modified funnel plot to detect possible publication bias for all indicators. The findings reveal that the majority of points are evenly distributed along both sides of the midline and are primarily focused there. This indicates that our results are robust and there is no significant publication offset. See Figures 8, 9 for further details.

Discussion

In our study, we tried to compare the curative effect of the four most popular MBE modes in improving pain intensity and physical function to identify optimal MBE interventions for patients with CNLBP. Pilates might be the best MBE mode for decreasing pain intensity, followed by TC, yoga, and qigong. However, the differences were minor for yoga and qigong. Pilates continued to be the best performer in improving physical function, with little difference in the remaining three modes. Interestingly, TC performed well in managing the pain but significantly less well than Pilates in improving physical function. Overall, Pilates is perhaps the most appropriate MBE intervention for treating patients with CNLBP.

Our NMA found that Pilates was the most effective mode in decreasing pain intensity, consistent with prior reviews on other exercise therapies (Owen et al., 2020). There was a close correlation between CNLBP and core muscles, particularly deep multifidus and transversus abdominis (Ferreira et al., 2010). In CNLBP patients, activation of multifidus psoas and transverse abdominis is delayed or reduced, and physiologic tonic activation of transverse abdominis is lost during gait and extremity movement. In addition, dysfunction of these muscles might lead to the loss of lumbar support and increase the stress and load on the joints and ligaments of the spine (Ferreira et al., 2010; Hides et al., 2011). This may cause pain and functional abnormalities in CNLBP patients, thus, improving core functions is the key to treating CNLBP (Tang et al., 2016). Developed by Joseph H. Pilates, Pilates exercise

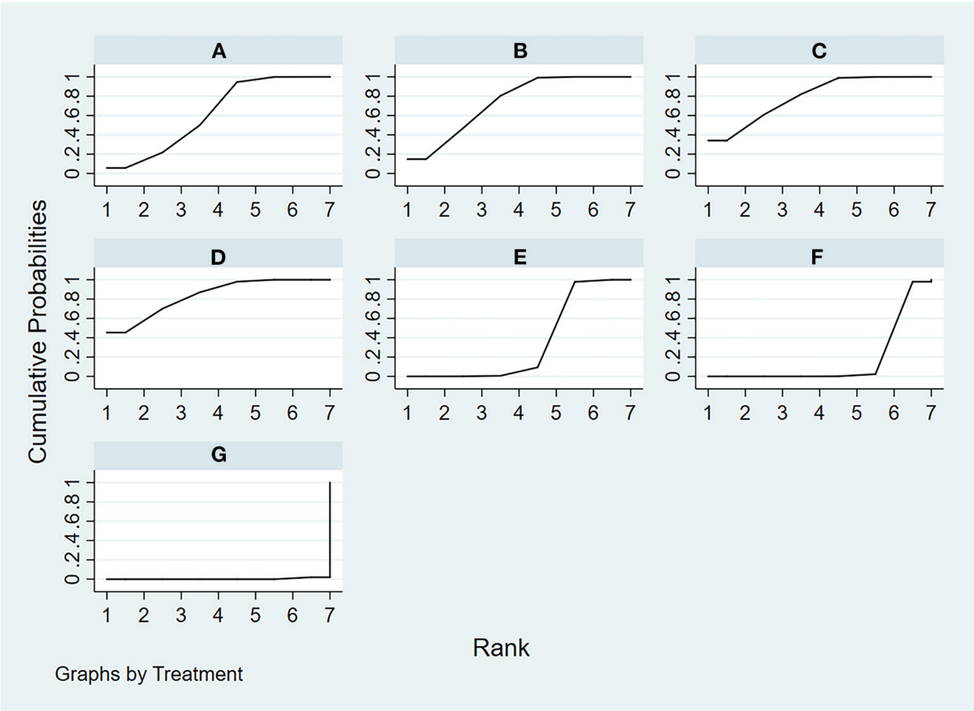

FIGURE 6
The rank probability of pain intensity various interventions based on the SUCRA. The SUCRA metric was used to rank the effectiveness of each treatment and identify the best treatment. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

TABLE 3 League table on physical function.

_D_	_C_	_A_	_B_	_E_	_F_	_G_
D	0.99 (−0.00, 1.98)	0.98 (−0.25, 2.21)	1.05 (0.21, 1.89)	1.20 (0.34, 2.06)	1.68 (0.86, 2.50)	1.73 (0.90, 2.56)
−0.99 (−1.98, 0.00)	C	−0.01 (−1.24, 1.23)	0.06 (−0.75, 0.86)	0.21 (−0.39, 0.82)	0.69 (−0.21, 1.59)	0.74 (−0.17, 1.66)
−0.98 (−2.21, 0.25)	0.01 (−1.23, 1.24)	A	0.06 (−1.02, 1.15)	0.22 (−0.88, 1.32)	0.70 (−0.30, 1.69)	0.75 (−0.51, 2.01)
−1.05 (−1.89, −0.21)	−0.06 (−0.86, 0.75)	−0.06 (−1.15, 1.02)	B	0.15 (−0.45, 0.76)	0.63 (0.05, 1.21)	0.68 (−0.10, 1.47)
−1.20 (−2.06, −0.34)	−0.21 (−0.82, 0.39)	−0.22 (−1.32, 0.88)	−0.15 (−0.76, 0.45)	E	0.48 (−0.25, 1.20)	0.53 (−0.31, 1.37)
−1.68 (−2.50, −0.86)	−0.69 (−1.59, 0.21)	−0.70 (−1.69, 0.30)	**−0.63 (−1.21, −0.05)**	−0.48 (−1.20, 0.25)	F	0.05 (−0.83, 0.93)
−1.73 (−2.56, −0.90)	−0.74 (−1.66, 0.17)	−0.75 (−2.01, 0.51)	−0.68 (−1.47, 0.10)	−0.53 (−1.37, 0.31)	−0.05 (−0.93, 0.83)	G

A, tai chi; B, yoga; C, qigong; D, Pilates; E, control group (conventional therapeutic exercises); F, control group (usual care); G, control group (no treatment). The bold font indicates a statistical difference.

therapy is used to improve an individual's "flexibility, strength, and body awareness" and it is referred to as a technique that focuses on core stability, posture, breathing, flexibility, strength, and muscle control (Wells et al., 2012). Moreover, the Pilates approach focuses on strengthening the lumbar region with the active involvement of the core muscles (Rydeard et al., 2006). Previous studies comparing core muscle activation in three different postures between Pilates practitioners and the general population have found that the core muscle activation in Pilates practitioners is significantly higher than that in the general population (Lee, 2021). Therefore, Pilates may decrease pain intensity by enhancing the core muscle. Although current evidence shows the analgesic effect of Pilates in patients with CNLBP, objective neurophysiological studies to elucidate the analgesic mechanism are lacking. Widespread oscillatory abnormalities in chronic pain patients and enhanced alpha activity by therapeutic means are associated with pain relief (Arendsen et al., 2018; Ahn et al., 2019). Bian et al. (2013) found that peak alpha power increased for healthy participants during Pilates training, which indicates that Pilates practice may relieve pain by modulating peak alpha frequency in chronic pain patients. Future studies may consider exploring the effect of

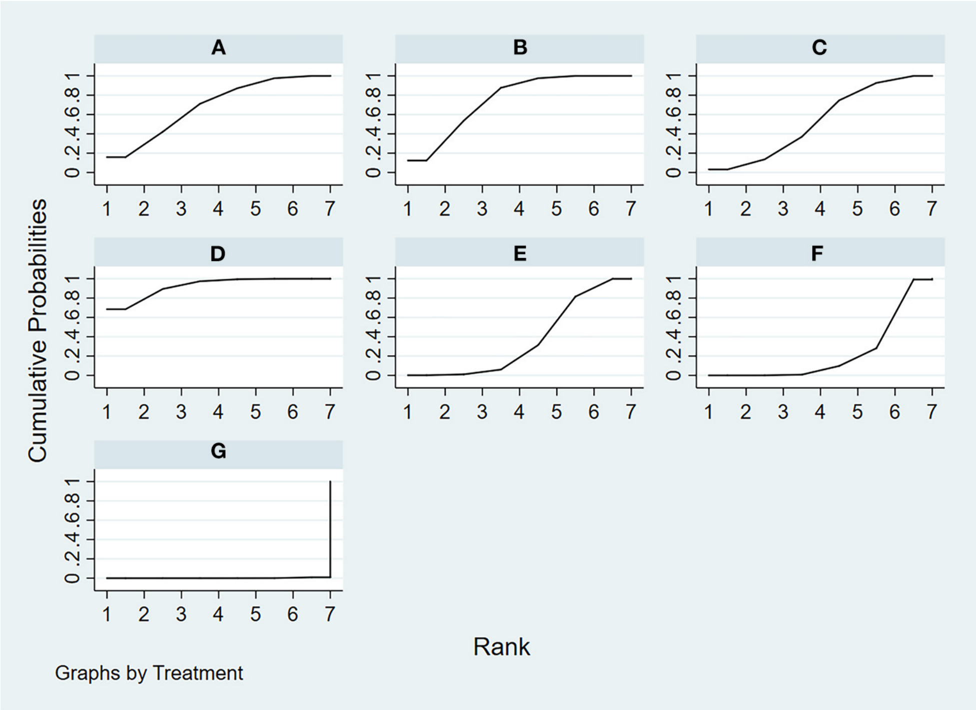

FIGURE 7
The rank probability of physical function various interventions based on the SUCRA. The SUCRA metric was used to rank the effectiveness of each treatment and identify the best treatment. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

Pilates training on peak alpha frequency in patients with CNLBP to further clarify the neurophysiological mechanism of Pilates analgesia. Apart from that, Pilates has the advantage that the exercises can be performed in various settings, with or without equipment, thereby keeping the spine in a neutral position and avoiding excessive impact or stress on muscles, joints, and tissues as compared with other MBE modes. As the exercises progress and an individual wishes to increase the difficulty of the activities performed, one can incorporate the use of various types of equipment, including the reformer, cadillac, ladder barrel, and step chair.

A novel finding from this NMA is that TC (SUCRA = 77.2%) may be the intervention that came closest to the effect of Pilates (SUCRA = 86.6%) in reducing pain intensity among the other three MBE modes. Meanwhile, TC originating in China is an established form of gentle MBE mode and incorporates physical, psychosocial, spiritual, and behavioral elements to improve physical and mental health (Wang et al., 2018). Although the underlying mechanism of TC remains unclear, the effect of TC may be attributable to the potential of these exercises to influence altered central elements. Furthermore, when practicing TC, the body's center of gravity constantly changes with the movements, the spine is in an unstable state, and the central nervous system recruits more muscle fibers to maintain stability, which strengthens the core muscles to some extent. Respiratory exercise therapy does have a therapeutic effect on patients with low back pain (Mehling et al., 2005). Herein, TC emphasizes reverse abdominal breathing, which

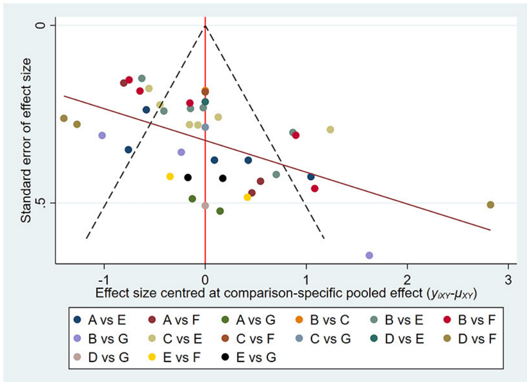

FIGURE 8
Pain intensity: Funnel plot showing the publication bias of the included randomized controlled trials. The red line represents the null hypothesis that independent effect size estimates do not differ from the comparison-specific pooled estimates. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

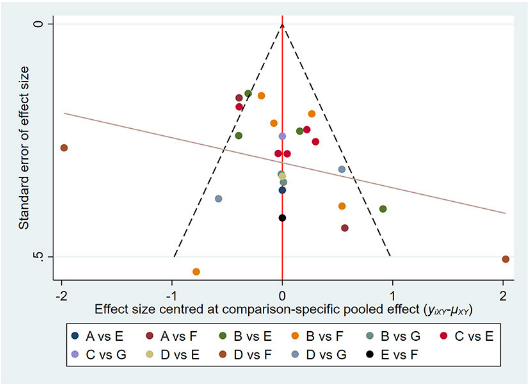

FIGURE 9
Physical function: Funnel plot showing the publication bias of the included randomized controlled trials. The red line represents the null hypothesis that independent effect size estimates do not differ from the comparison-specific pooled estimates. **(A)** tai chi, **(B)** yoga, **(C)** qigong, **(D)** Pilates, **(E)** control group (conventional therapeutic exercises), **(F)** control group (usual care), **(G)** control group (no treatment).

strengthens the core muscles during the breathing process. Notably, CNLBP is often accompanied by structural and functional connectivity abnormalities in brain regions (Ji and Neugebauer, 2011; Neugebauer et al., 2020). Regular TC practice can bring about regional structural changes in the precentral gyrus, insular sulcus, and middle frontal sulcus (Wei et al., 2013). A previous RCT also found moderate to high correlations between TC-associated pre-post differences in the functional connectivity of the amygdala-medial prefrontal cortex (Shen et al., 2021). Therefore, TC may directly affect the cerebral cortex to regulate pain through regular practice. Considering that it is not too difficult, cost-effective, and safe, TC and qigong are often chosen by elderly people to practice (Li et al., 2020; Siu et al., 2021). Pilates and yoga are more difficult than TC and qigong to practice and usually require the guidance of a professional instructor to ensure safety during practice (Achilefu et al., 2017; Zou et al., 2019). Therefore, TC and qigong seem to be worthy of promotion in the elderly population with CNLBP.

Guidelines about CNLBP suggest that treatment should pay more attention to improving pain intensity and its associated dysfunction (Oliveira et al., 2018). Our study suggested that Pilates (SUCRA = 98.4%) had the highest probability of improving physical function. Interestingly, TC was effective in reducing pain intensity, however, lagged far behind Pilates in improving physical function. Age is an essential factor affecting physical function (Maher et al., 2017). We compared the groups included in this study, and found that the average age of the Pilates group was younger than that of the TC group. It may be the reason why the function improvement effect of the Pilates group was better than that of the TC group. Therefore, it would be interesting to see if Pilates outperforms other MBE modes under strict age restrictions. There are various schools of TC in China, such as Yang-style TC and Chen-style TC. Although they are all based on the basic theories of the balance of Yin and Yang, the balance of the five elements, and the interaction between man and nature (Peng, 2012; Zhang et al., 2019), there are still great differences in movement characteristics and the degree of difficulty. Among the included studies, there are three that used Chen-style TC, one article designed an improved TC movement for CNLBP, and the other two did not tell, which may be partly responsible for the poor effect of TC in improving function. Similar to TC, there are various kinds of qigong, such as Neiyanggong (Blödt et al., 2015) and Wuqinxi (Yao et al., 2020). Different kinds of qigong have different effects on the physical function of CNLBP patients. A meta-analysis (Bai et al., 2015) involving 10 RCTs indicated that only internal qigong could improve chronic pain in adults. Therefore, it is a meaningful research direction to explore which style of TC or qigong movements are most suitable for enhancing physical function for patients with CNLBP.

Implication

Broadly, our NMA found Pilates may be the most recommended MBE mode for patients with CNLBP. As compared with previous studies (Owen et al., 2020; Hayden et al., 2021b; Fernández-Rodríguez et al., 2022), the results all agree that Pilates is best in terms of decreasing pain intensity and improving physical function. However, the difference is that our study included TC and qigong, which are often overlooked by previous studies. The findings suggest that TC is comparable to Pilates in decreasing pain intensity, which provides a new option for managing pain in patients with CNLBP.

Strengths and limitations

To our knowledge, this NMA is the first to compare the effects of different MBE modes in CNLBP. It explores a comprehensive ranking of four popular MBE treatments, thereby identifying the best options for improving pain intensity and physical function in CNLBP patients. Our searches were not limited by publication date or language, and included Chinese databases and gray literature. Given that TC and qigong originated in China, various high-quality studies have been published in Chinese journals, thus making our review more comprehensive.

Following are the limitations of our study. First, it is unable to blind subjects during an MBE intervention, which may lead to a potential risk of performance bias. However, this is an inherent limitation of such studies, usually reported in meta-analyses of exercise programs (Goh et al., 2019; Zou et al., 2019; Owen et al., 2020). Second, our review did not include psychology-related dependent variables such as depression, which is an important indicator for evaluating the success of CNLBP treatment. Based on several previous studies (Tekur et al., 2012; Park et al., 2020), MBE has reported positive results in treating psychological distress, such as depression and anxiety in patients with LBP. However, only six of our included studies reported depression-related results (Williams et al., 2009; Tekur et al., 2012; Lee et al., 2014; Teut et al., 2016; Kuvačić et al., 2018; Wang, 2018). Therefore, future studies should be considered to further explore the effect of MBE on psychological distress in CNLBP patients and the underlying mechanisms. Finally, because of the small number of studies and limited evidence for direct comparisons of interventions, readers should view these findings with caution. Therefore, it also emphasizes the need to further expand related research.

Conclusions

Our NMA shows that Pilates might be the best MBE therapy for the non-pharmacologic treatment of CNLBP in pain intensity and physical function. It has a reasonable benefit, which would be a powerful option for patients who don't profit from existing pharmacological medicines. Our study provides richer options for CNLBP management and more evidence for MBE treatment of CNLBP. However, more high-quality, large-sample, multicenter, long-term follow-up RCTs directly compare the efficacy of two or more MBE modes in patients with CNLBP to further confirm our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

JS and Z-YH wrote the manuscript. Y-FW, Z-YH, JS, and Y-LW contributed to the conception. Z-YH and H-ZZ searched the literature. JS and Y-RW were involved in the data analysis. Y-YL, JS, Z-YH, Y-TL, and Y-LW contributed to the acquisition of data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1046518/full#supplementary-material

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A coordinate-based meta-analysis of acupuncture for chronic pain: Evidence from fMRI studies

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Background: Chronic pain (CP) patients tend to represent aberrant functional brain activity. Acupuncture is an effective clinical treatment for CP, and some fMRI studies were conducted to discover the alternation of brain regions after acupuncture therapy for CP. However, the heterogeneity of neuroimaging studies has prevented researchers from systematically generalizing the central mechanisms of acupuncture in the treatment of CP.

Methods: We searched bibliographic databases, including PubMed, EMBASE, PsycINFO, Web of Science Core Collection, ScienceDirect, China Academic Journal Network Publishing Database, etc., and trials registration platforms (From inception to September 1st, 2022). Two independent researchers assessed the study's bias and quality. Furthermore, activation likelihood estimation (ALE) analysis was applied to explore aberrant brain functional activity and acupuncture's central mechanism for CP.

Results: Totally 14 studies with 524 CP patients were included in the study. ALE analysis showed that CP patients presented with decreased ALFF/ReHo in the precuneus, posterior cingulate cortex, right inferior parietal lobule, right superior temporal gyrus, cingulate gyrus, superior frontal gyrus, left medial frontal gyrus including medial prefrontal gurus, left middle frontal gyrus.

Conclusion: This ALE meta-analysis pointed out that acupuncture could modulate the default mode network, the frontoparietal network to treat CP. This provided a systematic summary of the neuroimage biomarker of acupuncture for the treatment of CP.

Systematic review registration: PROSPERO, identifier: CRD42021239633.

KEYWORDS

chronic pain, acupuncture, activation likelihood estimation, fMRI, systematic review

Introduction

Chronic pain (CP), one of the most common and long-standing neurological disease, persists affecting the health and quality of life of patients worldwide (Goldberg and McGee, 2011; Dureja et al., 2014; Dahlhamer et al., 2018). Neuroscience evidence pointed out that CP itself altered brain activities, including endogenous pain control, suggesting that controlling pain became increasingly difficult as the pain became chronic (Fine, 2011; Hasvik et al., 2022; Noori et al., 2022). The introduction of the biopsychosocial model of pain during the past decade stimulated the development of more therapeutically effective and cost-effective interdisciplinary CP management programs.

In 1998, the National Institutes of Health (NIH) first endorsed acupuncture for treating CP disorders (Ulett et al., 1998). And throughout the past few years, acupuncture as a complementary alternative therapy has gained increasing popularity in the treatment of CP, with a large number of clinical studies demonstrating its safety and efficacy (Manheimer et al., 2007; Yuan et al., 2016; Vickers et al., 2018; Berger et al., 2021; Turkistani et al., 2021).

Resting state-functional magnetic resonance (rs-fMRI), an imaging technique based on the assessment of hemodynamic blood oxygen level-dependent (BOLD) effects, is frequently utilized to explore the brain modification of acupuncture for CP. For instance, fMRI studies have demonstrated that acupuncture could achieve therapeutic effects by modulating a variety of brain networks in CP, such as the emotional response network (Kong et al., 2002; Liu et al., 2021), the default network (DMN) (Hou et al., 2014; Zou et al., 2019b; Liu et al., 2020), the frontoparietal network (FPN) (Kong et al., 2013), etc.

Individual experiments with limited sample sizes and low test thresholds were, nevertheless, susceptible to yielding false positive results. In addition to the variety of experimental designs employed in the study, these factors provided substantial variation in the reported outcomes. Therefore, a synthesis of results across experiments is needed to determine consistent and systematic brian modulation mechanisms of acupuncture for CP. Activation likelihood estimation (ALE) is a reliable meta-analysis method based on whole-brain coordinates established by Turkeltaub et al. (2002, 2012), aiming at determining above-chance convergence of activation probabilities between experiments. Although ALE has been widely utilized in the field of neuroimaging (Chen et al., 2018; Chavanne and Robinson, 2021; Xu et al., 2021), no researchers have used ALE algorithm to examine the modulation of whole-brain function changes by acupuncture in CP patients.

To address the abovementioned issues, the purpose of this study was to systematically evaluate and analyze the changes of brain functional activity in CP patients and the regulation of brain functional activity after acupuncture treatment using a meta-analytical approach based on ALE algorithm. Our results may provide a more illustrative visual basis for elucidating the underlying neural mechanisms of acupuncture therapy for CP.

Methods

Literature search and study selection

Retrieval strategies

This systematic and standardized meta-analyses was corresponding to the Preferred Reporting Items (PRISMA) for sources including bibliographic databases, reference lists of eligible studies and review articles, and trial registers (Page et al., 2021). Bibliographic databases included MEDLINE *via* PubMed, EMBASE, PsycINFO, Web of Science Core Collection, ScienceDirect, China Academic Journal Network Publishing Database, China Doctoral Dissertation Full-text Database, China Excellent Master Dissertation Full-Text Database, Wanfang Database, Database of Chinese Sci-Tech Journals, and China Biomedical Literature Database. Trials register platforms included ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, and the Chinese Clinical Trial Register. Search date was from inception to September 1st, 2022. We only included studies published in Chinese or English. The search strategy of PubMed was shown in Supplementary material.

Selection criteria

Inclusion criteria

Each article was subsequently reviewed (first by abstract, then by full-text) for relevance to the study and inclusion of all following criteria:

1) Adults diagnosed as CP (Treede et al., 2015, 2019) (musculoskeletal, osteoarthritis, and headache, diagnosed using any recognized diagnostic criteria);
2) Administered acupuncture (defined as inserting the needle into the skin surface of the acupoint, such as

Abbreviations: CP, Chronic pain; NIH, National Institutes of Health; rs-fMRI, Resting state-functional magnetic resonance; BOLD, blood oxygen level-dependent; ROI, region-of-interest; ROB, risk of bias; MwoA, migraine without aura; MMoa, menstrual migraine without aura; CNP, chronic neck pain; CSP, chronic shoulder pain; cLBP, chronic low back pain; KOA, chronic knee osteoarthritis; ALFF, amplitude of low-frequency fluctuations; ReHo, regional homogeneity; SFG, superior frontal gyrus; PCC, posterior cingulate cortex; mPFC, medial prefrontal gurus; MFG, middle frontal gyrus; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; CNS, central nervous system; FPN, frontoparietal network.

manual acupuncture, electroacupuncture, etc.) as a therapeutic measure;
3) Were rs-fMRI studies;
4) Whole-brain analysis that reported coordinates for brain activities with standard anatomical reference space (Talairach or MNI);
5) Performed a statistical comparison (patients before and after acupuncture therapy or patients vs. healthy people).

Exclusion criteria

The studies met one of the following items were excluded:

1) Based on partial coverage or employing only region-of-interest (ROI) analyses;
2) The subjects (or a subgroup of subjects) were included in another study;
3) Studies based on ROI analyses or non-fMRI studies;
4) Were reviews or meta-analysis;
5) Incomplete information or secondary processed studies.

Data extraction

Two reviewers (WRR and WW) independently selected, extracted, and checked the data. The items included: author name, published year, title, journal name, CP categories, acupuncture type, sample size, gender differences, patients' age, analysis methods, foci details etc. When there was any disagreement, a third reviewer (YZ) participated in the decision.

Quality assessments

Two reviewers (WRR and WW) scored the completeness using a 10-point checklist (Strakowski et al., 2003), and assessed the methodological quality using the Cochrane risk of bias (ROB) tools (https://training.cochrane.org/handbook). The measurement items of ROB tools contained seven different items: random sequence generation, allocation concealment, blinding of participants and personnel, blind of outcome assessment, incomplete outcome data and selective reporting and other sources of bias.

ALE analysis

Ginger ALE software (http://www.brainmap.org/ale) was used for coordinate based meta-analysis. The differences in coordinate-based brain activity changes between CP and health control (HC), or post-pre-acupuncture in CP patients were assessed in this review. A cluster-level family wise error (FWE) correction was applied ($P < 0.05$) with thresholding permutations of 5,000 times (Müller et al., 2018). The resulting peak coordinates are reported in Talairach space. Mricron (available at www.mricro.com) was applied to brain visualization for results of ALE analysis. We did not perform the sensitivity analysis because of the small number of included studies.

Results

Search flow

A total of 1,126 articles were retrieved. After excluding duplicate papers, a total of 851 articles were retained. Based on the title and abstract, a total of 820 papers were excluded, leaving 31 papers remaining. Following a comprehensive full-text scanning and application of established inclusion and exclusion criteria, 14 studies with 524 CP patients were included in the study (see Figure 1).

Study characteristics

The included CP conditions were migraine without aura (MwoA) (Zhao et al., 2014; Han et al., 2017; Li et al., 2020; Ning et al., 2020; Jia et al., 2021; Liu et al., 2021); menstrual migraine without aura (MMoa) (Zhang et al., 2021); chronic neck pain (CNP) (Hou et al., 2014; Chen et al., 2015); chronic shoulder pain (CSP) (Zhang et al., 2018); chronic low back pain (cLBP) (Makary et al., 2018; Zou et al., 2019a; Liu et al., 2020); chronic knee osteoarthritis (KOA) (Qu et al., 2021). The studies using amplitude of low-frequency fluctuations (ALFF) or regional homogeneity (ReHo) as fMRI analysis methods were included in this study. The characteristics of included studies are summarized in Table 1.

Quality assessment

The quality control assessments by Strakowski's checklist showed that the completeness scores of the included studies are generally high (see Supplementary Table 1). Furthermore, two reviewers (WRR and WW) independently evaluated the methodological quality of the 14 included studies (see Figure 2 and Supplementary Figure 1). Only two studies (Zhao et al., 2014; Chen et al., 2015) reported entirely random sequences and allocation concealment, and only one research (Liu et al., 2021) mentioned participant blinding, which indicates that the majority of publications have a moderate risk of bias, predominantly in the areas of selection and performance bias.

ALE results

Compared to the HC, patients with CP had decreased ALFF/ReHo of left caudate and left thalamus; increased ALFF/ReHo of right fusiform gyrus, left superior frontal

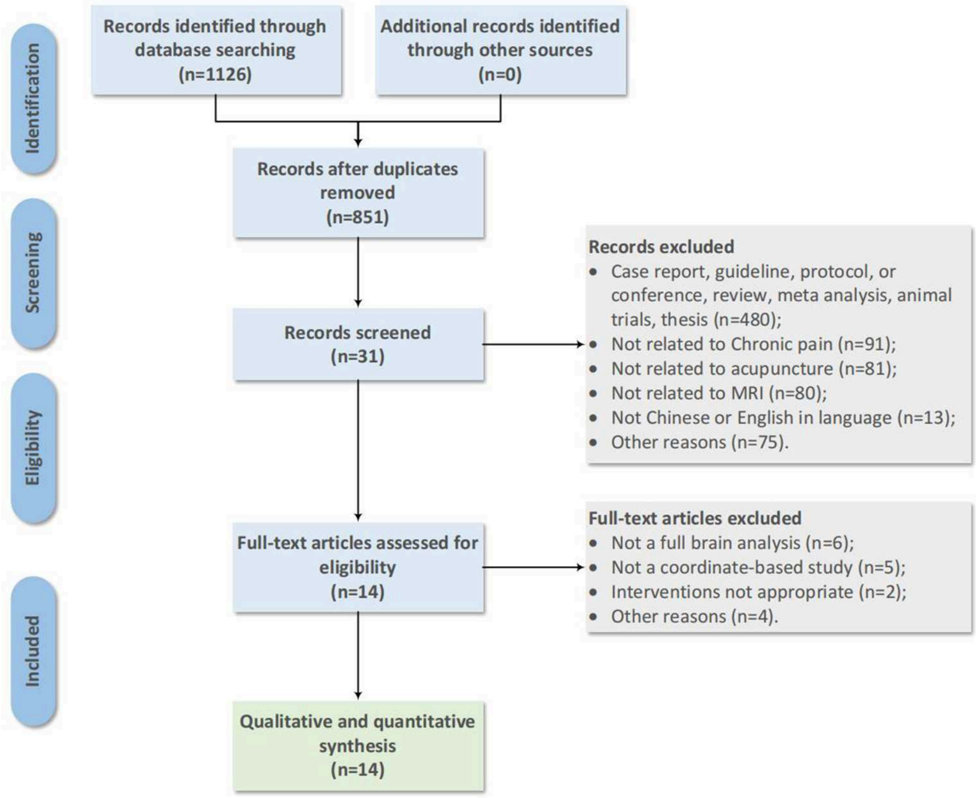

FIGURE 1
Flow diagram of literature search.

gyrus (SFG) and bilateral medial frontal gyrus, left rectus, left cingulate cortex including posterior cingulate cortex (PCC) (see Supplementary Table 2, Supplementary Figures 2, 3).

After acupuncture therapy, CP patients presented with decreased ALFF/ReHo in the precuneus, PCC, right inferior parietal lobule, right superior temporal gyrus (STG), cingulate gyrus, SFG, left medial frontal gyrus including medial prefrontal gurus (mPFC), left middle frontal gyrus (MFG) (see Figure 3 and Table 2).

Discussion

The current ALE meta-analysis pooled 14 fMRI studies based on coordinates encompassing 6 types of CP (MwoA, Mmoa, CNP, CSP, cLBP, KOA) to determine the effects of acupuncture on brain regions. The quality of the included studies were relatively moderate, as determined by the ROB checklist and quality reporting standard guidelines. According to rs-fMRI studies of CP patients treated with acupuncture, the modulation pattern of CP by acupuncture included a reduction of ALFF/ReHo signals in the DMN (precuneus, PCC), and FPN (SFG, mPFC, MFG). The findings confirmed that acupuncture may produce the therapeutic effect on CP by modulating the brain regions associated with emotion and cognition. In addition, similar to the findings of previous studies, abnormalities in the caudate, thalamus, fusiform gyrus, superior frontal gyrus, and medial prefrontal cortex were also identified in CP patients in this review. These abnormalities in CP were associated with pain processing, cognitive abnormalities, and emotion regulation functions.

The trajectory of chronic pain occurred over time, with intensity continuing and fluctuating (Mayr et al., 2022). Meanwhile, the perception of pain is a personal and multidimensional experience, with causes mood changes such as anxiety, depression and fear (Moriarty et al., 2011; Bushnell et al., 2013; Moseley and Vlaeyen, 2015). The present review partially revealed the abnormal functional activity in brain regions such as caudate, thalamus, and PFC in patients with CP. In fact, early studies already found abnormal functional activities in brain regions and networks, such as DMN and the salience network (Greenwald and Shafritz, 2018). At the cellular level, central sensitization may be reversed by degrading glutamate receptor pathways, but occurs rarely (Woolf, 2011). Instead, cortical brain regions may have top-down modulation to alleviate pain.

TABLE 1 Characteristics and clinical information of the included studies.

Source	Diagnosed	Sample size (n)	Gender (male/female)	Age (y)	Type of acupuncture	Foci (n)	Analysis method	Threshold
Zhao et al. (2014)	MwoA	PCs: VA1 (20), VA2 (20)	VA1 (6/14), VA2 (8/12)	VA1: 32.9 ± 10.99; VA2: 37.25 ± 9.68	MA	VA_up: 21 VA_down: 15	ReHo	$P < 0.05$ (FDR)
Hou et al. (2014)	CNP	PCs: VA1 (25), VA2 (24)	VA1 (7/18), VA2 (12/12)	VA1: 24.73 ± 1.46; VA2: 24.79 ± 1.55	EA	VA_up: 4 VA_down: 3	ReHo	*NA*
		HCs: 19	HCs (8/11)	HCs: 25.58 ± 3.32	-	PCs_HCs_up: 0 PCs_HCs_down: 1		
Chen et al. (2015)	CNP	PCs: VA1 (25), VA2 (24)	VA1 (7/18), VA2 (14/10)	VA1: 25 ± 1; VA2: 25 ± 2	EA	VA_up: 0 VA_down: 4	ReHo	$P < 0.01$
		HCs: 19	HCs (8/11)	HCs: 25 ± 3	-	PCs_HCs_up: 0 PCs_HCs_down: 1		
Han et al. (2017)	MwoA	PCs: 10	PCs (2/8)	PCs: 31.7	MA	VA_up: 0 VA_down: 3	ReHo	$P < 0.05$
		HCs: 10	HCs (2/8)	*NA*	-	PCs_HCs_up: 10 PCs_HCs_down: 5		
Zhang et al. (2018)	CSP	PCs: VA1 (12), VA2 (8)	VA1 (6/6), VA2 (4/4)	VA1: 53.33 ± 5.26; VA2: 54.13 ± 7.45	MA	VA_up: 1 VA_down: 3	ReHo	$P < 0.05$
Makary et al. (2018)	cLBP	PCs: VA (28), PA (19)	VA (16/12), PA (9/10)	VA: 38.7 ± 13.1; PA: 39.5±13.7	MA	VA_up: 65 VA_down: 36	fMRI signal	*NA*
Zou et al. (2019b)	cLBP	PCs: VA1 (16), VA2 (16)	VA1 (8/8), VA2 (7/9)	VA1: 48.53 ± 13.21; VA2: 44.21 ± 8.96	EA	*NA*	ReHo	$P < 0.05$
		HCs: 25	HCs (12/13)	PCs: 40.01 ± 9.75	-	PCs_HCs_up: 11 PCs_HCs_down: 11		
Liu et al. (2020)	cLBP	PCs: 12	PCs (6/6)	PCs: 61.42 ± 14.84	MA	VA_up: 0 VA_down: 1	ReHo/FC	$P < 0.05$ (FWE)
Ning et al. (2020)	MwoA	PCs: 19	PCs (3/16)	PCs: 28.23 ± 6.16	MA	VA_up: 1 VA_down: 4	ALFF	$P < 0.05$
		HCs: 18	PCs (4/14)	PCs: 27.16 ± 5.23	-	PCs_HCs_up: 3 PCs_HCs_down: 2		
Li et al. (2020)	MwoA	PCs: VA1 (12), VA2 (13), VA3 (14), SA (13), WT (18).	VA1 (2/10), VA2 (4/9), VA3 (2/12), SA (2/11), WT (4/14)	VA1:21.75 (20.70, 22.80); VA2:20.85 (19.57, 22.12); VA3: 20.78 (19.74, 21.83); SA: 21.38 (20.75, 22.02); WT: 21.61 (20.54, 22.68)	MA	*NA*	fALFF	$P < 0.05$ (FWE)
		HCs: 43	HCs (9/34)	HCs: 21.23 (20.96, 21.51)	-	PCs_HCs_up: 0 PCs_HCs_down: 4		
Zhang et al. (2021)	MMoa	PCs: VA (24), SA (20)	VA (0/24), SA (0/20)	VA (33.04 ± 6.43); SA (35.30 ± 9.43)	MA	VA_up: 4 VA_down: 3	ALFF/ReHo	$P < 0.05$
Qu et al. (2021)	KOA	PCs: 80	PCs (28/52)	PCs: 52.35 ± 4.62	MA	VA_up: 4 VA_down: 1	ALFF	$P < 0.05$
Liu et al. (2021)	MwoA	PCs: 37	PCs (6/31)	PCs: 37.97 ± 9.82	EA	VA_up: 1 VA_down: 0	ReHo	$P < 0.05$ (FWE)
		HCs: 15	HCs (2/13)	HCs: 34.88 ± 6.66	-	PCs_HCs_up: 0 PCs_HCs_down: 2		
Jia et al. (2021)	MwoA	PCs: 15	PCs (5/10)	PCs: 39.3 ± 12.1	MA	VA_up: 0 VA_down: 1	ReHo	$P < 0.05$

MwoA, migraine without aura; MMoa, menstrual migraine without aura; CNP, chronic neck pain; CSP, chronic shoulder pain; cLBP, chronic low back pain; KOA, chronic knee osteoarthritis; PCs, patient control; HCs, health controls; ReHo, regional homogeneity; ALFF, amplitude of low-frequency fluctuations; MA, manual acupuncture; EA, electroacupuncture; VA, verum acupuncture; PA, phantom acupuncture; SA, sham acupuncture; WT, waiting-list; FDR, false discovery rate; FWE, family wise error; NA, not available.

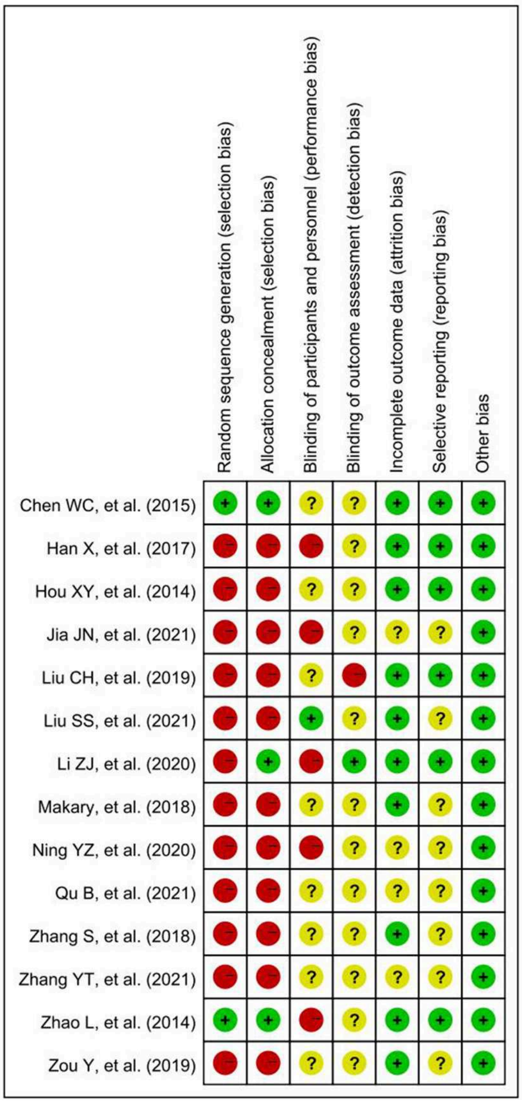

FIGURE 2
Risk of bias of each included study using Revman.

These results aligned with the previous ALE research (Ha et al., 2022) for acupuncture modifying musculoskeletal pain, in that both found therapeutic effects of acupuncture in the brain regions of the caudate, and thalamus. Methodological factors may have contributed to the differences between our study and those of earlier findings. Firstly, we included several kinds of CPs, including osteoarthritis, and headache, rather than just musculoskeletal pain. Secondly, we only included research reporting whole-brain analyses; some ROI-based approaches were omitted in order to eliminate the possibility of regional bias. We ultimately included 14 studies of moderate quality. Notably, the fact that almost all studies did not satisfy the recommended research a voxel-level threshold of $P < 0.001$ or a cluster-corrected threshold of $P < 0.05$ contributed to the drop in study quality. We also did not require such a test threshold in this study, as this may not have included enough studies.

Six different types of CP were covered in this study. Nevertheless, the mechanisms of acupuncture modulation of different type of CP might be distinct. For an instance, MwoA is neuropathic pain, whereas KOA is nociceptive pain. The pathogenic causes and mental state of the patients are diverse between these two disorders, resulting in modifications to distinct brain regions. In KOA, altered CNS activity led to a sense of pain in the absence of peripheral tissue injury or inflammation. Patients' anticipatory of pain may modify the forthcoming pain-evoking activation and pain sensation, as evidenced by limbic system brain activation (Jones et al., 2012). Nociceptive pain is somatic and visceral, which differ in their psychophysical and neurobiological mechanisms (Cervero, 2009). The main difference between them was the process of pain signaling and processing, which leads to different pain perception.

The ALE analysis in this study indicated the brain networks that acupuncture could modulate in CP patients were the DMN, FPN, suggesting a modulatory effect of acupuncture on CP at the neural network level. The DMN is an important resting brain functional network consisting of the precuneus, mPFC, inferior parietal lobule and PCC (Buckner et al., 2008; Raichle, 2010). As a major component of the DMN, the precuneus is responsible for processing negative emotions caused by pain or other discomfort and plays an important role in the cognitive function network (Cavanna and Trimble, 2006; Blessing et al., 2016). Our previous study discovered that acupuncture increased the unusually low precuneus brain metabolism in migraine sufferers (Yang et al., 2012). In conjunction with the results of ALE, it showed that acupuncture could modulate the abnormal precuneus function in CP to achieve a smooth strip of emotional cognition.

The cingulate gyrus is part of the DMN and limbic system, involving in pain perception and pain signaling. Patients with persistent neck and shoulder discomfort exhibited aberrant ALFF signal in the cingulate gyrus and precentral gyrus, compared to HCs (Yue and Du, 2020). Also, acupuncture could modulate brain regions involved in limbic system to achieve pain relief or relieve negative effects (Shi et al., 2020), such as hippocampus, parahippocampal gyrus, and anterior cingulate gyrus (Hui et al., 2010). In other words, acupuncture could modulate the abnormal functional activity of the limbic system in patients with CP.

The FPN was essential for pain processing involved in attention and cognitive control, especially the dorsolateral prefrontal cortex (DLPFC) and mPFC. Correspondingly, the present review suggested that acupuncture could modulate a wide range of FPN regions, including SFG, mPFC, MFG.

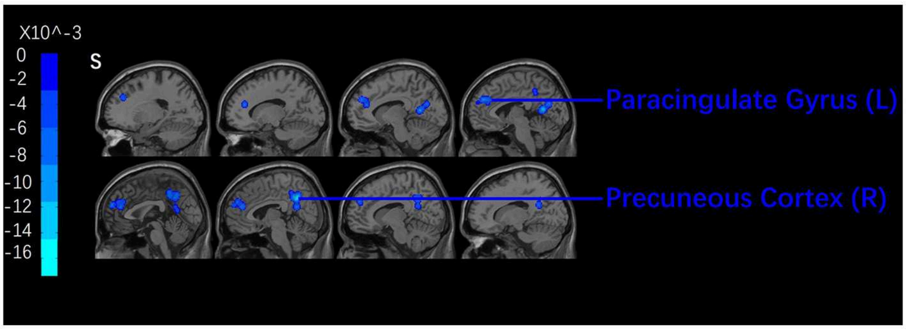

FIGURE 3
Brian regions with decreased signals pre- and post-acupuncture. A cluster-level FWE correction was applied ($P < 0.05$).

TABLE 2 The results pf peak coordinates from ALE analysis pre- and post- acupuncture.

Cluster #	x	y	z	ALE	*P*	Z	Label (nearest gray matter within 5 mm)
1	4	−54	36	0.017405074	0.000	−5.037	Right Cerebrum.Parietal Lobe.Precuneus.Gray Matter.Brodmann area 7
1	−8	−58	12	0.012505891	0.000	−4.055	Left Cerebrum.Limbic Lobe.Posterior Cingulate.Gray Matter.Brodmann area 23
1	50	−64	36	0.009757249	0.000	−3.583	Right Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 39
1	26	−56	34	0.009065375	0.000	−3.458	No Gray Matter found
1	58	−60	26	0.008594425	0.000	−3.329	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 39
1	42	−54	36	0.008330258	0.001	−3.244	Right Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 40
1	54	−52	46	0.008204443	0.001	−3.189	Right Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 40
1	−2	−44	46	0.008156347	0.001	−3.161	Left Cerebrum.Parietal Lobe.Precuneus.Gray Matter.Brodmann area 7
1	14	−52	24	0.007928049	0.001	−3.074	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 31
1	−8	−68	22	0.007889439	0.001	−3.009	Left Cerebrum.Occipital Lobe.Precuneus.Gray Matter.Brodmann area 31
1	−2	−46	40	0.007888975	0.001	−3.009	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 31
1	4	−54	22	0.006890667	0.004	−2.693	Right Cerebrum.Limbic Lobe.Posterior Cingulate.Gray Matter.Brodmann area 31
2	−6	40	30	0.009418508	0.000	−3.527	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
2	−2	58	24	0.009083679	0.000	−3.462	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 9
2	−8	48	30	0.009039057	0.000	−3.422	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 9
2	4	50	30	0.008590198	0.000	−3.329	Right Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 9
2	−14	40	22	0.008063627	0.001	−3.125	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
2	0	42	22	0.007801687	0.001	−2.988	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
2	−36	32	36	0.006627638	0.004	−2.665	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 9
2	−24	38	34	0.006448573	0.004	−2.634	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 9

A negative Z value means decreased fMRI signal after acupuncture.

Acupuncture has been extensively explored for its capacity to alleviate pain by modifying the dysfunctional DLPFC (He et al., 2022; Liu et al., 2022; Zhang et al., 2022). Consequencely, Ong's team revealed the importance of PFC during placebo analgesia and in establishing a connection between pain and pain alleviation in bouts of cognitive performance, anxiety, and cognitive decline (Ong et al., 2019). However, a PET-CT study revealed real acupuncture for KOA leaded to greater activation of the right DLPFC, ACC, and midbrain (Pariente et al., 2005) than sham acupuncture, indicating the differences in the modulation of brain regions by real and sham acupuncture.

Limitations

This meta-analysis focused on whole-brain, resting brain function alterations in chronic pain improvement with acupuncture. Due to the general quality of the included studies, the results should be interpreted with caution. However, we included only 14 studies and did not perform a sensitivity analysis. The findings should be interpreted with caution due to the small number of included studies and the heterogeneity in trial design and demographic baseline between studies.

Conclusion

This is the first cross-study coordinate-based meta-analysis to uncover the modulation mechanisms of acupuncture in CP. The results of this review provide neuroimaging evidence for acupuncture in the treatment of CP.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

ZY, R-RW, WW, and L-YL: concept and design. ZY, R-RW, and WW: acquisition of data. ZY, JY, L-YL, and X-LG: drafting of the manuscript. S-GY and C-BW: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1049887/full#supplementary-material

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The clinical efficacy and safety of acupuncture intervention on cancer-related insomnia: A systematic review and meta-analysis

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Objective: To evaluate the efficacy and safety of acupuncture in treating symptoms for Cancer-related Insomnia(CRI) patients.

Methods: Seven databases were searched from the time of database establishment to 31 March 2022. Randomized Controlled Trials (RCTs) on acupuncture intervention for CRI were collected. Literature screening and data extraction were performed independently by two researchers. Meta-analysis was performed using RevMan 5.4 software.

Results: A total of 13 articles with 1,109 participants were included. Five hundred and seventeen in the treatment group and 592 in the control group. Ten of the RCTs used the PSQI rating scale and four randomized controlled trials used the ISI rating scale, and the PSQI and ISI were analyzed together as continuous data. The results of the meta-analysis were: MD = −1.83, 95%CI = [−2.71, −0.94], $P < 0.0001$, indicating a significant improvement in PSQI scores in patients with CRI by acupuncture intervention; MD = 0.79, 95%CI = [−0.46, 2.03], $P = 0.22$. Acupuncture was not statistically significant on ISI scores for patients with CRI compared to controls, which does not yet indicate that acupuncture is effective for symptoms in patients with CRI. The results of the meta-analysis of the other 4 items using sleep disorder logs as efficacy analysis data were as follow, relative risk RR = 0.47, 95%CI = [0.33, 0.66], $P < 0.0001$. The difference was statistically significant, indicating that acupuncture can improve the symptoms of CRI patients compared to control group.

Conclusion: Acupuncture can improve the symptoms of patients with CRI to some extent, but due to the relatively small number and low quality of the included literature in this study, more high-quality clinical trials are needed as supplement the evidences in future.

Systematic review registration: https://www.crd.york.ac.uk/prospero/.

KEYWORDS

acupuncture, cancer-related insomnia, systematic review, meta-analysis, PSQI, efficacy

Introduction

Cancer-related Insomnia (CRI) is also called tumor-related sleep disorder. It refers to the subjective experience of cancer patients who experience insufficient sleep time and sleep quality to meet normal physiological needs after the onset of cancer, thus affecting their daily life and health (Induru and Walsh, 2014; Zhuang and Fang, 2022). It is a more common clinical symptom, especially in patients with breast cancer, lung cancer and head and neck cancer (Induru and Walsh, 2014). Studies have shown that the incidence of CRI significantly exceeds that of the general insomnia population by a factor of two, accounting for 52.6–67.4% (Reilly et al., 2013), and the incidence of insomnia in cancer patients is 70.1% in China (Schieber et al., 2019). CRI is the second most urgent concomitant symptom of cancers after fatigue (Reilly et al., 2013). CRI affects the quality of life of most patients (Holtdirk et al., 2020) and prolonged insomnia can lead to greater physical and psychological damage, leading to many other serious problems, such as anxiety, depression and impairment of the body's immune function (Fleming et al., 2010; Yao and Tian, 2020), as well as other complications, such as obesity, hypertension, cardiovascular disease, etc. (Knutson et al., 2009). Most clinical studies have shown that most of the drugs are currently commonly used in clinical practice that approving by the Food and Drug Administration (FDA), such as benzodiazepines, anticonvulsants, antihistamines, and melatonin agonists (Asnis et al., 2015), and the treatment effect is often <80% and many adverse effects (Asnis et al., 2015; Wilt et al., 2016; Lu and Guo, 2021), such as drug resistance, memory loss and dependence, etc. (Zhao, 2013). At the same time, not only does it take a long time to treat, but it also increases the financial burden on patients and their families, which affects the long-term survival of patients (Groenvold et al., 2007). Therefore, finding an effective and inexpensive alternative therapy has become an urgent task.

Acupuncture and moxibustion in traditional Chinese medicine has a long history, and its advantages of quit onset, simplicity and low side effects also have an irreplaceable role in modern treatment. As a non-pharmacological interventional technique, acupuncture has been shown to be beneficial for most patients from physical to psycho-spiritual aspects compared to other alternative therapies (Gould and MacPherson, 2001; Choi et al., 2017). Studies have shown that acupuncture can relieve pain, fatigue, hot flashes, anxiety and depression in cancer patients (Choi et al., 2012; Garcia et al., 2013; Posadzki et al., 2013). Therefore, acupuncture has gradually become one of the most popular treatment for patients (Gould and MacPherson, 2001). With the gradual increase of clinical studies using acupuncture for CRI in domestic and abroad, most of the meta-analysis were made for different therapies of acupuncture combined therapies of acupuncture and medicine or moxibustion (Chen, 2021; Yin et al., 2021; Wang et al., 2022; Zhuang and Fang, 2022). The results all showed that the combined therapy were more effective for CRI, but there were fewer studies on acupuncture alone, and no meta-analysis of acupuncture alone for CRI was found in recent years. Recently, some new randomized controlled trials were found to verify the efficacy of acupuncture for CRI (Lee et al., 2022) and meta-analysis was conducted for articles that met the study criteria to evaluate the efficacy and safety of acupuncture for CRI and to provide a medical reference for clinical treatment with acupuncture therapy.

Methods and materials

Retrieval policy

Using computer to search Chinese databases: Chinese National Knowledge Infrastructure (CNKI), WANFANG, VIP. English databases: PubMed, Web of science, Cochrane, Embase. Studies published from the establishment of the databases to 31 March 2022 were searched. The retrieval strategy of "subject words+free words" was adopted, The search terms used are as follows: ["acupuncture" or "electroacupuncture" or "transcutaneous electrical acupoint stimulation (TEAS) "or "auricular acupuncture" or "needle warming moxibustion"] and ["Cancer-related Insomnia" or "tumor" or "cancer" or "neoplasia" or "CRI"] and ["sleep" or "insomnia" or "sleep disorder"]. The rest of the database is retrieved according to different retrieval methods. The search strategy and search process are detailed in the Supplementary material. PROSPERO registration has been completed in March 2022 with the registration number CRD42022309870.

Inclusion criteria

(1) Research type: Randomized Controlled Trial (RCT). (2) Participants: all adults cancer patients met the diagnostic criteria of insomnia in *National Comprehensive Cancer Network* and *The Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5), regardless of cancer type, stage or disease duration. (3) Intervention: acupuncture, electroacupuncture, transcutaneous electrical acupoint stimulation, auricular acupuncture, needle warming moxibustion, while western medicine, routine care or sham acupuncture were used in the control group. (4) Outcome index: the curative effect of acupuncture on CRI was measured by any validated tool. The curative effect evaluation index includes one of the following, PSQI, ISI, sleep efficiency, sleep disorder log and subjective self-report sleep questionnaires.

Exclusion criteria

(1) Articles on the combination of acupuncture and medicine or the combination of acupuncture and moxibustion with other therapeutic interventions. (2) Insomnia was not caused by tumor or cancer. (3) The outcome indicators did not meet the inclusion criteria, the data and information are incomplete. (4) Repeated articles. (5) Articles with Jadad scores below 3 scores.

Outcomes

Currently the most commonly outcome indicators are PSQI, ISI and sleep efficiency. PSQI can evaluate sleep quality, sleep dysfunction in clinical and non-clinical samples (Mollayeva et al., 2016). The secondary outcomes included ISI and effective rate. The ISI is used to assess the character and symptoms of the subject's sleep disorder. ISI has beneficial internal consistency, temporal stability and construct validity of instrument for diagnosing CRI patients (Savard et al., 2005). Effective rate included sleep disturbance after treatment, sleep information recorded with sleep diaries, or sleep quality assessed with other validated questionnaires. Security indicators include adverse events.

Data extraction

Two researchers (CaiYun Liu and DongSheng Ba) independently screened articles that met the inclusion criteria and extracted data, and summarized the authors, publication year, subjects (gender-age characteristics, tumor type, sample size), intervention mode, control mode, outcome index and adverse events into an excel table. If the two researchers disagree, they will be reviewed by a third researcher (HaiXin Yu).

Quality assessment of included studies

The evaluation of the literature was performed using the risk of bias assessment tool in the RevMan 5.4 software provided by the Cochrane Collaboration Network, which focuses on the following components: (1) Random sequence generation; (2) Allocation concealment scheme; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data; (6) Selective outcome reporting; (7) Other bias (Higgins et al., 2011). The above seven biases were assessed, with red representing high risk, yellow representing unclear risk, and green representing low risk.

Statistical methods

Meta-analysis was performed using RevMan 5.4 software, and Relative Risk (RR) was used for efficacy analysis results; Mean Difference (MD) was used for continuous analysis results, and 95% confidence intervals (CI) were given. The I^2 statistic (0–100%) was used to assess the heterogeneity between the results of studies expressing different intervention modalities, and when the statistical heterogeneity between studies was small ($P>0.1$, $I^2 < 50\%$), it indicated that the results were not statistically significant and a fixed-effects model was used. When there was a large statistical heterogeneity between studies ($P < 0.1$, $I^2 \geq 50\%$), it indicated that the results were statistically significant, and the source of heterogeneity was identified and subgroup analysis was performed. When statistical heterogeneity existed between subgroups without significant clinical heterogeneity, a random-effects model was used and the results were analyzed.

Results

Study selection

Through the retrieval of various databases, a total of 1,229 articles were identified from the preliminary searches, including 85 Chinese articles and 1,144 English articles. After eliminating

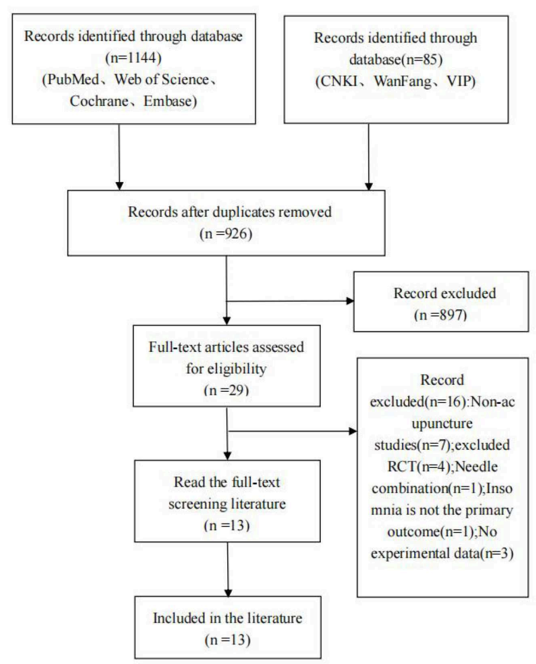

FIGURE 1
PRISMA flow diagram of included articles.

duplicate articles ($n = 303$), remaining 926 articles, and after reading the titles and abstracts of the articles, the articles were excluded according to the requirements of the inclusion criteria ($n = 897$), 29 remaining articles were excluded after reading the full text ($n = 16$), and finally 13 RCTs were included, 3 in Chinese (Song et al., 2015; Peng et al., 2016; Shen et al., 2016) and 10 in English (Feng et al., 2011; Bokmand and Flyger, 2012; Frisk et al., 2012; Mao et al., 2014; Garland et al., 2017, 2019; Bao et al., 2021; Höxtermann et al., 2021; Zhang et al., 2021; Lee et al., 2022). The flow of trials outlined in Figure 1.

Study information

The basic information in the articles were collected after reading the full text and plotted in Table 1, which included the author, year of publication, tumor type, gender-age characteristics, sample size, intervention, control modality, outcome indicators and adverse events. As known from the table, a total of 1,109 subjects were included in the 13 RCTs, including 517 in the treatment group and 592 in the control group. The treatment group included 3 treatment: electroacupuncture (Frisk et al., 2012; Mao et al., 2014; Shen et al., 2016; Garland et al., 2017; Bao et al., 2021; Zhang et al., 2021; Lee et al., 2022) ($n = 7$), manual acupuncture (Feng et al., 2011; Bokmand and Flyger, 2012; Song et al., 2015; Peng et al., 2016; Garland et al., 2019) ($n = 5$) and auricular acupuncture (Höxtermann et al., 2021) ($n = 1$). Of the 13 included articles, 11 (Feng et al., 2011; Mao et al., 2014; Song et al., 2015; Peng et al., 2016; Shen et al., 2016; Garland et al., 2017, 2019; Bao et al., 2021; Höxtermann et al., 2021; Zhang et al., 2021; Lee et al., 2022) provided results for PSQI and ISI as continuous data measures, of which 7 (Feng et al., 2011; Mao et al., 2014; Song et al., 2015; Peng et al., 2016; Shen et al., 2016; Garland et al., 2017; Höxtermann et al., 2021) had PSQI as the primary outcome indicator and 3 (Garland et al., 2019; Zhang et al., 2021; Lee et al., 2022) had ISI as the primary outcome indicator; 3 (Garland et al., 2019; Zhang et al., 2021; Lee et al., 2022) had PSQI as the secondary outcome indicator and 1 paper (Bao et al., 2021) had ISI as the secondary outcome indicator. Another four (Bokmand and Flyger, 2012; Frisk et al., 2012; Song et al., 2015; Peng et al., 2016) provided results for efficacy analysis measures.

Risk of bias and quality assessment

All included RCTs correctly used the randomization allocation method, with 9 items (Feng et al., 2011; Bokmand and Flyger, 2012; Mao et al., 2014; Song et al., 2015; Peng et al., 2016; Shen et al., 2016; Garland et al., 2017; Höxtermann et al., 2021; Zhang et al., 2021) using random number tables, 2 items (Frisk et al., 2012; Lee et al., 2022) using stratified randomization, and 2 items (Garland et al., 2019; Bao et al., 2021) using random squares. Seven items (Bokmand and Flyger, 2012; Mao et al., 2014; Garland et al., 2017, 2019; Höxtermann et al., 2021; Zhang et al., 2021; Lee et al., 2022) mentioned allocation concealment (six Bokmand and Flyger, 2012; Mao et al., 2014; Garland et al., 2017, 2019; Zhang et al., 2021; Lee et al., 2022 for opaque or closed envelope hiding and one Höxtermann et al., 2021 for central random hiding), and the rest were not mentioned. Three items (Bokmand and Flyger, 2012; Bao et al., 2021; Zhang et al., 2021) were blinded to subjects and researchers. Four items (Garland et al., 2019; Bao et al., 2021; Zhang et al., 2021; Lee et al., 2022) implemented blinding of outcome assessors. Five items (Frisk et al., 2012; Mao et al., 2014; Peng et al., 2016; Bao et al., 2021; Zhang et al., 2021) reported cases missing visits or active withdrawals, of which the number and reasons for missing visits or withdrawals were unbalanced, and the remaining eight (Feng et al., 2011; Bokmand and Flyger, 2012; Song et al., 2015; Shen et al., 2016; Garland et al., 2017, 2019; Höxtermann et al., 2021; Lee et al., 2022) had no personnel withdrawal. Selective reporting bias was low. For the presence of other biases, none of the 13 RCTs mentioned (Figure 2).

Primary outcome

PSQI: Ten of the included studies (Feng et al., 2011; Mao et al., 2014; Song et al., 2015; Peng et al., 2016; Shen et al., 2016; Garland et al., 2017, 2019; Höxtermann et al., 2021; Zhang et al., 2021; Lee et al., 2022) addressed changes in PSQI before and after treatment, with a total of 831 participants, of whom 416 were in the experimental group and 415 in the control group. The heterogeneity test was first performed with $P = 0.001$ and $I^2 = 67\%$, showing a large heterogeneity between studies, and a random effects model was adopted for meta-analysis. The results showed that the effect size MD $= -1.83$, 95% CI $= [-2.71, -0.94]$, $P < 0.0001$. The difference was statistically significant, indicating acupuncture was effective in treating patients with CRI compared to the control group (Figure 3).

Subgroup analysis was performed according to the different intervention methods, and the results of the subgroup analysis showed that the heterogeneity among the three subgroups was $P = 0.84$, $I^2 = 0\%$, indicating that there was no heterogeneity among the subgroups, and the effect size after the three subgroups were combined was $P = 0.001$, $I^2 = 67\%$, indicating that there was heterogeneity. As we can see from the figure, the literature data on manual acupuncture for patients with CRI may be a source of heterogeneity, so a random effects model was used for analysis, MD $= -1.83$, 95%CI $= [-2.71, -0.94]$, $P < 0.0001$. The difference is statistically significant, indicating that acupuncture treated CRI patients with better symptoms than the control group (Figure 4).

TABLE 1 Basic information of the included literature.

Reference	Age; Gender (T/C)	Cancer type	sample dose	Interventions	Control (regimen)	Outcomes	Adverse events
Bao et al. (2021)	Age:60.3/62.7/57.3 Gender (F:M) : 20:7/ 19:5/ 21:3	13 types of cancer including breast cancer, colon cancer, lung cancer, ovarian cancer, and endometrial cancer	$n = 75$ T:27 C:24 UC:24	EA	Sham EA (Sham-Retractable nonpenetrating needles at non-acupoints); routine care	ISI	T: Adverse events were reported in 6 patients, 3 with pain at the acupuncture site, 2 with abrasions, and 1 with claustrophobia after wearing an eye patch
Bokmand and Flyger (2012)	Age:54.1/53. 4 Gender:F	breast cancer	$n = 94$ T:31 C:29 NT:34	Manual acupuncture	Sham acupuncture (superficial penetrating needles at non-acupoint); no treatment	Sleep disturbance (logged as yes or no)	T: 5 women had side effects, colds and sensitivities. C: 5 women had side effects including fatigue and joint tenderness.
Feng et al. (2011)	Age:63.8/63.6 Gender: (F:M) :14:26/13:27	7 types of malignant tumors including lung cancer, gastric cancer, lymphoma,breast cancer, colorectal cancer, and ovarian cancer	$n = 80$ T:40 C:40	Manual acupuncture	Fluoxetine capsules (20 mg/day for 30 days)	PSQI	None
Frisk et al. (2012)	Age:54.1/53.4 Gender:F	Breast cancer	$n = 45$ T:26 C:18	EA	Hormone therapy (tamoxifen/tolimifen)	Sleep Disorder Log (1) Hours of sleep per night; (2) Number of wake-ups during the night	None
Garland et al. (2017)	Age:52.9/50.4 Gender:F	Breast cancer	$n = 58$ T:30 C:28	EA	Gabapentin tablets (300 mg for 3 days,followed twice daily for 3 days, then thrice daily for rest 50 days (8 weeks totally)	PSQI,specific PSQI domain	None
Garland et al. (2019)	Age:62.3/60.7 Gender (F:M) :43:37/48:32	Breast cancer, prostate cancer, hematologic cancer	$n = 160$ T:80 C:80	Manual acupuncture	Cognitive behavioral therapy (5 weekly sessions, followed by 2 biweekly sessions,7 sessions totally over 8 weeks)	ISI, PSQI	T: Soreness, itching and pain at the acupuncture site ($n = 9$). C: Lethargy and daytime fatigue ($n = 5$)

(Continued)

TABLE 1 (Continued)

Reference	Age; Gender (T/C)	Cancer type	sample dose	Interventions	Control (regimen)	Outcomes	Adverse events
Lee et al. (2022)	Age:57.63/62.33/61.38 Gender (F:M) :6:1:5/2:5:3	Breast, thyroid and other cancers	$n = 22$ T:8 C:6 UC:8	EA	Sham EA (a blunt end not penetrating the skin); routine care	ISI, PSQI	T: 2 cases of headache, 1 case of cough, low back pain, common cold, enteritis, dizziness, knee joint pain, rhinitis, and 1 case of dyspepsia. C: 2 cases of common cold,1 case of shoulder joint pain, skin allergy, lymphadenitis, hematuria, and 1 case of dyspepsia. UC: arthritis, skin spots, diarrhea, dyspepsia, toothache, and intestinal obstruction in 1 case each.
Mao et al. (2014)	Age:59.7 (41–76) Gender:F	breast cancer	$n = 67$ T:22 C:22 WLC:23	EA	Sham EA (nonpenetrating needles at non-acupoints); waiting list comparison	PSQI	T: tingling, numbness, pain at needling site ($n = 6$); C: 4 case.
Zhang et al. (2021)	Age:52.5/52.7 Gender:F	Breast cancer	$n = 28$ T:13 C:15	EA	waiting list comparison	ISI, PSQI	T: Soreness, itching and pain at the acupuncture site ($n = 9$), mild and moderate. C: Lethargy and daytime fatigue ($n = 5$),mild and moderate.
Peng et al. (2016)	Age:59.36/60.95 Gender: (F:M) :36/68	Tumor type unknown	$n = 208$ T:104 C:104	Manual acupuncture	Eszolam tablets (1mg/day for 7 days)	PSQI, Effective rate	None
Höxtermann et al. (2021)	Age:56.6/54.8 Gender:F	Breast cancer	$n = 52$ T:26 C:26	auricular acupuncture	Psychoeducation (1 session psychoeducation+insomnia advice booklet)	PSQI	T: 39 cases of bruising, pain, hot flashes, pressure sensitivity, etc.
Song et al. (2015)	Age:n.r Gender:n.r	Tumor type unknown	$n = 120$ T:60 C:60	Manual acupuncture	Eszolam tablets (1 mg/day for 7 days)	PSQI, Effective rate	None
Shen et al. (2016)	Age:54.9/58.1 Gender (F:M) : 28:22/31:19	Lung cancer	$n = 100$ T:50 C:50	EA	Analgesic drugs combined with zolpidem (10 mg/day for 4 weeks)	PSQI	None

N, total number of subjects, F, female; M, male; T, experimental group; C, control group; UC, usual care group; EA, electroacupuncture; NT, blank group; WLC, waiting list control group; n.r, not reported.

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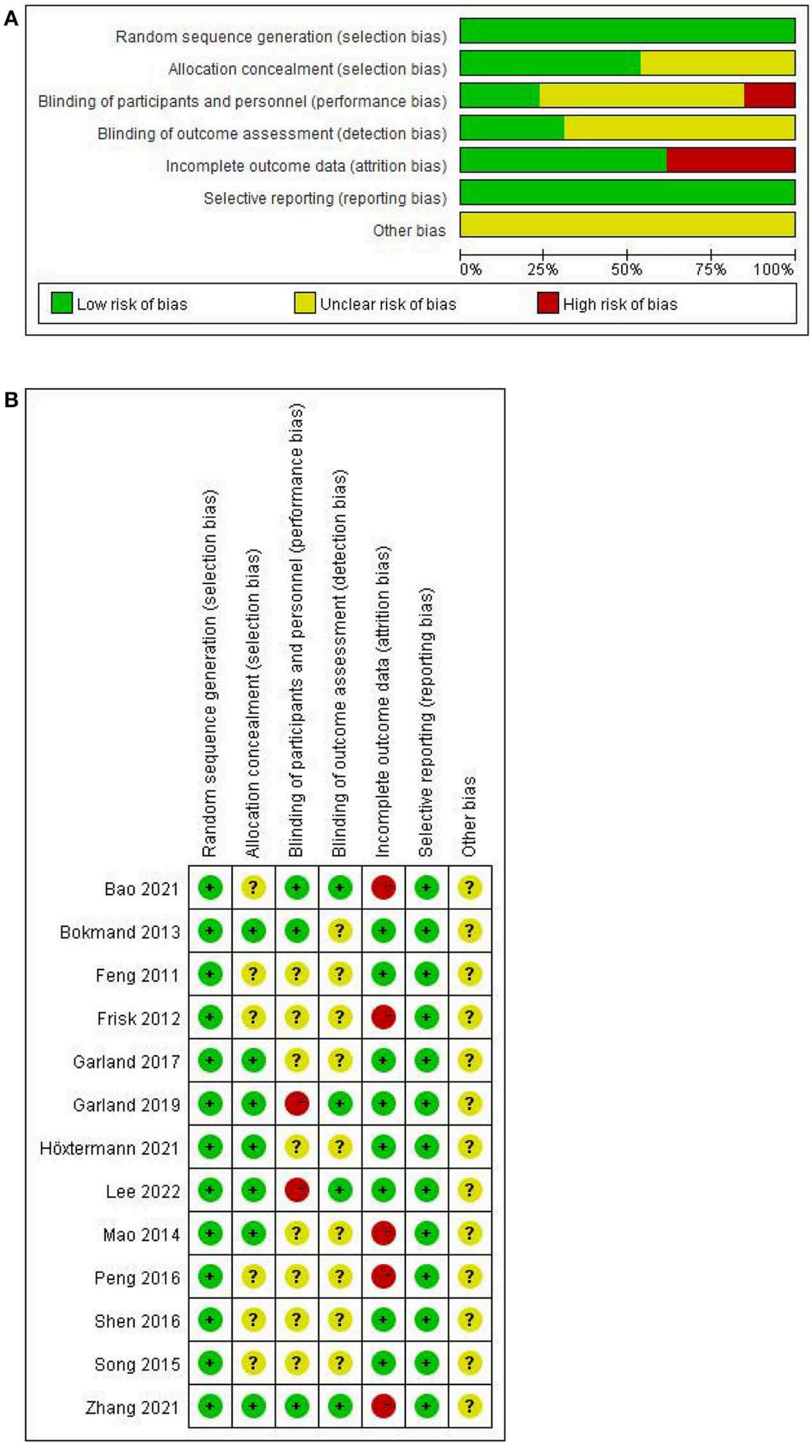

FIGURE 2
Risk of bias of included trials. **(A)** Assessment of risk of bias presented as percentages across all included studies. **(B)** Risk of bias summary for each included study.

Secondary outcome

ISI: Four of the included studies (Garland et al., 2019; Bao et al., 2021; Zhang et al., 2021; Lee et al., 2022) addressed the changes in ISI before and after treatment in a total of 237 participants, of which 120 were in the experimental group and 117 in the control group. A heterogeneity test was first performed with $P = 0.15$, $I^2 = 44\%$, so a fixed-effects model was

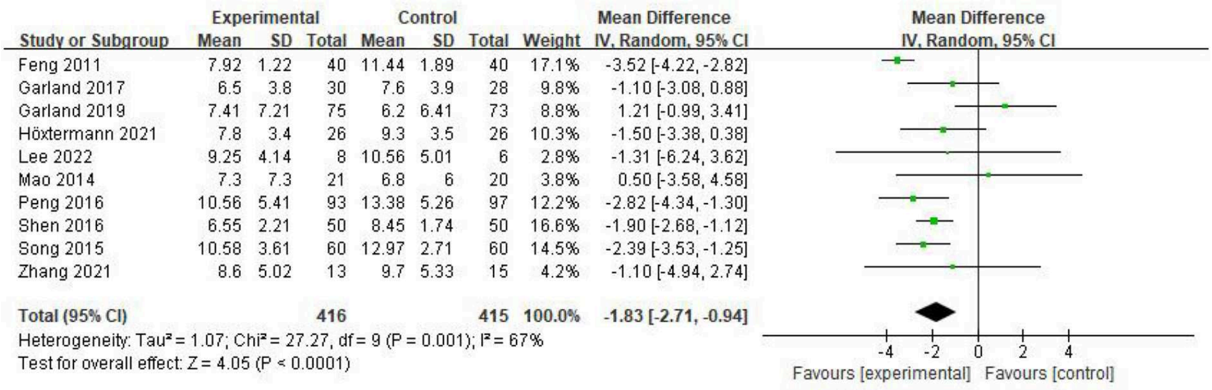

FIGURE 3
Forest plot of PSQI scale scores.

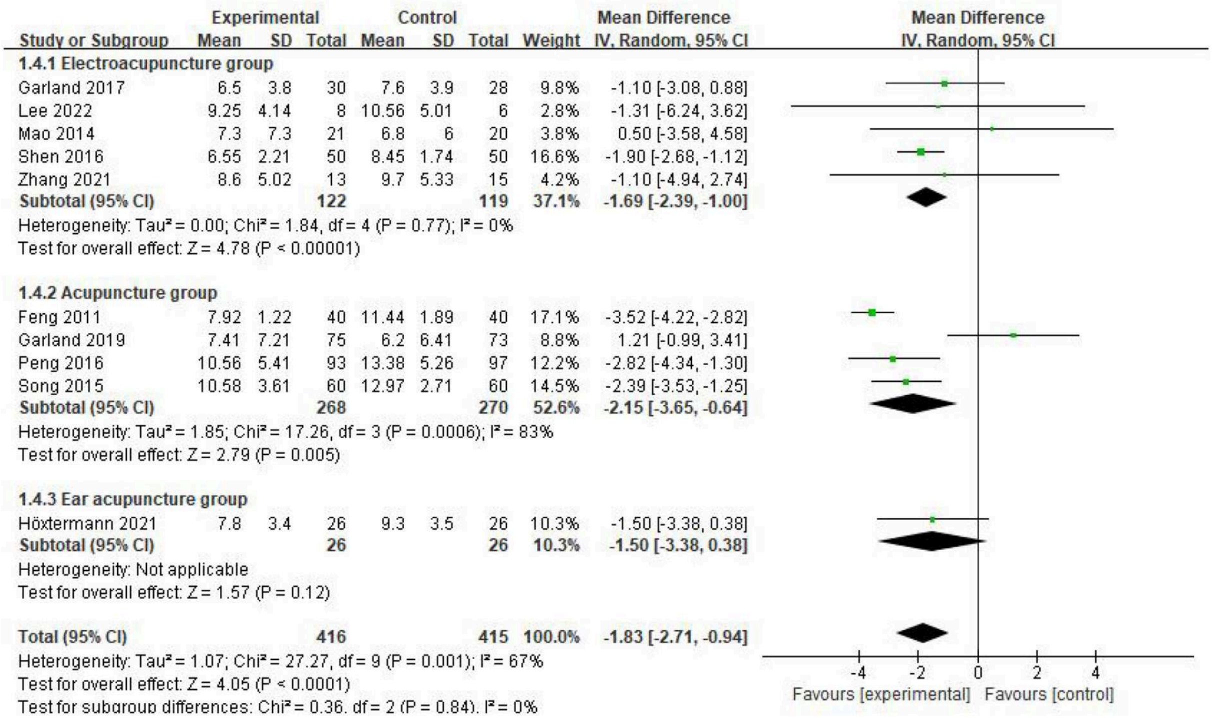

FIGURE 4
Subgroup analysis of PSQI scores.

adopted for meta-analysis. The results showed that the effect size MD = 0.79, 95%CI = [−0.46, 2.03], $P = 0.22$. The ISI scores of patients with CRI in the treatment group intervention were not statistically significant compared to the control group (Figure 5).

Subgroup analysis was performed according to the different intervention methods and the results of the subgroup analysis showed that the heterogeneity between the two subgroups was $P = 0.15$, MD = 0.16, $I^2 = 44\%$, indicating that there was no heterogeneity between the two subgroups, and the effect size after the combination of the two subgroups was $P = 0.07$, $I^2 = 70.1\%$, indicating that there was heterogeneity. As can be seen from the figure, literature data on electroacupuncture for CRI patients may be a source of heterogeneity, so meta-analysis was performed using a random effects model, MD = 0.16, 95%CI =

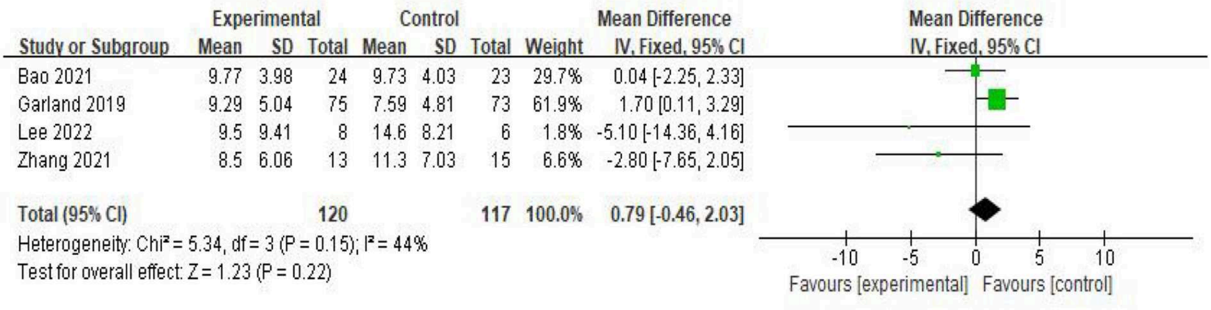

FIGURE 5
Forest plot of ISI scale scores.

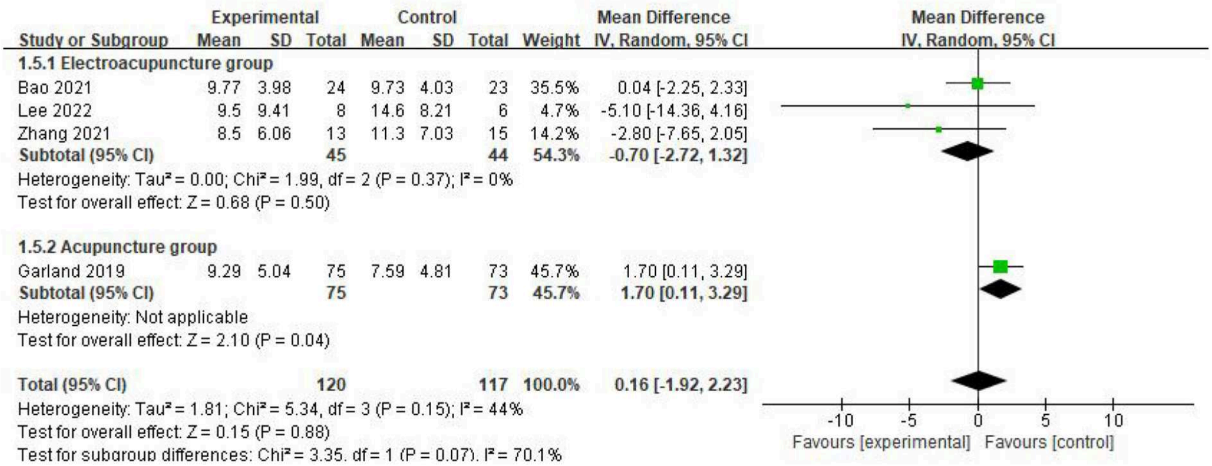

FIGURE 6
Subgroup analysis of ISI scores.

[−1.92, 2.23], $P = 0.88$ indicating that acupuncture improved ISI decline in CRI patients compared to controls without statistical significance (Figure 6).

Efficacy analysis

Four of the included studies (Bokmand and Flyger, 2012; Frisk et al., 2012; Song et al., 2015; Peng et al., 2016) reported changes before and after sleep disorders in a total of 407 participants, including 203 in the experimental group and 204 in the control group. A heterogeneity test was first performed with $P = 0.58$, $I^2 = 0\%$, and a fixed-effect model was adopted for meta-analysis, which showed that acupuncture improved CRI patients better than controls in terms of sleep disturbances (RR = 0.47, 95%CI = [0.33, 0.66], $P < 0.0001$) (Figure 7).

Summary of acupuncture treatment and security analysis

The acupuncture treatment sessions varied among studies (Table 2). The most commonly used acupoints were: Baihui (GV20), Shenting (GV24), Neiguan (PC6), Sishencong ((EX-HN1), Yintang (EX-HN3), Zusanli (ST36), all of which were used at least three times, with a possible selection of 2-12 points in each study, and a minimum treatment duration of 1 week and a maximum of 10 weeks, ranging from 20 to 30 minutes. Another study chose auricular acupuncture (Höxtermann et al., 2021) with a duration of 33 days, shorter than manual acupuncture and electroacupuncture. The most common adverse effects of acupuncture in the included studies were pain, pruritus, bruising, and colds. Comparison the relatively low number of adverse events in the experimental group compared to the control group indicates that acupuncture

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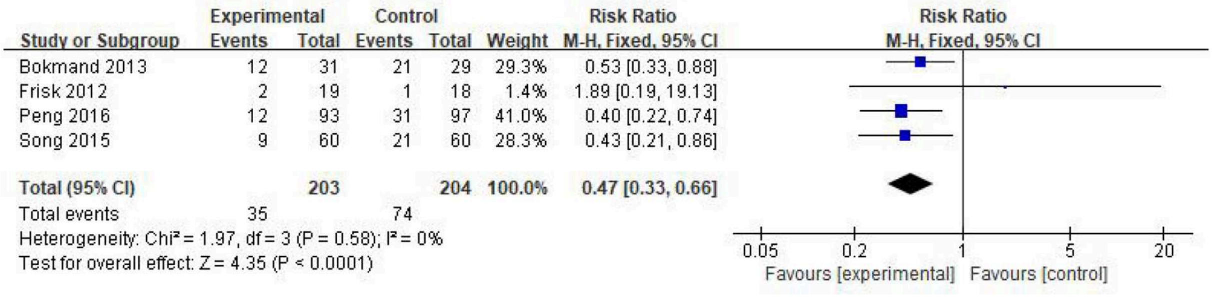

FIGURE 7
Forest plot of dichotomous data.

has fewer side effects in the treatment of CRI and has advantages in terms of safety compared to other treatments (e.g., sham acupuncture and cognitive behavioral therapy).

Discussion

Cancer-related insomnia should belong to the category of "insomnia" from the perspective of Traditional Chinese Medicine, and "insomnia" can be traced back to the "*The Yellow Emperor's Canon of Internal Medicine*". CRI is due to the fact that after chemoradiotherapy drugs enter the human body, the struggle between anti-pathogenic *qi* and pathogenic factors, resulting in disharmony between *yin* and *yang*, which leads to insomnia. In addition, the tumor itself belongs to the deficiency of the essence and excess, mostly due to the intertwined phlegm and blood stasis, which affects the function of viscera, the phlegm mists the heart, and the blood stasis stagnates the *qi* movement (Lu and Guo, 2021). Acupuncture therapy has the effect of regulate and harmonize *yin* and *yang*, dredging the meridians, and exerting its effect through related acupoints. Modern research has shown that the pathogenesis of insomnia is complex and closely related to the central nervous system (Bonnet and Arand, 1997), and studies have shown that patients with insomnia often over-active the sympathetic nerves during sleep thus accelerating metabolism in the body (Liu et al., 2022), what's more, acupuncture can affect sleep by activating parasympathetic nerves and inhibiting sympathetic nerves (Li et al., 2003; Liu et al., 2022). In addition, acupuncture can regulate central neurotransmitters, immune cytokines (Li, 2021), a series of chemical factors (Wei et al., 2021) and antioxidant defense systems (Li, 2021) to promote the restoration of balance between *yin* and *yang* in the body and achieve improved sleep.

Meta-analysis of 11 RCTs studies of acupuncture for the treatment of symptoms in patients with CRI showed that acupuncture was effective in improving sleep disturbance and reducing PSQI scores, but it could not be stated whether it could reduce ISI scores, due to the small sample size included in this study and the low quality of the articles. In addition, the type of tumor included in the study was not homogeneous, which could have an impact on the results. The control group of RCTs selected for the studies had not only sham acupuncture, but also a variety of interventions such as western medicine and routine care, which may have caused some error in the results. In terms of outcome indicators, the use of sleep logs and questionnaires as evaluation indicators in some RCTs may also have some limitations on the final results. In addition, in terms of adverse events, seven of the included articles (Bokmand and Flyger, 2012; Mao et al., 2014; Garland et al., 2019; Bao et al., 2021; Höxtermann et al., 2021; Zhang et al., 2021; Lee et al., 2022) mentioned mild to moderate reactions with different symptoms, such as acupuncture pain, cough, skin allergy, bruising and so on. In the subgroup analysis results showed that acupuncture or electroacupuncture had more positive efficacy and higher safety compared to drugs such as eszopiclone and gabapentin for the treatment of CRI, while some articles were less good and there were no good solutions mentioned in the text for these adverse reactions, which is something we need to improve in the future when using acupuncture therapy. The study shows that the probability of selecting these acupoints Baihui, Shenting, Neiguan, Sishencong, Yintang, and Zusanli is high, which may indicate that these acupoints have some improvement effect on the treatment of CRI, but the specific acupuncture protocol is not clear, and further investigation on the selection of acupuncture points is needed in the future. Moreover, although acupuncture treatment has fewer side effects, there is no clear solution to these adverse effects, which is what we need to improve in the use of acupuncture in the future, such as pain, itching, bruising, colds,etc. We found the funnel plot was highly biased (Supplementary Figure S1), we think the main reasons are as follows: Firstly, interventions are complex; Secondly, different acupoints selection. Therefore, reducing bias greatly is also an area for us to improve in the future.

Limitations of the study: (1) The reason of large heterogeneity in meta-analysis may be due to the diversity of intervention methods, as well as differences in the types of drugs, doses, acupuncture times, and acupuncture point selection in the control group. (2) The different

TABLE 2 Summary of acupuncture treatment.

Include literatures	Acupuncture type	Acupoints	Treatment regimen
Bao et al. (2021)	EA	Hegu (LI4), Neiguan (PC6), Houxi (SI3), Taichong (LR3), Xiaxi (GB43), Fenglong (ST40), Bafeng 2, Bafeng 3	Biweekly for first 2 weeks, then weekly for 6 weeks;30 min/session;10 sessions totally
Bokmand and Flyger (2012)	Manual acupuncture	Neiguan (PC6), Sanyinjiao (SP6), Taichong (LR3), Taixi (KI3)	Once weekly for 5 wks;15–20 min/session;5 sessions totally
Feng et al. (2011)	Manual acupuncture	Sishencong (EX-HN1), Baihui (GV20), Yintang (EX-HN3), Neiguan (PC6), Shenmen (HT7), Fenglong (ST40), Sanyinjiao (SP6), Yinlingquan (SP9), Xuehai (SP10)	Once daily for 30 days;20–30 min/session;30 sessions totally
Frisk et al. (2012)	EA	Baihui (GV20), Xinshu (BL15), Shenshu (BL23), Ciliao (BL32), Neiguan (PC6), Shenmen (HT7), Yinlingquan (SP9), Sanyinjiao (SP6), Taichong (LR3)	Twice weekly for 2 weeks, followed by once weekly for 10 weeks;30 min/session;14 sessions totally
Garland et al. (2017)	EA	Taixi (KI3), Sanyinjiao (SP6), plus Guanyuan (CV4) if supine position or Shenshu (BL23) if prone position;and up to 4 supplemental points	Twice weekly for 2 weeks, followed by once weekly for 6 weeks;30 min/ session; 10 sessions totally
Garland et al. (2019)	Manual acupuncture	Shenmen (HT7), Sanyinjiao (SP6)	Twice weekly for 2 weeks, followed by once weekly for 6 weeks;30 min/ session;10 sessions totally
Lee et al. (2022)	EA	Baihui (GV20), Yintang (EX-HN3), Neiguan (PC6), Shenmen (HT7), Jinmen (BL63), Dazhong (KI4), and 4 more additional points	2–3 times a week for 4 weeks, for 30min/session, 10 sessions totally
Mao et al. (2014)	EA	distant acupoints plus at lease 4 local acupoints around the most painful joint	Twice weekly for 2 weeks, followed by once weekly for 6 weeks;30 min/ session;10 sessions totally
Zhang et al. (2021)	EA	Shenting (GV24), Baihui (GV20), Sishencong (EX-HN1), Neiguan (PC6), Sanyinjiao (SP6)), Taixi (KI3), and 4 additional points	Twice weekly for 6 weeks;25 min/session;12 sessions totally
Peng et al. (2016)	Manual acupuncture	Baihui (GV20), Shenting (GV24), Yintang (EX- HN3), Shenmen (HT7), Zusanli (ST36), Sanyinjiao (SP6)	Once daily for1 week; 30 min/session
Höxtermann et al. (2021)	Auricular acupuncture	Postantitragal belt, helix channel, shen men. Additional points were used to address comorbid symptoms	Twice weekly for 5 weeks; 20 min/session; 10 sessions totally
Song et al. (2015)	Manual acupuncture	Shenting (GV24), Baihui (GV20), Yintang (EX-HN3), Shenmen (HT7), Zusanli (ST36), Sanyinjiao (SP6)	Once daily for 7 days;30 min/session;7 sessions totally
Shen et al. (2016)	EA	Yintang (EX-HN3), Sishencong (EX-HN1), Anmian (EX- HN16), Qihai (CV6), Hegu (LI4), Quchi (LI11), Shenmen (HT7), Zusanli (ST36), Zhaohai (KI6), Shenmai (BL62), Taichong (LR3), and additional points	Once daily for 4 weeks;30 min/session;28 sessions totally

EA, electroacupuncture.

types of cancer in studies, included types of breast cancer, thyroid cancer, colon cancer, and lung cancer, may also lead to different analysis results. In order to obtain better efficacy of acupuncture for CRI, future clinical trials can be conducted on different acupuncture interventions, compatibility of acupuncture point selection, needle retention time, and different cancer types and periods of onset to determine the clinical benefits of acupuncture for this disease.

Conclusion

This study shows that acupuncture can improve the symptoms of CRI patients to some extent, sleep quality evaluated by PSQI improved, which is clinically useful and safe, and provides a basis for clinical treatment. Empirically, if combined with acupuncture and pharmacotherapy or alternative therapies, there may be a greater improvement in improving sleep quality. In terms of the safety of acupuncture efficacy, there is a need to further improve and ameliorate the adverse effects associated with acupuncture. However, because of the small amount and low quality of data included in this study, more large samples and high-quality clinical trials are needed to supplement the literature.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Author contributions

Thesis guidance: BC, JZ, AC, BW, YG, YL, and ZC. Essay writing: HY, CL, and ZZ. Data analysis and collation: HY, CL, and DB. Illustration of the paper: HY and NL. Table design: HY and ZZ. Thesis translation: PL and HY. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1026759/full#supplementary-material

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Efficacy of traditional Chinese exercise for sarcopenia: A systematic review and meta-analysis of randomized controlled trials

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Objective: To conduct a systematic review and meta-analysis to evaluate the effectiveness of Traditional Chinese Exercise (TCE) for sarcopenia.

Methods: A literature search was conducted in eight online databases from inception until September 2022. Based on the Cochrane risk of bias tool, randomized controlled trials (RCTs) with RoB score $\geq$ 4 were included for further analyses. The primary outcome was muscle strength and physical function, and the secondary outcomes were adverse events. Data collection and analyses were conducted by RevMan 5.4 Software. GRADE system was used to evaluate the certainty of evidence.

Results: A total of 13 eligible RCTs with 718 subjects were identified and included in this study. Among them, 10 RCTs involved Yijinjing; 2 involved Tai Chi; and 1 involved Baduanjin. Meta-analyses showed that TCE had better clinical effects than control measures in the chair stand test ($P < 0.00001$, $I^2 = 38\%$; Certainty of evidence: Moderate), squatting-to-standing test ($P < 0.00001$, $I^2 = 0\%$; Certainty of evidence: Moderate), 6-m gait speed ($P < 0.00001$, $I^2 = 13\%$; Certainty of evidence: Moderate), Time Up and Go Test ($P = 0.03$, $I^2 = 81\%$; Certainty of evidence: Low), peak torque of the extensors ($P = 0.03$, $I^2 = 0\%$; Certainty of evidence: Moderate), total work of the extensors ($P = 0.03$, $I^2 = 35\%$; Certainty of evidence: Moderate), peak torque of the flexors ($P = 0.03$, $I^2 = 47\%$; Certainty of evidence: Low), total work of the flexors ($P = 0.02$, $I^2 = 42\%$; Certainty of evidence: Low), the average power of the flexors ($P = 0.03$, $I^2 = 30\%$; Certainty of evidence: Moderate), and balance function ($P < 0.00001$, $I^2 = 53\%$; Certainty of evidence: Low). In additional, no adverse events were reported in participants who receive TCE.

Conclusion: The findings of the present systematic review, at least to a certain extent, provided supporting evidence for the routine use of TCE for sarcopenia.

KEYWORDS

traditional Chinese exercise, traditional Chinese medicine, sarcopenia, systematic review, meta-analysis

Introduction

Sarcopenia, a skeletal muscle disorder, is related to the accelerated loss of physical function and muscle mass (Cruz-Jentoft and Sayer, 2019). It is a progressive and generalized disease that is common in the elderly and is associated with various adverse outcomes including fall down, functional decline, and bodily weakness (Cruz-Jentoft et al., 2019). It severely affects the normal physiological function and quality of life of the elderly, and even shortens their lifespan (Mohd Nawi et al., 2019). In recent years, the aging of the population has become a serious social problem all over the world, and sarcopenia has received increasing attention (Jensen et al., 2020). Exercise, nutrition, and pharmacotherapy are the mainstays of treatment for sarcopenia in the elderly (Cruz-Jentoft et al., 2014). There is currently no specific cure for sarcopenia. Some drugs may benefit muscles, such as hormones, but these drugs may cause serious adverse effects (Gaskin et al., 2003; Veldhuis et al., 2011). Exercise therapy is regarded as one of the major means of treating sarcopenia in the elderly, mainly including resistance exercise and aerobic exercise (Kakehi et al., 2022).

Traditional Chinese exercise (TCE) is a therapeutic, aerobic, and mind-body exercise, which originated from traditional Chinese medicine and can be traced back to approximately 3,000 years ago (Zhang et al., 2017). As a major integral part of non-pharmacological traditional Chinese medicine, TCE mainly includes Yijinjing, Tai Chi, Baduanjin, and Wuqinxi, and are characterized by gentle movements emphasizing physical and mental relaxation (Zhou et al., 2019; Zeng et al., 2020). Previous studies had reported the significant effects of TCE in improving patients' physical status in various diseases including metabolic diseases (Zou et al., 2019), degenerative diseases (Fidan et al., 2019), cardiovascular diseases (Wu et al., 2020), respiratory disease (Reychler et al., 2019), endocrinopathies (Meng et al., 2018), and cancer (Wayne et al., 2018).

Currently, increasing numbers of clinical trials have reported that TCE has been used for treating sarcopenia. More and more randomized controlled trials (RCTs) demonstrated that TCE can significantly improve patients' physical status (Zhu Y. et al., 2019). However, results from different studies are inconsistent, and sometimes are contrary due to different sample sizes or duration time. The conclusions from current studies have remained controversial, and the evidence provided by these studies are require assessment. Therefore, it is worth undertaking a systematic review and meta-analysis to investigate the effectiveness of TCE for patients with sarcopenia.

Methods

The present study is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Moher et al., 2009).

Database and search strategies

We searched four international online databases (PubMed, EMBASE, Cochrane library, and Web of Science) and four Chinese online databases (VIP information database, Chinese National Knowledge Infrastructure (CNKI), Wan Fang Data Information Site, and Chinese Biomedical Literature Database) from inception to September 2022. Additionally, other relevant studies including references cited by previously published systematic reviews, conference proceedings, and dissertations were also manually searched in this study. The following search strategy was used for PubMed and was modified to suit other databases.

1. Traditional Chinese exercise
2. Qigong
3. Tai Chi
4. Yijinjing
5. Baduanjin
6. Kungfu
7. Wuqinxi
8. OR/1-7
9. Sarcopenia
10. Sarcopenias
11. OR/8-9
12. 8AND11

Eligibility criteria

Types of studies

In the present study, we only included RCTs that evaluate the efficacy and safety of TCE for sarcopenia. As some studies used the birthday, ID number, or hospitalization number as the basis for random generation, these Quasi-RCTs studies were excluded. There is no limitation on language, blinding, or publication type of included studies.

Types of participants

All participants with a diagnosis of sarcopenia met one of the following criteria: (i) established definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010); (ii) established definition of sarcopenia by Roubenoff (2000); (iii) established definition by the Asia Working Group for Sarcopenia (AWGS) (Chen et al., 2014). Other diagnostic criteria with comparable definitions were also used.

Types of interventions

Traditional Chinese exercise monotherapy was used in the treatment groups. There is no limitation on the frequency, intensity, or course of TCE. The comparator was one of the followings: no training or health education. The included studies should include one of the following comparisons: (1) TCE *vs.* no training; (2) TCE *vs.* health education.

Types of outcome measures

The primary outcome was muscle strength and physical function, which was assessed by different measures including the Grip Strength Test, Chair Stand Test, Squatting-To-Standing Test, 6-m gait speed, Peak Torque of muscle, Total Work of muscle, Average Power of muscle, Timed-Up-and-Go Test, Berg Balance Scale. All of the outcome measurements were conducted at the endpoint of treatment by the researchers in each trial.

Study selection and data collection

Two investigators of our group selected the potential references by screening the title and abstract of each article. For those potentially eligible studies, full articles were downloaded from databases. The two investigators read the whole article independently and made the final decision on including the articles or not. For each eligible study, the following information was collected: the first author's name and year of publication, final diagnosis, diagnosis criteria, study design, sample size, gender composition, the mean age of participants, interventions, duration of treatment, follow-up, main outcome measures, and its corresponding *p*-value. If the necessary data were expressed graphically or not recorded in the manuscripts, we tried to contact the original author for further information by phone or email or calculated by ourselves if available. Any disagreement between the two investigators was resolved through a discussion with the third author.

Risk of bias

We assessed the methodological quality of the RCTs included in the present study with the seven criteria recommended by the Cochrane Collaboration (Cumpston et al., 2019). The seven components were as follows: A. adequate sequence generation; B. concealment of allocation; C. blinding (participants and personnel); D. blinding (outcome assessor); E. incomplete outcome data addressed (ITT analysis); F. selective reporting; G. other biases. Each of these indicators was categorized as high risk of bias, low risk of bias, and unclear. For each item, a score of 1 or 0 was given depending on whether the study provided adequate information in the relevant domain. Only RCTs with a cumulative score of at least 4 out of 7 for the Cochrane RoB tool domains were included in this systematic review. Adequate sequence generation must achieve status as low risk of bias as it is the certain key criteria. Disagreements were settled by a discussion with the corresponding author.

Grading the certainty of the evidence

The updated GRADE system (Guyatt et al., 2013) was applied to assess the certainty of evidence using four grades: high, moderate, low, and very low. The low and very low certainty of evidence means that the true effect is likely to be substantially different from the estimate of effect, and we have little or very little confidence in the effect estimate. Any discrepancy about grading the certainty of the evidence was resolved through discussion with the corresponding author.

Data synthesis and analysis

The software Cochrane Collaboration Review Manager (RevMan 5.4) was used to summarize the data of eligible studies and performed meta-analysis. Weighted mean difference (WMD) was adopted to analyze the continuous data, and risk ratio (RR) was adopted to analyze the dichotomous data. The standard chi-square test and I^2 statistic were used to evaluate heterogeneity among trials. A fixed effect model or a random effect model was used to analyze pooled effects depending on heterogeneity. When there is no obvious heterogeneity, a fixed effect model was used ($P > 0.1$, $I^2 < 50\%$), otherwise, the random effect model was applied. Subsequent sensitivity analyses were used to explore the possible sources of heterogeneity. A probability value of $P < 0.05$ was considered significant.

Results

Description of studies

A total of 1,087 studies were retrieved, of which 659 studies remained after excluding duplicates. After screening the title and abstract of the remaining studies, 583 studies were excluded; among which 124 studies were case reports or reviews, 274 were not clinical trials and 185 were irrelevant with the efficacy of TCE for sarcopenia. By reading the full text, 62 studies were excluded, including 46 studies that were not RCTs or not real RCTs, 16 that were high risk of bias studies with Cochrane score < 4. Eventually, 13 studies (Gong et al., 2011; Jin et al., 2011; Liu et al., 2012; Liu et al., 2014; Liu et al., 2016; Wang et al., 2016; Zhao et al., 2016; Zhu et al., 2016; Zhu et al., 2017; Zhu G. et al., 2019; Zhu Y. et al., 2019; Fang et al., 2020; Zhou et al., 2020; Peng et al., 2022) with Cochrane RoB score ≥ 4 were included in the present study. The process of screening is presented in a PRISMA flow chart (**Figure 1**).

Study characteristics

The detailed characteristics of the included 13 studies were summarized in **Table 1**. All eligible RCTs were conducted in China and 2 (Zhu et al., 2016; Zhu et al., 2017) of them were published in the English language. The diagnosis criteria included the established definition of sarcopenia reported by the EWGSOP, Roubenof et al., and the AWGS. The sample size of the included studies ranged from 12 to 77, enrolling a total of 718 participants, including 356 patients in treatment groups and 362 patients serving as controls. Comparisons of TCE therapies versus no training were conducted in seven studies [(Gong et al., 2011; Jin et al., 2011; Liu et al., 2016; Wang et al., 2016; Zhao et al., 2016; Fang et al., 2020; Peng et al., 2022)], while TCE therapies versus health education were conducted in six studies

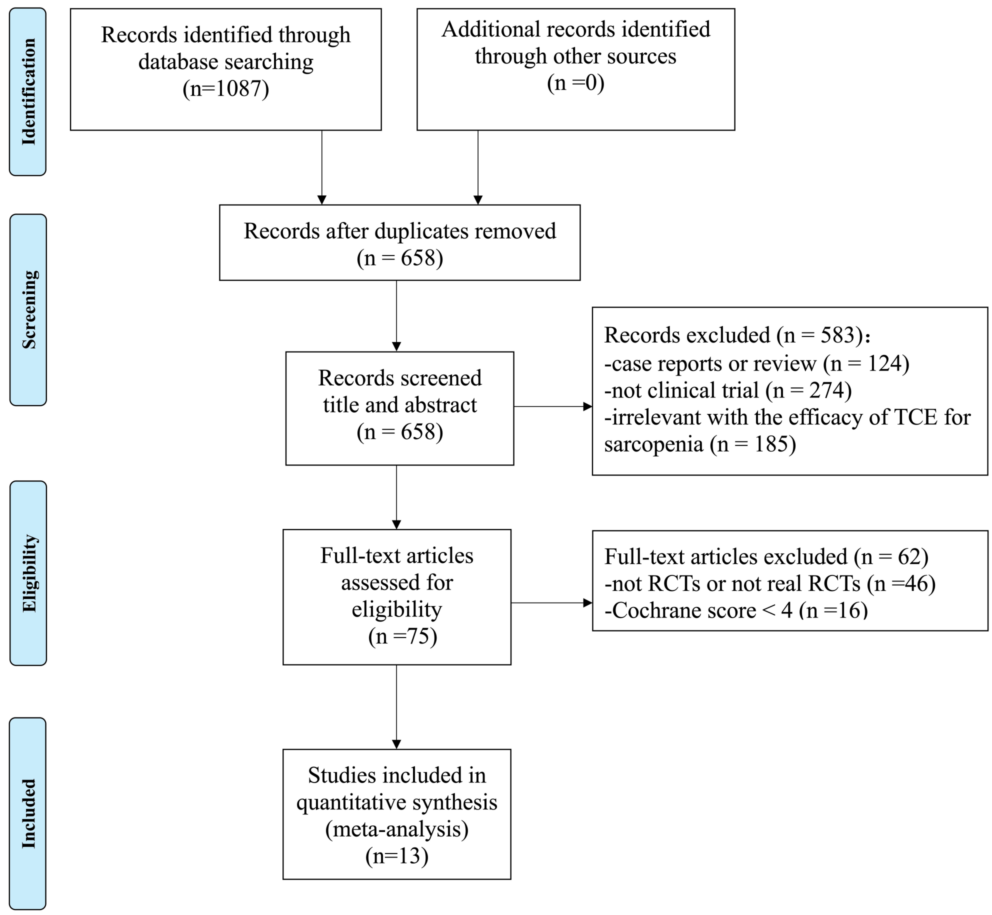

FIGURE 1
PRISMA 2009 flow diagram.

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TABLE 1 Characteristics of included studies.

No.	References	Final diagnosis	Eligibility criteria	Study designs	Sample and characteristics (male/female; mean age)		Interventions		Course of treatment	Follow up	Outcome index	Intergroup differences
					Trial	Control	Trial	Control				
1	Wang et al., 2016	Sarcopenia	Roubenoff's view	RCT	38(15/23) 66.79 ± 4.76	37(7/30) 65.59 ± 3.59	Yijinjing	No training	12w	NR	Grip Strength Test Chair Stand Test Squatting-To-Standing Test	1. $P > 0.05$ 2. $P < 0.05$ 3. $P > 0.05$
2	Jin et al., 2011	Sarcopenia	Roubenoff's view	RCT	26(14/22) 68.22 ± 4.09	35(7/28) 65.09 + 3.95	Yijinjing	No training	8w	NR	6-m gait speed Chair Stand Test Squatting-To-Standing Test	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$
3	Gong et al., 2011	Sarcopenia	Roubenoff's view	RCT	30(7/23) 66.4 ± 5.47	30(9/21) 67.0 ± 5.28	Yijinjing	No training	8w	NR	Peak Torque Total Work Average Power	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$
4	Zhao et al., 2016	Sarcopenia	AWGS	RCT	6 67.8 ± 3.8	6 66 ± 3.11	Yijinjing	No training	8 w	NR	Grip Strength Test 6-m gait speed	1. $P < 0.05$ 2. $P < 0.05$
5	Peng et al., 2022	Sarcopenia	AWGS	RCT	39 (17/23) 72.12 ± 6.47	38 (16/24) 71.85 ± 5.73	Yijinjing	No training	8 w	NR	Berg Balance Scale 6-m gait speed	1. $P < 0.05$ 2. $P < 0.05$
6	Liu et al., 2016	Sarcopenia	Roubenoff's view	RCT	31 (12/19) 67.86 ± 6.86	30 (12/18) 69.10 ± 6.69	Yijinjing	No training	8 w	NR	Peak Torque Total Work Average Power	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$
7	Fang et al., 2020	Sarcopenia	EWGSOP	RCT	18 (5/13) 82.8 ± 8.5	18 (7/11) 76.3 ± 9.9	Yijinjing	No training	6 m	NR	TUGT	1. $P < 0.05$
8	Liu et al., 2014	Sarcopenia	Roubenoff's view	RCT	31 (12/19) 67.86 ± 6.86	30 (12/18) 69.10 ± 6.69	Yijinjing	Health education	8 w	NR	Balance Test Adverse effect	1. $P < 0.05$ 2. $P > 0.05$
9	Liu et al., 2012	Sarcopenia	Roubenoff's view	RCT	31 (12/19) 67.86 ± 6.86	30 (12/18) 69.10 ± 6.69	Yijinjing	Health education	8 w	NR	Adverse effect	1. $P > 0.05$
10	Zhu et al., 2017	Sarcopenia	AWGS	RCT	32 (17/15) 65.6 ± 11.4	31 (15/16) 66.3 ± 10.8	Yijinjing	Health education	12 w	NR	Grip Strength Test Chair Stand Test Squatting-To-Standing Test	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$
11	Zhou et al., 2020	Sarcopenia	AWGS	RCT	20 (8/12) 72.67 ± 9.56	20 (9/11) 73.25 ± 8.54	Baduanjin	Health education	8 w	NR	Grip Strength Test Chair Stand Test Berg Balance Scale TUGT	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$ 4. $P < 0.05$

(Continued)

TABLE 1 (Continued)

No.	References	Final diagnosis	Eligibility criteria	Study designs	Sample and characteristics (male/female; mean age)		Interventions		Course of treatment	Follow up	Outcome index	Intergroup differences
					Trial	Control	Trial	Control				
12	Zhu Y. et al., 2019	Sarcopenia	AWGS	RCT	24 88.8 ± 3.7	27 87.5 ± 3.0	Tai Chi	Health education	8 w	NR	Grip Strength Test 6-m gait speed TUGT Chair Stand Test Berg Balance Scale	1. $P > 0.05$ 2. $P < 0.05$ 3. $P < 0.05$ 4. $P < 0.05$ 5. $P < 0.05$
13	Zhu et al., 2016	Sarcopenia	AWGS	RCT	30 (10/20) 64.0 ± 3.0	30 (13/17) 64.0 ± 4.0	Tai Chi	Health education	18m	NR	TUGT Chair Stand Test Berg Balance Scale	1. $P < 0.05$ 2. $P < 0.05$ 3. $P < 0.05$

RCT, randomized controlled trials; TUGT, timed-up-and-go test; NR, not report; w, week; m, month.

(Liu et al., 2012; Liu et al., 2014; Zhu et al., 2016; Zhu et al., 2017; Zhu G. et al., 2019; Zhu Y. et al., 2019; Zhou et al., 2020). As for interventions, Yijinjing was used in 10 studies (Gong et al., 2011; Jin et al., 2011; Liu et al., 2012; Liu et al., 2014; Liu et al., 2016; Wang et al., 2016; Zhao et al., 2016; Zhu et al., 2017; Fang et al., 2020; Peng et al., 2022), Baduanjin was used in 1 study (Zhou et al., 2020), and Tai chi was used in 2 studies (Zhu et al., 2016; Zhu Y. et al., 2019). The treatment duration ranged from 8 weeks to 18 months, and 8 weeks was used most widely. No study mentioned the length of follow-up. The outcomes index included the Grip strength test, chair stand test, squatting-to-standing test, 6-m gait speed, Time Up and Go Test, Isokinetic muscle strength test, balance function, and adverse effect.

Risk of bias

The assessment information of RoB is presented in **Table 2**. Of the 13 included studies, 1 met six Cochrane criteria (Fang et al., 2020), 1 met five (Liu et al., 2012), and 11 met four (Gong et al., 2011; Jin et al., 2011; Liu et al., 2014; Liu et al., 2016; Wang et al., 2016; Zhao et al., 2016; Zhu et al., 2016; Zhu et al., 2017; Zhu Y. et al., 2019; Zhou et al., 2020; Peng et al., 2022). All 14 included studies had random allocation using a random number table. Only 1 study (Fang et al., 2020) mentioned allocation concealment with sealed envelopes. 2 studies (Liu et al., 2012; Fang et al., 2020) mentioned the blinding of outcome assessment. All studies either had complete data or had dropouts

TABLE 2 Risk of bias.

References	7-item criteria							
	A	B	C	D	E	F	G	T
Fang et al., 2020	+	+	?	+	+	+	+	6
Gong et al., 2011	+	?	?	?	+	+	+	4
Jin et al., 2011	+	?	?	?	+	+	+	4
Liu et al., 2012	+	?	?	+	+	+	+	5
Liu et al., 2014	+	?	?	?	+	+	+	4
Liu et al., 2016	+	?	?	?	+	+	+	4
Peng et al., 2022	+	?	?	?	+	+	+	4
Wang et al., 2016	+	?	?	?	+	+	+	4
Zhao et al., 2016	+	?	?	?	+	+	+	4
Zhou et al., 2020	+	?	?	?	+	+	+	4
Zhu et al., 2017	+	?	?	?	+	+	+	4
Zhu et al., 2016	+	?	?	?	+	+	+	4
Zhu Y. et al., 2019	+	?	?	?	+	+	+	4

A to G, the 7-item criteria. A, adequate sequence generation; B, concealment of allocation; C, Blinding of participants and personnel; D, Blinding of out-come assessment; E, Incomplete out-come data; F, Selective reporting; G, Other bias; +, low risk of bias; –, high risk of bias; ?, unclear risk of bias.

TABLE 3 Summary of GRADE on evidences of outcomes of traditional Chinese exercise (TCE) for sarcopenia.

Certainty assessment							No of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trial	Control	Relative (95% CI)	Absolute (95% CI)		
Grip strength test												
5	randomized trials	serious[a]	not serious	not serious	not serious	none	120	121	–	MD **1.43 higher** (0.54 lower to 3.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Chair stand test												
5	randomized trials	serious[a]	not serious	not serious	not serious	none	158	154	–	MD **2.56 higher** (2.09 higher to 3.03 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Squatting-to-standing test												
4	randomized trials	serious[a]	not serious	not serious	not serious	none	138	134	–	MD **2.60 higher** (2.25 higher to 2.96 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
6-m gait speed												
3	randomized trials	serious[a]	not serious	not serious	not serious	none	81	79	–	MD **0.31 higher** (0.30 higher to 0.32 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Time up and go test												
3	randomized trials	serious[b]	serious[c]	not serious	not serious	none	68	68	–	MD **1.91 lower** (3.64 lower to 0.19 lower)	⊕⊕◯◯ LOW	CRITICAL
Peak torque of the extensors												
2	randomized trials	serious[a]	not serious	not serious	not serious	none	61	60	–	MD **10.12 higher** (0.90 higher to 19.36 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Total work of the extensors												
2	randomized trials	serious[a]	not serious	not serious	not serious	none	61	60	–	MD **113.42 higher** (13.95 higher to 212.89 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Peak torque of the flexors												
2	randomized trials	serious[a]	serious[c]	not serious	not serious	none	61	60	–	MD **5.57 higher** (0.60 higher to 10.55 higher)	⊕⊕◯◯ LOW	CRITICAL
Total work of the flexors												

(Continued)

TABLE 3 (Continued)

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients: Trial	No of patients: Control	Effect: Relative (95% CI)	Effect: Absolute (95% CI)	Certainty	Importance
2	randomized trials	serious[a]	serious[c]	not serious	not serious	none	61	60	–	MD **61.79 higher** (10.11 higher to 113.47 higher)	⊕⊕◯◯ LOW	CRITICAL
Average power of the flexors												
2	randomized trials	serious[a]	not serious	not serious	not serious	none	61	60	–	MD **3.25 higher** (0.32 higher to 6.19 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Berg balance scale												
4	randomized trials	serious[a]	serious[c]	not serious	not serious	none	107	106	–	MD **1.37 higher** (0.92 higher to 0.83 higher)	⊕⊕◯◯ LOW	CRITICAL

CI, Confidence interval; MD, Mean difference.
[a]Allocation concealment and blinding were unclear.
[b]Unclear blinding in all studies, allocation concealment in one study.
[c]The statistical test for heterogeneity shows a low *P*-value and the I^2 is large.
Bold values refers to the MD values.

with adequate explanations and appropriate methods to treat missing data. All studies had a low risk of other biases, which included funding bias, conflict of interest, and incomparable baseline characteristics between the groups. Funding bias means that the research was funded by relevant stakeholders, such as drug companies. In general, most of the 14 trials were deemed to have a relatively moderate risk.

Effectiveness

Grip strength test

The grip strength test was conducted in five studies (Wang et al., 2016; Zhao et al., 2016; Zhu et al., 2017; Zhu G. et al., 2019; Zhu Y. et al., 2019; Zhou et al., 2020). Pooled analysis of these five studies indicated that TCE had no significantly greater clinical effects in improving grip strength [MD = 1.43, 95% CI (−0.54, 3.41), $P = 0.15$, $I^2 = 2\%$; Certainty of evidence: Moderate; **Table 3**; **Figure 2**].

Isokinetic muscle strength test

Two studies (Gong et al., 2011; Liu et al., 2016) assessed the effect of TCE on the isokinetic muscle strength of participants, and the tests include the Peak torque of the extensors and flexors, the total work of the extensors and flexors, and average power of the extensors and flexors. Meta-analysis indicated that TCE significantly improve participants' performance in the peak torque of the extensors [MD = 10.12, 95% CI (0.90, 19.35), $P = 0.03$, $I^2 = 0\%$; Certainty of evidence: Moderate; **Figure 3A**], the total work of the extensors [MD = 113.42, 95% CI (13.95, 212.89), $P = 0.03$, $I^2 = 35\%$; Certainty of evidence: Moderate; **Figure 3B**], the average power of the extensors [MD = 4.99, 95% CI (−0.14, 10.12), $P = 0.17$, $I^2 = 48\%$; **Figure 3C**], the peak torque of the flexors [MD = 5.57, 95% CI (0.60, 10.55), $P = 0.03$, $I^2 = 47\%$; Certainty of evidence: Low; **Figure 3D**], the total work of the flexors [MD = 61.79, 95% CI (10.11, 113.47), $P = 0.02$, $I^2 = 42\%$; Certainty of evidence: Low; **Figure 3E**], and the average power of the flexors [MD = 3.25, 95% CI (0.32, 6.19), $P = 0.03$, $I^2 = 30\%$; Certainty of evidence: Moderate; **Figure 3F**].

Chair stand test

Meta-analysis of four studies (Jin et al., 2011; Wang et al., 2016; Zhu et al., 2017; Zhu G. et al., 2019; Zhou et al., 2020) showed a significant effect of TCE on chair stand test [MD = 2.45, 95% CI (1.88, 3.01), $P < 0.00001$, $I^2 = 38\%$; Certainty of evidence: Moderate; **Figure 4**].

Squatting-to-standing test

Meta-analysis of three studies (Jin et al., 2011; Wang et al., 2016; Zhu et al., 2017; Zhu G. et al., 2019) indicated that TCE could improve participants' performance in the squatting-to-standing test [MD = 2.58, 95% CI (2.12, 3.04), $P < 0.00001$, $I^2 = 0\%$; Certainty of evidence: Moderate; **Figure 5**].

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Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Wang bin 2016	50.56	17.11	38	48.43	12.41	37	8.5%	2.13 [−4.62, 8.88]
Zhao yongjun 2016	23.77	6.88	6	21.92	6.65	6	6.6%	1.85 [−5.81, 9.51]
Zhou supo 2020	19.54	8.23	20	18.41	5.68	20	20.2%	1.13 [−3.25, 5.51]
Zhu gaofeng 2017	54.5	11.38	32	48.13	10.67	31	13.1%	6.37 [0.92, 11.82]
Zhu yaqiong 2019	15.29	5.38	24	15.16	4.52	27	51.5%	0.13 [−2.62, 2.88]
Total (95% CI)			**120**			**121**	**100.0%**	**1.43 [−0.54, 3.41]**

Heterogeneity: Chi² = 4.09, df = 4 (P = 0.39); I² = 2%
Test for overall effect: Z = 1.43 (P = 0.15)

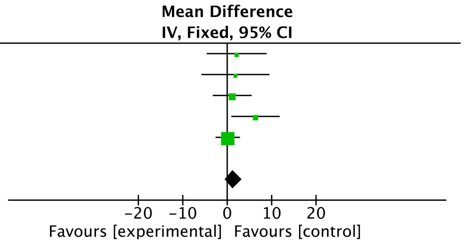

FIGURE 2
Forest plot of grip strength test.

6-m gait speed

Meta-analysis of three studies (Jin et al., 2011; Zhao et al., 2016; Peng et al., 2022) showed a significant effect of TCE in improving the 6-m gait speed of participants [MD = 0.31, 95% CI (0.30, 0.32), $P < 0.00001$, $I^2 = 13\%$; Certainty of evidence: Moderate; **Figure 6**].

Time up and go test

Pooled analysis of three studies (Zhu et al., 2016; Fang et al., 2020; Zhou et al., 2020) showed that TCE significantly improved the preference of participants in the Time Up and Go Test [MD = −1.91, 95% CI (−3.64, −0.19), $P = 0.03$, $I^2 = 81\%$; Certainty of evidence: Low; **Figure 7**].

Balance function

Meta-analysis of four studies (Zhu et al., 2016; Fang et al., 2020; Zhou et al., 2020; Peng et al., 2022) showed a significant effect of TCE in improving balance function according to Berg balance scale [SMD = 1.37, 95% CI (0.92, 1.83), $P < 0.00001$, $I^2 = 53\%$; Certainty of evidence: Low; **Figure 8**]. The Biodex system was used to assess the balance function in 1 study (Liu et al., 2014), and the results indicated that Yijinjing had significantly greater clinical effects in improving balance function with open eyes ($P < 0.05$).

Adverse events

Side effects of TCE were evaluated in two studies (Liu et al., 2012; Liu et al., 2014), but adverse events were not observed in these two studies.

Discussion

This study is the first meta-analysis assessing the efficacy of TCE for sarcopenia. Thirteen studies with 718 subjects were identified. The methodological quality of included RCTs was moderate totally. The quality of the evidence of primary outcomes was low to moderate according to the GRADE profiler. The main findings of the present study were that the TCE had a greater clinical effect in improving the severity of sarcopenia compared with no training or health education.

In this study, the primary outcomes of TCE for sarcopenia were muscle strength and physical function, since the decrease in muscle strength and physical function were the primary problem caused by sarcopenia (Hanach et al., 2019). The results of the pooled analysis indicated that TCE had no significantly greater clinical effects in improving grip strength, but had significantly greater clinical effects in physical function according to various outcomes including chair stand test, squatting-to-standing test, 6-m gait speed, Time Up and Go Test, peak torque of the extensors, total work of the extensors, peak torque of the flexors, total work of the flexors, the average power of the flexors, and balance function. In Western society, as many as 42% of individuals under 60 years of age have difficulties performing the activities of daily life, 15–30% report being unable to lift or carry 10 pounds or more, and more than 30% are confronted with physical disabilities (Zhou et al., 2019). Therefore, the positive results of TCE in improving physical function have great clinical significance.

Traditional Chinese exercise were formed by the concept of viewing the situation as a whole, the Five-Zang manifestation theory and meridian doctrine as theoretical guidance, and body movement as presentation. They are aimed to enhance fitness and prevent and treat diseases (Yang et al., 2021). TCE may be used to delay sarcopenia by regulating the synthesis and degradation of muscle-related proteins, replenishing, nutrients, promoting blood circulation, and eliminating inflammation (Colleluori and Villareal, 2021). The potential mechanism of TCE for enhancing muscle strength and physical function is related to the activation of key signaling pathways (Liu et al., 2021). After high-intensity interval static exercise, the PGC-1α/FNDC5/UCP1 signaling pathway was activated, PGC-1α was up-regulated, mitochondria increased, muscle fiber thickening was observed, and the skeletal muscle atrophy state was improved in aging rats (Liu et al., 2021). Compared with general exercise, TCE are more like gymnastic exercise consisting of various components such as endurance, resistance, balance, flexibility, breathing, and meditation, which emphasize the appropriate form and intensity of exercise, resulting in a better response (Villareal et al., 2017; Colleluori and Villareal, 2021).

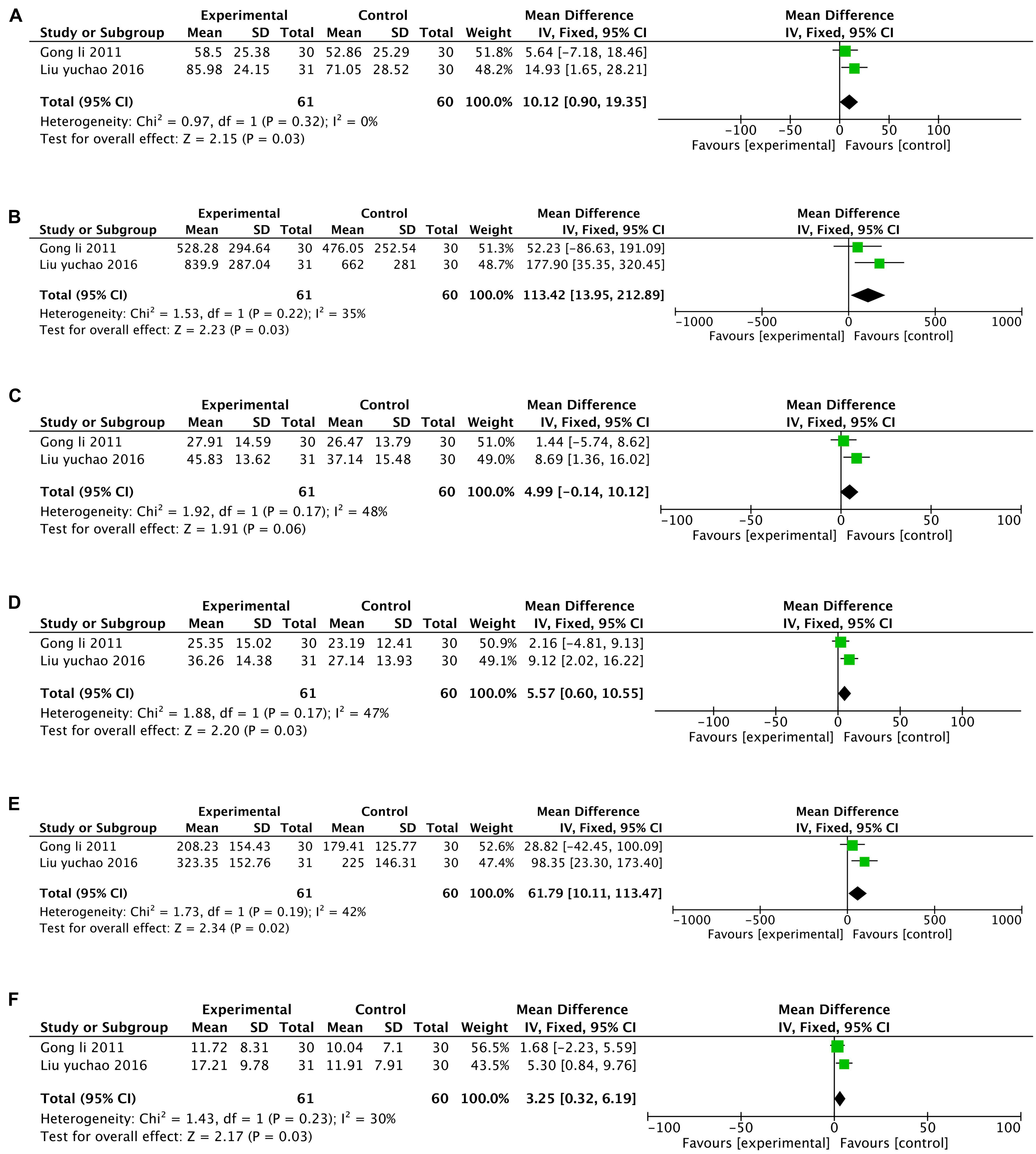

FIGURE 3
Forest plot of isokinetic muscle strength test: **(A)** the peak torque of the extensors; **(B)** the total work of the extensors; **(C)** the average power of the extensors; **(D)** the peak torque of the flexors; **(E)** the total work of the flexors; **(F)** the average power of the flexors.

The major strength of the current systematic review is that it has adhered to appropriate systematic review guidelines. However, there are also some limitations. First, some methodological limitations exist in the primary studies. Only one study (Fang et al., 2020) reported the concealment of allocation. Trials with adequate concealment had an average of 18% less "beneficial" effect than trials with inadequate or unclear concealment of allocation (Cumpston et al., 2019). Performance bias and detection bias can be effectively avoided by the use of blinding. However, some studies were unable to be blinded because participants have a high degree of understanding of TCE moves. Only two studies reported the blinding of outcome assessment. Second, formal pretrial sample size calculation was not conducted in most clinical trials and the majority

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Jin daopeng 2011	12.78	3.26	36	9.71	2.27	35	18.6%	3.07 [1.77, 4.37]
Wang bin 2016	10.67	2.35	38	9.15	2.15	37	30.4%	1.52 [0.50, 2.54]
Zhou supo 2020	8.53	2.66	20	6.12	3.53	20	8.4%	2.41 [0.47, 4.35]
Zhu gaofeng 2017	12.72	1.61	32	9.88	1.86	31	42.6%	2.84 [1.98, 3.70]
Total (95% CI)			**126**			**123**	**100.0%**	**2.45 [1.88, 3.01]**

Heterogeneity: $Chi^2 = 4.86, df = 3 (P = 0.18); I^2 = 38\%$
Test for overall effect: Z = 8.53 (P < 0.00001)

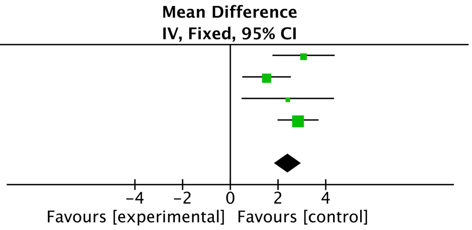

FIGURE 4
Forest plot of chair stand test.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Jin daopeng 2011	12.31	3.19	36	9.19	2.16	35	13.5%	3.12 [1.86, 4.38]
Wang bin 2016	11.3	2.64	38	9.3	1.98	37	19.4%	2.00 [0.95, 3.05]
Zhu gaofeng 2017	12.26	1.12	32	9.62	1.17	31	67.2%	2.64 [2.07, 3.21]
Total (95% CI)			**106**			**103**	**100.0%**	**2.58 [2.12, 3.04]**

Heterogeneity: $Chi^2 = 1.91, df = 2 (P = 0.39); I^2 = 0\%$
Test for overall effect: Z = 10.91 (P < 0.00001)

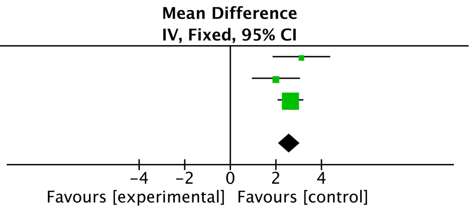

FIGURE 5
Forest plot of squatting-to-standing test.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Zhao yongjun 2016	0.91	0.2	6	0.76	0.17	6	0.3%	0.15 [−0.06, 0.36]
Peng tianzhong 2022	1.42	0.03	39	1.11	0.02	38	96.8%	0.31 [0.30, 0.32]
Jin daopeng 2011	1.54	0.12	36	1.24	0.16	35	2.9%	0.30 [0.23, 0.37]
Total (95% CI)			**81**			**79**	**100.0%**	**0.31 [0.30, 0.32]**

Heterogeneity: $Chi^2 = 2.30, df = 2 (P = 0.32); I^2 = 13\%$
Test for overall effect: Z = 54.21 (P < 0.00001)

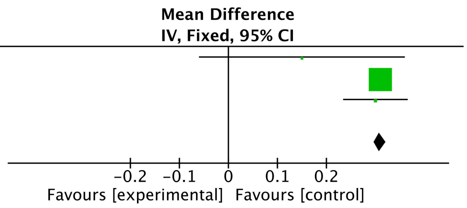

FIGURE 6
Forest plot of 6-m gait speed.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Fang lei 2020	12.6	2.8	18	15.4	4.1	18	24.5%	−2.80 [−5.09, −0.51]
Zhou supo 2020	10.23	2.34	20	13.05	2.38	20	32.9%	−2.82 [−4.28, −1.36]
Zhu yaqiong 2016	5.3	0.6	30	6	0.5	30	42.6%	−0.70 [−0.98, −0.42]
Total (95% CI)			**68**			**68**	**100.0%**	**−1.91 [−3.64, −0.19]**

Heterogeneity: $Tau^2 = 1.80; Chi^2 = 10.74, df = 2 (P = 0.005); I^2 = 81\%$
Test for overall effect: Z = 2.17 (P = 0.03)

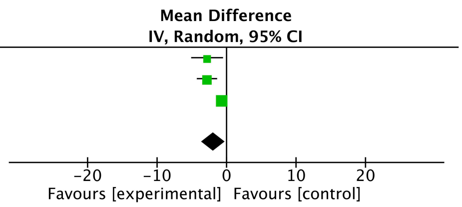

FIGURE 7
Forest plot of time up and go test.

of the included trials had relatively small sample sizes. Trials with insufficient statistical power may induce the high a risk of overestimating therapeutic efficacy (Kjaergard et al., 2001). Third, no study describes the duration of follow-up, making it difficult to assess the long-term efficacy of TCE treatment for sarcopenia. Fourth, we only searched for papers published in Chinese or English databases, thus the eligible studies published in other languages may be left out, which may limit the generalizability of the findings. Fifth, a statement published in September 2004 requiring that all clinical trials must be registered to be considered for publication (De Angelis et al., 2004). The transparency of clinical trials would be improved with registration, which would ultimately strengthen the validity and value of the scientific evidence base (Wang et al., 2019a). However, none of the included studies had been registered formally.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fang lei 2020	116.7	12.1	18	75.9	23	18	18.1%	2.17 [1.33, 3.01]
Peng tianzhong 2022	43.64	10.53	39	27.03	12.27	38	30.0%	1.44 [0.94, 1.94]
Zhou supo 2020	44.23	5.34	20	40.15	4.38	20	24.2%	0.82 [0.17, 1.47]
Zhu yaqiong 2016	55.4	0.8	30	53.7	1.7	30	27.7%	1.26 [0.71, 1.82]
Total (95% CI)			**107**			**106**	**100.0%**	**1.37 [0.92, 1.83]**

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.45$, df = 3 (P = 0.09); $I^2 = 53\%$
Test for overall effect: Z = 5.91 (P < 0.00001)

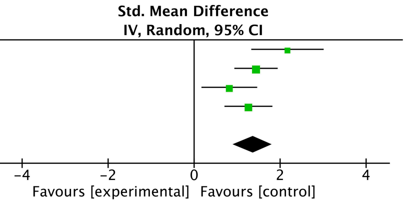

FIGURE 8
Forest plot of Berg Balance Scale.

The finding from the present systematic review revealed that TCE may be beneficial for sarcopenia patients. However, as the low-quality studies included cannot be reproduced, there is a need for conducting further rigorous RCTs on TCE for sarcopenia. Recommendations for further research are as follows: (1) the protocol of further clinical trials should be registered in the international clinical trials registry platform prospectively, and should follow the requirement of the Clinical Trial Data Sharing Statement (Taichman et al., 2016) by the International Committee of Medical Journal Editors; (2) the quality of study designs including randomization, allocation concealment, and blinding should be improved. CONSORT statement (Moher et al., 2009) should be applied throughout the whole process of the study including trial design, reporting, and publication; (3) international cooperation should be conducted in further studies to complete more qualified studies and ensure generalizability of research findings; (4) greater consistency in outcome measures should be warranted; (5) adequate sample size plays an important positive role in improving the methodologic quality, intervention effects, and publication bias (Kjaergard et al., 2001; Moher et al., 2009). Thus, it is necessary to conduct formal pretrial sample size calculations in further studies.

The significance of the present systematic review possibly lies in the following aspects: (1) to reveal current problems in the treatment of sarcopenia and identify areas worthy of improvement and development in the future (Chan et al., 2012). Several studies have reported the effectiveness of TCE in the treatment of sarcopenia, however, no previous study has evaluated the quality of this evidence. (3) to report a specific area of Traditional Chinese Medicine in the English language as these experiences are not readily accessible to western clinicians because of language barriers (Wang et al., 2019b).

Conclusion

The present finding indicated that TCE provided statistically significant benefits for sarcopenia. Therefore, the findings of the present systematic review, at least to a certain extent, provided supporting evidence for the routine use of TCE for sarcopenia.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

KN, Y-LL, X-ZZ, and QQ performed conceptualization. KN and Y-LL contributed to the formal analysis, visualization, methodology, and writing the original draft. KN, Y-LL, FY, and YW performed data curation. KN, FY, YW, X-ZZ, and QQ performed writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Tuina for peripherally-induced neuropathic pain: A review of analgesic mechanism

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Peripherally-induced neuropathic pain (pNP) is a kind of NP that is common, frequent, and difficult to treat. Tuina, also known as massage and manual therapy, has been used to treat pain in China for thousands of years. It has been clinically proven to be effective in the treatment of pNP caused by cervical spondylosis, lumbar disc herniation, etc. However, its analgesic mechanism is still not clear and has been the focus of research. In this review, we summarize the existing research progress, so as to provide guidance for clinical and basic studies. The analgesic mechanism of tuina is mainly manifested in suppressing peripheral inflammation by regulating the TLR4 pathway and miRNA, modulating ion channels (such as P2X3 and piezo), inhibiting the activation of glial cells, and adjusting the brain functional alterations. Overall, tuina has an analgesic effect by acting on different levels of targets, and it is an effective therapy for the treatment of pNP. It is necessary to continue to study the mechanism of tuina analgesia.

KEYWORDS

neuropathic pain, tuina, peripheral nerve injury, inflammation, glial cells, brain function

1. Introduction

Neuropathic pain (NP) is a pain directly caused by injury or disease of the somatosensory nervous system (Jensen et al., 2011; Colloca et al., 2017), which can be caused by injury of the nerve, spinal cord, or brain, as well as diabetes, herpes zoster, etc. (Alles and Smith, 2018). According to the injury or anatomical location, NP can be divided into peripherally-induced neuropathic pain (pNP) and centrally-induced neuropathic pain. pNP is the most common with a prevalence rate of 6.9∼10% (Finnerup et al., 2015). A recent survey shows that the prevalence rate in China is 29.53∼31.54% (Yongjun et al., 2020). pNP is a risk factor leading to sleep disorders, anxiety, depression, and suicide, and seriously affects the quality of human life (Petrosky et al., 2018). The treatment of pNP depends largely on pharmacology, but some studies have shown that medications are insufficiently effective and not innocuous

(Finnerup et al., 2015, 2018; Meacham et al., 2017), while traditional Chinese medicine (TCM) therapies are effective in relieving pain with little side effects.

As one of the characteristic therapies of TCM, tuina has been used in China for thousands of years to treat pain. Under the guidance of TCM and western medicine anatomy and pathology, tuina acts on the body surface by various manipulations, such as rubbing, kneading, and pressing, to regulate the physiological and pathological state, so as to treat diseases (Wang et al., 2008). A survey in China showed that 66.8% of patients with chronic pain chose tuina or cupping (Yongjun et al., 2020). Pain is an advantageous symptom for tuina treatment, especially pNP caused by cervical spondylosis radiculopathy (CSR) (Cao et al., 2021; Aboagye et al., 2022), lumbar disc herniation (LDH) (Mo et al., 2019; Zhou et al., 2022), etc. A meta analysis showed that tuina and acupuncture were more effective than traction and TCM in the treatment of LDH (Mo et al., 2019). Through a clinical trial, Cao et al. (2021) showed that both three-dimensional balanced tuina therapy and traditional tuina can effectively relieve pain in patients with CSR. Based on the clinical advantages of tuina analgesia, its mechanism is always the focus of research, and some progress has been made in recent years. Hence, this review aims to summarize the existing research progress on the analgesic mechanism of tuina.

2. Tuina exerts analgesic effects by suppressing peripheral inflammation

Inflammation is the key to peripheral and central sensitization and plays an important role in the initiation and maintenance of pNP (Ellis and Bennett, 2013). Peripheral nerve injury (PNI) leads to a local inflammatory response, activates related inflammatory pathways in mast cells and macrophages to release inflammatory mediators, which enhance the sensitivity of nociceptive receptors. Some studies have shown that tuina can reduce the levels of inflammatory factors in blood and dorsal root ganglion (DRG), such as tumor necrosis factor-α (TNF-α) and interleukins (IL-6 and IL-1β) (Tao et al., 2017; Yang et al., 2020; Yao et al., 2022a), an effect that is mainly achieved by regulating related pathways.

Toll-like receptor 4 (TLR4) pathway, one of the key inflammatory signal transduction pathways, exerts an important role in mediating pNP (Liu et al., 2012; Li et al., 2019). After nerve injury, TLR4 pathway is activated in sensory neurons, which induces the expression of proinflammatory cytokines through two pathways, one of which is the MyD88 pathway (Liu et al., 2012). TLR4 binds to MyD88 and activates interleukin 1 receptor kinase (IRAK1), which binds to TRAF6 to form a receptor complex, and then activates mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways. Rodent studies have shown that activation of TLR4 pathway in DRG or spinal dorsal horn leads to hyperalgesia in NP models (Agalave et al., 2014; Lin et al., 2015). Spinal nerve ligation (SNL) is a model for simulating spinal nerve injury, which shows typical pNP manifestations, such as spontaneous pain, thermal hyperalgesia, mechanical hyperalgesia, etc. (Seto et al., 2021). A study showed that 14 days after modeling, the mRNA expression of TLR4, IRAK1, and TRAF6 were significantly increased in SNL rats, and the expression levels of TNF-α and IL-6 also increased. After 14 days of tuina intervention, including pointing, stroking, and kneading methods, the levels of TLR4, IRAK1, TRAF6, TNF-α, and IL-6 decreased (Wang et al., 2020), which suggests that tuina may reduce the expression of inflammatory factors by inhibiting TLR4 pathways. He et al. (2021) also found the increased levels of TLR4, MyD88, NF-κB p65, IL-6, IL-1β, and TNF-α in LDH rats. And after giving the intervention of pressing, kneading, and pushing manipulations, these levels were decreased. Furthermore, the levels decreased after injection of TLR4 inhibitors in the model group and increased after administration of TLR4 activator in the tuina group. Wang et al. (2022), using RNA-Seq, found that one-time tuina intervention could regulate TLR and NF-κB signaling pathways in minor chronic constriction injury (CCI) rats. It is suggested that tuina can reduce the expression of inflammatory factors by inhibiting the activation of TLR4/NF-κB signaling pathways, thereby achieving anti-inflammatory and analgesic effects. However, the specific mechanism of how tuina regulates these pathways remains unclear.

MicroRNAs (miRNAs) are the master switch linking nerve injury, pain, and inflammation, which play an important regulatory role in pain signal transduction (Sakai and Suzuki, 2014; Sommer et al., 2018; Gada et al., 2021). In recent years, an increasing number of studies found that miRNAs are involved in the occurrence and development of NP after nerve injury. Peng et al. (2017) found that miR-183 can control more than 80% of NP regulatory genes and regulate mechanical sensitivity and mechanical pain abnormalities, proving that miRNA can inhibit NP transduction. Sakai et al. (2017) found that the expression of all cluster members of miR-17-92 in DRG was upregulated after nerve injury. In a bilateral CCI rat model, the expression of miR-341 in DRG was upregulated, while miR-203, miR-181a-1*, and miR-541* were downregulated (Li et al., 2013). MiRNAs mediate their role in NP through signal transduction pathways, such as TLR4, NF-κB, NLRP3, etc. (Gada et al., 2021). Jing et al. (2022) found that upregulating the expression of miR-146a in rats with LDH could reduce the activity of the TLR4 signaling pathway, thus relieving pain. Through high-throughput sequencing technology, Yao et al. (2022b) found that there were 19 expressed miRNAs that were related to inflammation in chronic compression of dorsal root ganglia (CCD) rats treated with pressing and kneading "Weizhong" (BL40) compared to CCD model rats. Furthermore, miR-547-3p may be a key target of tuina analgesia, since its overexpression can reduce the expression of Map4k4, and then inhibit the expression of IκBα, p-IκBα, p65, and p-p65 in the NF-κB signaling pathway, suggesting that tuina can exert an analgesic effect by targeting Map4k4 *via* miR-547-3p.

3. Tuina exerts analgesic effects by modulating the peripheral ion channels

The transmission and processing of pain signals heavily depend on the activity of ion channels. In nerve injury, dysregulation of ion channel expression leads to increased neuronal excitability, which is the basis of pNP (Waxman and Zamponi, 2014). Ion channels include voltage-gated, ligand-gated, and mechanosensitive ion channels (MSC). P2 purinergic receptors, divided into P2X ion ligand-gated receptor and P2Y metabolic G protein-coupled receptor, are a class of ligand-gated receptors activated by extracellular ATP and its metabolites. P2X3 receptor is selectively expressed in primary sensory neurons and is involved in pain signal transduction. It was found that P2X3 receptor expression was upregulated in DRG neurons after nerve injury (Krajewski, 2020). It was found that tuina can inhibit the expression of P2X3 receptor in DRG of CCI model rats (Chen et al., 2022) and LDH model rats (Lin et al., 2017), and it can also reduce the amplitude of inward current in P2X3 channel (Chen et al., 2022), which proved that tuina can downregulate the expression of P2X3 as well as the degree of channal opening in DRG. MSC are ion channels that convert the mechanical stimulation sensed by the cell membrane into bioelectric or biochemical signals. Piezo, including Piezo1 and Piezo2, plays an important role in the sensation and transmission of mechanical stimuli such as pain and touch (Kim et al., 2012). Tuina that included clockwise pressing and rubbing can increase the expression of Piezo2 and decrease the expression of Piezo1 in CCD rats (Song et al., 2018). As a mechanical stimulation, tuina acts on the skin through manipulation, so tuina may play a role by activating MSC.

4. Tuina exerts analgesic effects by inhibiting the activation of glial cells in spinal cord

Glial cells, including microglia, astrocytes, and oligodendrocytes, play a critical role in the production and maintenance of pNP (Ji et al., 2014; Inoue and Tsuda, 2018). After nerve injury, glial cells are activated and the activated state is mainly manifested by glial reaction, upregulation of glial receptor, proliferation, etc. (Ji et al., 2013). Glial reaction refers to the upregulation of markers and morphological changes of glial cells. Wu et al. (2022) found the expression of microglia and astrocyte gene in the spinal dorsal horn of the CCI model rats was significantly higher than that of control rats, and the expression of astrocyte marker GFAP, microglia marker Iba-1, and M1 receptor CD68 increased significantly. In contrast, the expression of activated glial cell genes as well as the glial markers and receptors decreased significantly after tuina intervention. Morphological changes are the most direct manifestation of microglial activation (Nair et al., 2019). Partially activated or inactivated microglia are branched. After activation, the cytosol becomes larger, processes are shortened, and become round or rod-shaped. Mo et al. (2020) observed that the microglia in rats with sciatic nerve injury had short processes and enlarged cytoplasm, whereas the microglia after tuina treatment *via* three-method (pressing, plucking, and kneading manipulations) and three-acupoint (BL37, GB34, and BL57) treatment had longer protrusions and smaller cytoplasm, demonstrating that tuina could inhibit the activation of microglia.

In addition, activation of intracellular signaling pathways, such as MAPK, are also a manifestation of glial cell activation (Ji et al., 2013). MAPK, including extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK), can transduce extracellular stimulation into intracellular transcriptional and post-translational effects. p38 plays a key role in microglia signal transduction of pNP and is a valuable target for the treatment of pNP (Ji and Suter, 2007). Activation of p38 was found in spinal cord microglia of SNL (Ji and Suter, 2007), spinal cord injury (Hains and Waxman, 2006), and ventral root lesion (Xu et al., 2007). In a CCI model, Wei et al. (2018) found that the expression of phosphorylated p38 and IL-1β in the spinal cord increased, whereas these same factors were decreased after tuina intervention, suggesting that tuina may inhibit the activation of microglia by regulating the MAPK pathway.

5. Tuina exerts analgesic effects by adjusting the functional alterations in brain

The brain, the main site of pain production, is critical in the development and relief of pNP. After the nociceptive stimulation passes through the periphery and spinal cord, it will be further transmitted to the brainstem network structure, thalamic and hypothalamic nucleus, and then projected to the cerebral cortex and limbic system to produce pain sensation and pain response (Meacham et al., 2017). Pain is a complex multi-channel subjective experience, including sensory and emotion. After the nociceptive information is uploaded to the brain, it will be divided into several parallel pathways, in which the somatosensory cortex is involved in the sensory aspect of pain processing, and anterior cingulate cortex (ACC) is involved in the emotional aspect of pain processing (Weizman et al., 2018).

It was found that after tuina intervention, the amplitude of low-frequency fluctuation (ALFF) value of the somatosensory cortex increased, indicating that tuina can participate in pain management by activating the somatosensory cortex (Xing et al., 2021).

When the body receives a painful stimulus, a number of cortical and subcortical brain areas are activated together, and these brain areas are linked together to form a brain network (Legrain et al., 2011). It has been shown that some brain regions of the pain-related network are involved in the generation and transmission of pain (Giesecke et al., 2004; Shi et al., 2021). For example, the marginal and striatal structures, including anterior cingulate cortex (ACC), superior frontal gyrus, medial thalamus, and anterior insular cortex, show enhanced responses in patients with pNP caused by diabetic peripheral nerve deformation (Tseng et al., 2013). The primary sensory cortex, cingulate gyrus, amygdala, thalamus, and insula are activated in patients with chronic low back pain (cLBP) (Sharma et al., 2011). Yuan et al. (2015) found that spinal manipulation can effectively reduce the VAS score of patients with LDH. Furthermore, brain functional magnetic resonance imaging showed that the brain functional activity was mainly inhibited, and the inhibitory area was mainly located in the right prefrontal lobe and cerebellum, indicating that tuina may relieve pain by inhibiting the functional activities of the frontal lobe and cerebellum. Tan et al. (2020) found that the brain activity in the right parahippocampal gyrus, the right dorsolateral prefrontal cortex, and the left precuneus was significantly increased after one time of spinal manipulative treatment, and the brain activity in the posterior cingulate cortex (PCC) and right inferior frontal gyrus was significantly increased after six times of treatment.

Cerebral functional alterations depend on changes in neurotransmitter levels (Tabassum et al., 2020). Huo et al., 2022a,b found that after one time of tuina treatment in patients with cLBP, the level of *N*-acetylaspartic acid (NAA) in the PCC increased and Glutamate complex (Glx) decreased, and the level of Glx3 in the PCC decreased after six times of tuina treatment. Existing studies have shown also decreased NAA levels in multiple brain regions in patients with pNP. For example, NAA levels were reduced in the ACC of cLBP patients (Zhao et al., 2017), and also decreased in the PCC of patients with trigeminal neuralgia (Fayed et al., 2014). NAA is the main marker of neuronal integrity, the decrease of NAA levels suggests neuronal dysfunction or injury (Moffett et al., 2013; Zhang et al., 2013). Tuina can increase the level of NAA, indicating that tuina participates in analgesia by enhancing neuronal repair. Glx, one of the main excitatory neurotransmitters in mammalian nervous system, plays an important role in neuronal regulation. High concentrations of Glx can induce neuronal hyperexcitability and sustained activation, and it can also increase oxidative stress, causing neuronal injury and death (Zhang et al., 2013). Tuina can reduce the level of Glx, indicating that it can exert analgesic effects by reducing neuronal hyperexcitability and reduce oxidative stress. Glx is also involved in mood regulation. A study has shown that tuina can relieve the negative emotions in pain patients (Xu et al., 2022), suggesting that tuina may reduce pain sensitivity by improving negative emotions. Zhang et al. (2014) found that the levels of gama amino-butyrlc-acid (GABA) and GABAAR in the periaqueductal gray and rostral ventromedial medulla of CCI rats increased after pressing and kneading the "Huantiao" (GB30). GABA can inhibit the transmission of nociceptive information. After nerve injury, the

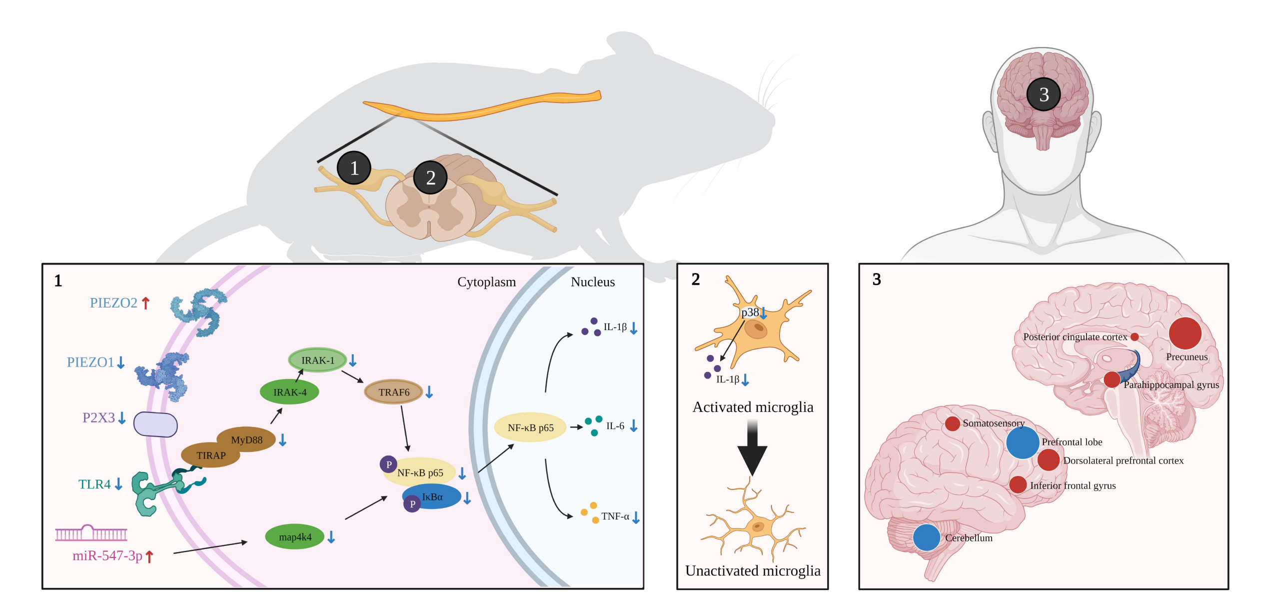

FIGURE 1
The analgesic mechanism of tuina [images with permission created with BioRender. https://biorender.com (2022)].

activity of GABA is decreased, therefore resulting in an inability to exert GABA's effect of central inhibition, thus inducing abnormal pain and hyperalgesia (Gwak and Hulsebosch, 2011). So tuina can upregulate the expression of GABA and GABAAR, and then reduce the transmission of harmful information.

6. Conclusion

Tuina treats pNP by acting on different levels of targets (**Figure 1**). At the peripheral level, tuina can inhibit the expression of inflammatory factors, such as IL-1β, IL-6, and TNF-α by inhibiting the TLR4/NF-κB pathways in DRG, which may be achieved by upregulating miR-547-3p. Tuina can also modulate the ligand-gated and mechanosensitive ion channels, as evidenced by the fact that it can downregulate the expression of the P2X3 receptor and Piezo1, and upregulate the expression of Piezo2. At the central level, tuina can inhibit the activation of microglia and astrocytes by changing the level of markers and cell morphology, as well as the activation of MAPK pathway in microglia. In addition, tuina can adjust the functional alterations in brain, mainly by inhibiting the activity of the prefrontal lobe and cerebellum, enhancing the activity of the parahippocampal gyrus, dorsolateral prefrontal cortex, precuneus, PCC, etc., and regulating the expression of neurotransmitters, such as NAA, Glx3, and GABA.

Although some progress has been made on elucidating the mechanism of tuina analgesia, there are still some limitations. First, lack of in-depth research on each part. For example, it has been showed that tuina can inhibit the activation of glial cells and change the cerebral function, but the specific pathway or target is not clear enough. Next, lack of connection among the parts. Pain is a complex and multi-channel subjective experience, which requires a series of reactions from the afferent of nociceptive stimulation to the generation of pain. Furthermore, a series of reactions is also required from the action of tuina on the skin to the relief of pain, so the analgesic mechanism should be a dynamic process. Most of the existing studies are independent of each part, and there is a lack of connection between each part. What's more, there is a lack of comprehensive research, such as an immediate analgesic mechanism. Clinical experience shows that the pain can be obviously be relieved and last for a period of time after one tuina treatment, but the mechanism is not clear.

In conclusion, tuina, as a characteristic TCM therapy, can effectively treat pNP, and its analgesic mechanism includes many parts. Elucidating the analgesic mechanism of tuina is not only conductive to the treatment of pain, but may also lay a foundation for the development of tuina as well as TCM. Therefore, it is extremely important to continue studying the analgesic mechanism of tuina.

Author contributions

Z-FL drafted the manuscript. H-RW drew the picture. Y-QZ and YJ collected the literature. Z-FL, T-YY, and X-YW put forward the idea. All authors contributed to the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effects of acupuncture on cartilage p38MAPK and mitochondrial pathways in animal model of knee osteoarthritis: A systematic evaluation and meta-analysis

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Background: Most previous studies on acupuncture in the treatment of knee osteoarthritis (KOA) have focused on improving functional efficacy and safety, while related mechanisms have not been systematically reviewed. Acupuncture modulates cytokines to attenuate cartilage extracellular matrix degradation and apoptosis, key to the pathogenesis of KOA, but the mechanisms are complex.

Objectives: The purpose of this study is to assess the efficacy of acupuncture quantitatively and summarily in animal studies of KOA.

Methods: Nine databases including PubMed, Embase, Web of Science (including Medline), Cochrane library, Scopus, CNKI, Wan Fang, and VIP were searched to retrieve animal studies on acupuncture interventions in KOA published since the inception of the journal. Relevant literature was screened, and information extracted. Meta-analysis was performed using Revman 5.4 and Stata 17.0 software.

Results: The 35 included studies involved 247 animals, half of which were in acupuncture groups and half in model groups. The mean quality level was 6.7, indicating moderate quality. Meta-analysis showed that acupuncture had the following significant effects on cytokine levels in p38MAPK and mitochondrial pathways: (1) p38MAPK pathway: It significantly inhibits p38MAPK, interleukin-1beta (IL-1β), tumor necrosis factor alpha (TNF-α), phosphorylated (p)-p38MAPK, matrix metalloproteinase-13 (MMP-13), MMP-1, a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMST-5) expression, and significantly increased the expression of collagen II and aggrecan. (2) mitochondrial pathway: It significantly inhibited the expression of Bcl-2-associated X protein (Bax), cysteine protease-3 (caspase-3), caspase-9, and Cytochrome-c (Cyt-c). And significantly increased the expression of B cell lymphocytoma-2 (Bcl-2). In addition, acupuncture significantly reduced chondrocyte apoptosis, Mankin's score (a measure of cartilage damage), and improved cartilage morphometric characteristics.

Conclusion: Acupuncture may inhibit cytokine expression in the p38MAPK pathway to attenuate cartilage extracellular matrix degradation, regulate cytokines in the mitochondrial pathway to inhibit chondrocyte apoptosis, and improve cartilage tissue-related phenotypes to delay cartilage degeneration. These findings provide possible explanations for the therapeutic mechanisms and clinical benefits of acupuncture for KOA.

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KEYWORDS

knee osteoarthritis, acupuncture, animal models, p38MAPK pathways, mitochondrial pathways, cytokines, meta-analysis

1. Introduction

Knee osteoarthritis (KOA) has become a socially prevalent and disabling disease, with severe pain and impaired function seriously affecting quality of life and imposing a significant economic burden on many developed countries (Bedenbaugh et al., 2021). The pathology of KOA is characterized by apoptosis of chondrocytes and progressive destruction of articular cartilage, restoring the integrity and function of articular cartilage plays a key role in preventing or delaying the progression of KOA (Goldring and Berenbaum, 2015). However, the lack of nerves, blood or lymphatic vessels in articular cartilage limits the scope for repair after injury (Thomas et al., 2021). Current treatments in the field of KOA cartilage repair are complex, cause significant autologous damage, and may only reach the periosteal rather than cartilage level (Pallante et al., 2009; Hunziker et al., 2015), therefore other non-pharmacological therapies with alternative and preventive effects and fewer side effects are needed.

Acupuncture, a kind of traditional Chinese non-pharmaceutical treatment, has therapeutic and preventive effects on KOA (Corbett et al., 2013). Acupuncture was suggested for the treatment of KOA as early as 2019 by the International Guidelines for the Non-Surgical Management of Osteoarthritis (OA) by the OA Research Society (Bannuru et al., 2019) and the American College of Rheumatology (ACR)/Arthritis Foundation(AF) management guidelines (Kolasinski et al., 2020). In the acute phase of KOA, acupuncture offers quick alleviation of pain and dysfunction, according to two randomized controlled trials published in *Pain* and *Arthritis & Rheumatology* (Lin et al., 2020; Tu et al., 2021). This sensational finding provides a powerful response to a study (Hinman et al., 2014) published in *JAMA* that concluded that acupuncture is ineffective in the treatment of arthritis, and has important implications for the future of acupuncture clinical practice internationally, as well as for the inclusion of acupuncture in mainstream medical clinical treatment guidelines and health insurance. At the same time, a growing body of evidence (Jie et al., 2021; Qin et al., 2022) suggests that acupuncture can repair cartilage microarchitecture and delay or even reverse cartilage defects by altering KOA phenotypic changes caused by the inflammatory environment, slowing cartilage matrix degradation, and inhibiting chondrocyte apoptosis.

The therapeutic mechanism of acupuncture is complex and in KOA may involve modulating the relevant pathway signals in cartilage to inhibit disease progression. In KOA, inflammatory factors mediate chondrocyte differentiation by signaling to various transcription factors through intracellular signaling pathways. These induce a change from chondrocyte to fibroblast phenotype, prompting chondrocyte apoptosis n the joint and fibrosis of the surrounding tissue (Xie et al., 2021). The pathways include mitogen-activated protein kinase (MAPK) and mitochondrial signaling pathways (Brown et al., 2008; Sun et al., 2019). MAPK plays an important role in regulating various cellular processes such as apoptosis, survival, proliferation, and migration. For example, isoform p38MAPK has been widely used as a target to inhibit cytokines for the treatment of inflammatory diseases (Schindler et al., 2007). p38MAPK signaling (Zhou et al., 2015) is essential for the expression and activity of MMP and ADAMTS, which are protein hydrolases that contribute to matrix degradation and cartilage destruction. In the mitochondrial pathway, B cell lymphocytoma-2 (Bcl-2) and Bcl-2-associated X protein (Bax) are the main factors regulating apoptosis, and apoptosis-associated protein cysteine protease 3 (Caspase-3) is the final apoptosis execution molecule (Zhang et al., 2014).

Acupuncture can delay KOA progression by modulating p38MAPK and the mitochondrial signaling pathway (Liao et al., 2016; Liu J. W. et al., 2021), but the mechanism by which it effects cartilage repair in KOA has not been systematically studied. Systematic review methods facilitate evidence-based clinical decision making (Ritskes-Hoitinga et al., 2014), indicate gaps in research, reduce unnecessary duplication of studies, and support the "replacement, refinement, and reduction of animals" principle in animal research (Murphy and Murphy, 2010). Therefore, the purpose of this review is to systematically review the research on the effect of acupuncture on cartilage repair signaling pathways in animal models of KOA, to quantitatively assess pooled effects, and to provide indicators for future clinical studies.

2. Materials and methods

2.1. Search strategy

In conducting this systematic review, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review was conducted in accordance with our previously published protocol (INPLASY202290125).[1] Two authors (Ye, JN and Su, CG) independently searched the databases of Pubmed, Embase, Web of Science (including Medline), Cochrane library, Scopus, CNKI, Wan Fang, and VIP. No date constraints were imposed on the search, which was completed in September 2022. Take PubMed for example, the specific search formula is: (*Acupuncture* [Title/Abstract] OR *Osteoarthritis, Knee* [Title/Abstract] OR *Models, Animal* [Title/Abstract]). Each search term was used individually or in combination, and the specific search strategy is described in **Supplementary material**. In addition, the reference lists of studies included in the review were manually screened for further studies.

2.2. Eligibility criteria

For this study, we devised the following inclusion and exclusion criteria in full line with the PICOS (Participation, Intervention, Comparison, Outcome, Type of Study) principles:

Participant type (P): all research on animals with KOA were considered, regardless of species, gender, month of age, or modeling approach, but the indicator measured must be derived from cartilage tissue. Non-animal and non-chondrogenic level KOA studies were omitted.

Intervention type (I): Acupuncture was used to treat KOA in the intervention group, with no limits on method, time per treatment, treatment course, or acupuncture locations. If several electro-acupuncture frequencies or intervention sessions were available, to better fit the characteristics of the function of acupuncture, the highest frequency or longest intervention duration was chosen for analysis. Excluded were studies in which non-acupuncture or acupuncture was not the principal intervention.

Comparison type (C): The model group was modeled only without any interventions.

Outcome type (O): (1) Main result markers in cartilage tissue: cytokines of the p38MAPK pathways (including p38MAPK, IL-1β, TNF-α, p-p38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, aggrecan) and mitochondrial pathways (including Bax mRNA, Bcl-2 mRNA,Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, caspase-3, Caspase-9, Cyt-c); (2) secondary outcome indicators: chondrocyte apoptosis rate, Mankin's score measuring the extent of cartilage damage and cartilage morphometric score, including the cartilage and subchondral volume ratio/total volume ratio (BV/TV), average thickness of trabecular column structures (Tb.Th), average number of trabeculae per unit length (Tb.N), and average distance between trabeculae (column structures) (Tb.Sp).

Study type (s): All randomized controlled trials that looked at the cartilage component of acupuncture interventions in KOA animal models were considered. There were no clinical case reports, reviews, or conferences. No language limits were applied to ensure that the most extensive research could be provided.

2.3. Data extraction

Two authors independently extracted data from articles meeting the inclusion criteria. The following were extracted: first author's name and year of publication, animal species, animal sex and number of animals in each group, modeling methods, interventions, duration of treatment, outcome indicators and sample tissue. When primary data were missing from the included literature or were only presented graphically, attempts were made to contact the authors to obtain the original data. If the authors did not respond, the values in the graphs were extracted using GetData Graph Digitizer 2.26 software (Wang R. et al., 2021).

2.4. Quality assessment

Two researchers assessed the methodological quality of each study using a 10-item checklist modified from the Collaborative Methods for the Analysis and Review of Experimental Research Animal Data (CAMARADES) checklist (Lee and Kim, 2022). These included: sample size calculations, statements describing temperature and humidity control, randomization of groups,

1 https://inplasy.com/inplasy-2022-9-0125/

use of reasonable KOA models, assessment of modeling success, use of anesthetics with no apparent specificity, blinding of results, compliance with animal ethics regulations, published in a peer-reviewed journal or have passed peer review, and declaration of potential conflicts of interest. A sum of quality scores for each article was calculated out of a maximum score of 10. Disagreements between the researchers were resolved by discussion with a third author.

2.5. Statistical analysis

Meta-analysis was performed using Cochrane Collaboration Network RevMan 5.4 and Stata 17.0 software. The data of this study were continuous variables. Standardized mean difference (SMD) was used as an indicator of effect size when the units of measurement information differed between studies, when the values differed significantly, or when the methods of measurement differed, and mean difference (MD) was used in the remaining cases. All effect sizes were expressed as 95% confidence intervals (95% CI). When the heterogeneity among included studies was low ($P > 0.1$ and $I^2 \leq 50\%$), the fixed-effects model (FEM) was used for analysis; when $P \leq 0.1$ or $I^2 > 50\%$, heterogeneity was deemed to be present, and subgroup analysis and sensitivity analysis were used to investigate the sources of heterogeneity. The reasons for heterogeneity were analyzed to determine whether Meta-analysis could be performed using random effects models (REM), but if there was significant heterogeneity between studies, only descriptive qualitative analysis was performed without combining it. Sensitivity analysis was performed by using the single-study method of Revman removal to remove "high risk of bias" literature one by one and sensitivity plotting with Stata to assess the reliability and stability of positive study results. We investigated whether potential confounding factors could influence the acupuncture effects of cytokines like MMP-13, which were highly heterogeneous in the study results. We also carried out additional analyses stratified by variables that are frequently disregarded but crucial in animal experiments, such as animal population selection and animal sex configuration. For differences in estimates between these subgroups, $P < 0.05$ were deemed significant. Potential publication bias was assessed by visualizing asymmetries in funnel plots (≥10 studies) by combining Egger's test and Begg's test.

3. Results

3.1. Literature screening results

Literature search yielded 1,560 articles, of which 1,186 were in Chinese, 372 in English, and two in Korean. Of these, 604 duplicates were excluded using Endnote20 check. After reading the abstracts and titles of the remaining 956 papers a further 632 (including reviews, systematic reviews, conferences, patents, subject irrelevant, acupuncture non-primary therapies, KOA non-target diseases, case reports, and non-animal studies) were excluded based on the predetermined criteria. On accessing the remaining 315 articles, 226 were excluded due to unavailable full text, incomplete data, duplicate data publication, or non-chondrogenic level studies. About 89 that met the basic requirements and 54 articles with irrelevant outcome indicators. Ultimately 35 articles were included in the meta-analysis, 25 of which were in Chinese and 10 in English. **Figure 1** shows details of the literature search process.

3.2. Quality of the literature

The included studies' quality scores ranged from 4 to 9 out of 10: one study (Zhou et al., 2018) received a score of 9, eight studies (Liao et al., 2016; Ma et al., 2017; Wu et al., 2019, 2022; Wang et al., 2020; Jie et al., 2021; Liu J. W. et al., 2021; Zhu S. Q. et al., 2021) received a score of 8, 16 studies (Xiong et al., 2012; Liang et al., 2015; Fu et al., 2016a; Fu et al., 2016b; Xi et al., 2016; Yu, 2016; Liu N. G. et al., 2018; Wan et al., 2019; Zhang et al., 2019a; Zhang et al., 2019b; Wang, 2020; Chen, 2021; Liu H. et al., 2021; Zeng et al., 2021; Zhu D. Y. et al., 2021; Qin et al., 2022) received a score of 7, four studies (Liang, 2015; Lin and Xu, 2019; Chen et al., 2020; Liu D. et al., 2021) received a score of 6, three studies (Wu et al., 2018; Liu, 2019; Wan et al., 2021) received a score of 5, and three studies (Bao et al., 2011; Liu D. et al., 2017; Wang D. et al., 2021) received a score of 4. There was no research that reported on the sample size calculation. Except for five investigations (Bao et al., 2011; Liu D. et al., 2017; Wu et al., 2018; Wan et al., 2021; Wang D. et al., 2021), all detailed laboratory temperature and humidity control. All research showed randomization of animal groups and employed adequate animal models, and all but three studies (Xiong et al., 2012; Liao et al., 2016; Liu H. et al., 2021) assessed modeling success and failure metrics. Thirty-three research employed anesthetic supplies that had no effect on the experiment, while the remaining six experiments (Bao et al., 2011; Liu D. et al., 2017; Wu et al., 2018; Liu, 2019; Liu J. W. et al., 2021; Wang D. et al., 2021) did not require anesthesia during the experiment. Three studies (Liao et al., 2016; Zhou et al., 2018; Liu J. W. et al., 2021) used blinding during the statistical analysis of the data. Nine research (Bao et al., 2011; Liang, 2015; Liu D. et al., 2017; Lin and Xu, 2019; Liu, 2019; Chen et al., 2020; Liu D. et al., 2021; Wan et al., 2021; Wang D. et al., 2021) did not declare compliance with animal welfare regulations and a further 11 (Xiong et al., 2012; Liao et al., 2016; Ma et al., 2017; Zhou et al., 2018; Wu et al., 2019; Wang et al., 2020; Jie et al., 2021; Liu H. et al., 2021; Liu J. W. et al., 2021; Zhu S. Q. et al., 2021; Wu et al., 2022) reported no possible conflict

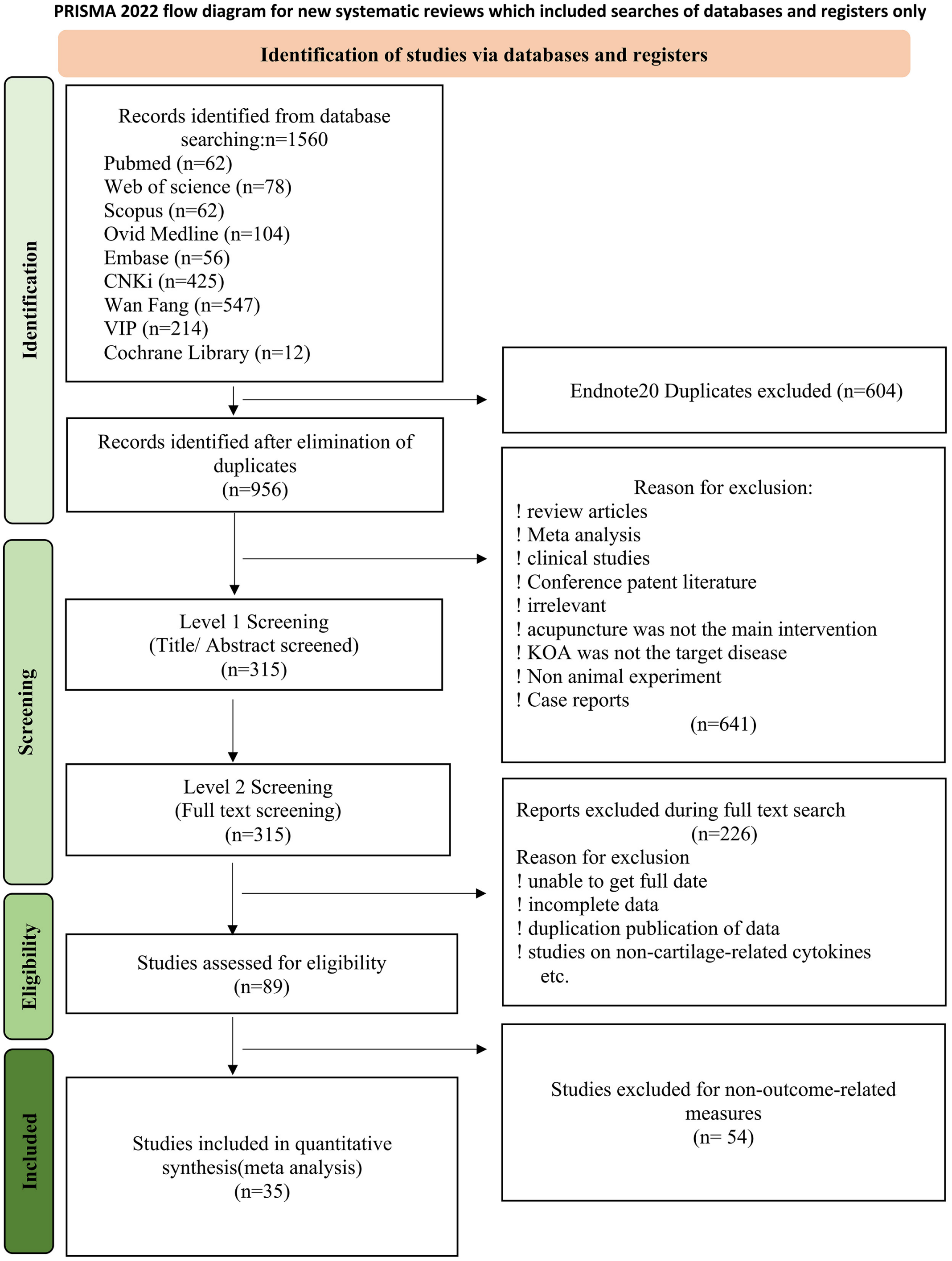

FIGURE 1
Flow diagram of study selection process.

of interest. Thirty-two studies were published in peer-reviewed journals, and five (Liang, 2015; Yu, 2016; Liu, 2019; Wang, 2020; Chen, 2021) were master's or doctorate theses that were peer-reviewed at the time of defense and so met the standards as well. For more information, see Table 1.

3.3. Basic characteristics of the literature

Table 2 provides a summary of the features of the included studies. The animal models utilized in the included research were rabbit and rat, and the sex classification was pure male, pure female, half of each, and limitless sex, with a few studies not specified. The modeling methods included the Hulth-Telhag method, the Videman method, anterior cruciate ligament dissection, ovaries resection, femoral vein ligation, hind limb achilles tendon resection, external fixation of the hind knee, natural aging degeneration method, sodium iodoacetate solution injection, and LPS induction method. Acupuncture intervention methods include traditional

TABLE 1 Quality assessment.

References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Chen et al., 2020		✓	✓	✓	✓	✓			✓		6
Fu et al., 2016b		✓	✓	✓	✓	✓		✓	✓		7
Liao et al., 2016		✓	✓	✓		✓	✓	✓	✓	✓	8
Zhu D. Y. et al., 2021		✓	✓	✓	✓	✓		✓	✓		7
Wang, 2020		✓	✓	✓	✓	✓		✓	✓		7
Chen, 2021		✓	✓	✓	✓	✓		✓	✓		7
Liu D. et al., 2021		✓	✓	✓	✓	✓			✓		6
Wu et al., 2019		✓	✓	✓	✓	✓		✓	✓	✓	8
Wang et al., 2020		✓	✓	✓	✓	✓		✓	✓	✓	8
Jie et al., 2021		✓	✓	✓	✓	✓		✓	✓	✓	8
Lin and Xu, 2019		✓	✓	✓	✓	✓			✓		6
Liu D. et al., 2017			✓	✓	✓				✓		4
Wu et al., 2018			✓	✓	✓			✓	✓		5
Xi et al., 2016		✓	✓	✓	✓	✓		✓	✓		7
Zhang et al., 2019a		✓	✓	✓	✓	✓		✓	✓		7
Bao et al., 2011			✓	✓	✓				✓		4
Liu H. et al., 2021		✓	✓	✓		✓		✓	✓	✓	7
Liang, 2015		✓	✓	✓	✓	✓			✓		6
Yu, 2016		✓	✓	✓	✓	✓		✓	✓		7
Liu N. G. et al., 2018		✓	✓	✓	✓	✓		✓	✓		7
Ma et al., 2017		✓	✓	✓	✓	✓		✓	✓	✓	8
Liu J. W. et al., 2021		✓	✓	✓	✓		✓	✓	✓	✓	8
Liang et al., 2015		✓	✓	✓	✓	✓		✓	✓		7
Liu, 2019		✓	✓	✓	✓				✓		5
Wan et al., 2019		✓	✓	✓	✓	✓		✓	✓		7
Wu et al., 2022		✓	✓	✓	✓	✓		✓	✓	✓	8
Zhang et al., 2019b		✓	✓	✓	✓	✓		✓	✓		7
Fu et al., 2016a		✓	✓	✓	✓	✓		✓	✓		7
Wan et al., 2021			✓	✓	✓	✓			✓		5
Zeng et al., 2021		✓	✓	✓	✓	✓		✓	✓		7
Xiong et al., 2012		✓	✓	✓		✓		✓	✓	✓	7
Wang D. et al., 2021			✓	✓	✓				✓		4
Qin et al., 2022		✓	✓	✓	✓	✓		✓	✓		7
Zhou et al., 2018		✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Zhu S. Q. et al., 2021		✓	✓	✓	✓	✓		✓	✓	✓	8

Q1, sample size calculation; Q2, statements describing control of temperature; Q3, randomly assigned to treatment or control groups; Q4, use of animals with Knee osteoarthritis; Q5, Evaluation of Knee osteoarthritis model building; Q6, use of anesthetic without marked intrinsic properties; Q7, blinded assessment of outcome; Q8, compliance with animal welfare regulations; Q9, published in a peer-reviewed journal or have passed peer review; and Q10, declared any potential conflict of interest.

TABLE 2 Study characteristics.

References	Species	Gender, amount	Model (method)	Treatment method	Course	Outcome index	Originate from
Chen et al., 2020	New Zealand rabbits	Un-limited, 8/group	Anterior cruciate ligament transection(ACLT)	Acupotomy	6 times	p38MAPK	Cartilaginous tissue of tibial plateau and femoral condyle
Fu et al., 2016b	New Zealand rabbits	Un-limited, 10/group	Hulth-Telhag	Needling	4 weeks	Caspase-3, Bax, Bcl-2, caspase-3 mRNA	Cartilaginous tissue of tibial plateau and femoral condyle
Liao et al., 2016	SD rat	Male, 10/group	Anterior cruciate ligament transection(ACLT)	Electroacupuncture	12 weeks	p38MAPK, mankin	Tibial plateau cartilage tissue
Zhu D. Y. et al., 2021	SD rat	Male,6/group	LPS inducing	Electroacupuncture	12 weeks	p38MAPK, P-p38MAPK, collagen II	Chondrocyte
Wang, 2020	Hartley guinea pigs	Female, 8/group	Spontaneity	Electroacupuncture	30 days	IL-1β	Tibial plateau cartilage tissue
Chen, 2021	SD rat	Male, 12/group	Induced by sodium iodoacetate solution	Electroacupuncture	4 weeks	IL-1β, MMP-13	Cartilaginous tissue of tibial plateau and femoral condyle
Liu D. et al., 2021	New Zealand rabbits	Un-limited,10/group	Cast fixation of knee joint in extension position	Warm Acupuncture	2 weeks	IL-1β, MMP-13, mankin	Cartilaginous tissue
Wu et al., 2019	New Zealand rabbits	Un-limited, 9/group	Hulth-Telhag	Electroacupuncture	8 weeks	IL-1β, mankin	Tibial plateau cartilage tissue
Wang et al., 2020	Hartley guinea pigs	Un-limited, 6/group	Spontaneity	Electroacupuncture	4 weeks	IL-1β, MMP-13	Cartilaginous tissue
Jie et al., 2021	SD rat	Male, 8/group	Anterior cruciate ligament transection (ACLT)	Electroacupuncture	12 weeks	MMP-13, ADAMTS-5, mankin	subchondral bone, Tibial plateau cartilage tissueand subchondral bone
Lin and Xu, 2019	Wistar rat	Male, 8/group	Modified videman	Needling	4 weeks	MMP-13	Cartilaginous tissue
Liu D. et al., 2017	New Zealand rabbits	Male, 10/group	Extension fixation of right hind limb	Warm Acupuncture	2 weeks	MMP-13, MMP-1	Tibial plateau cartilage tissue
Wu et al., 2018	New Zealand rabbits	Male, 10/group	Videman	Warm Acupuncture	2 weeks	MMP-13	Tibial plateau cartilage tissue
Xi et al., 2016	New Zealand rabbits	Un-limited, 10/group	Hulth-Telhag	Needling	4 weeks	MMP-13, collagen II	Meniscus and cartilage tissue
Zhang et al., 2019a	SD rat	Male, 10/group	Modified Hulth-Telhag	Electroacupuncture	12 weeks	MMP-13, mankin	Tibial plateau cartilage tissue
Bao et al., 2011	SD rat	Female, 10/group	Unilateral hindlimb Achilles tendinectomy	Needling	2 weeks	MMP-1	Cartilaginous tissue of the femoral condyle
Liu H. et al., 2021	rat	Male, 10/group	Anterior cruciate ligament transection (ACLT)	Needling	8 weeks	ADAMTS-5, collagen II, aggrecan, Apoptosis rate	Cartilaginous tissue
Liang, 2015	New Zealand rabbits	Male, 6/group	Modified extension cast fixation of knee joint	Acupotomy	3 times	Bax mRNA, Bcl-2 mRNA, Caspase-3 mRNA, Bax, Bcl-2, Caspase-3, mankin	Cartilaginous tissue of the femoral condyle
Yu, 2016	New Zealand rabbits	Male, 6/group	Modified Videman	Acupotomy	8 times	Collagen II, aggrecan, mankin	Cartilaginous tissue of tibial plateau and femoral condyle
Liu N. G. et al., 2018	New Zealand rabbits	Male, 6/group	Modified Videman	Acupotomy	4 weeks	Aggrecan	Cartilaginous tissue from the distal femur and proximal tibia

(Continued)

TABLE 2 (Continued)

References)	Species	Gender, amount	Model (method)	Treatment method	Course	Outcome index	Originate from
Ma et al., 2017	New Zealand rabbits	Male, 6/group	Videman	Electroacupuncture	4 weeks	Aggrecan	Cartilaginous tissue
Liu J. W. et al., 2021	rabbits	Half and half, 10/group	Extension fixation of right hind limb	Warm Acupuncture	2 weeks	Bax mRNA, Bcl-2 mRNA, Caspase-3 mRNA, Apoptosis rate, mankin	Cartilaginous tissue
Liang et al., 2015	New Zealand rabbits	Half and half, 6/group	Modified Videman	Acupotomy	3 times	Collagen II, aggrecan, mankin	Cartilaginous tissue of the femoral condyle
Liu, 2019	New Zealand rabbits	Half and half, 10/group	Extension fixation of right hind limb	Warm Acupuncture	2 weeks	Bax mRNA, Bcl-2 mRNA, Caspase-3 mRNA, Bax, Bcl-2, Caspase-3	Cartilaginous tissue of tibial plateau and femoral condyle
Wan et al., 2019	Wistar rat	Male, 8/group	Modified Videman	Needling	3 weeks	Caspase-3 mRNA, Caspase-3, Apoptosis rate	Cartilaginous tissue
Wu et al., 2022	New Zealand rabbits	Male, 10/group	Extension fixation of right hind limb	Warm Acupuncture	4 weeks	Bax mRNA, Bcl-2 mRNA, Bax, Bcl-2, Apoptosis rate, mankin	Articular cartilage of tibial plateau and subchondral bone
Zhang et al., 2019b	SD rat	Male, 10/group	Modified Hulth-Telhag	Electroacupuncture	12 weeks	Bax mRNA, Bcl-2 mRNA, Bax, Bcl-2, mankin	Tibial plateau cartilage tissue
Fu et al., 2016a	New Zealand rabbits	Un-limited, 10/group	Hulth-Telhag	Needling	4 weeks	p38MAPK, Apoptosis rate	Tibial plateau cartilage tissue
Wan et al., 2021	Wistar rat	Male, 8/group	Videman	Needling	3 weeks	Bax mRNA, Bcl-2 mRNA, Bax, Bcl-2	Cartilaginous tissue
Zeng et al., 2021	New Zealand rabbits	Male, 8/group	Modified Videman	Acupotomy	4 times	Caspase-3 mRNA, Caspase-3, mankin, Apoptosis rate	Cartilaginous tissue of the femoral condyle
Xiong et al., 2012	Japanese white rabbit	Male, 8/group	Ligate the femoral vein	Warm Acupuncture	8 weeks	Bax, Bcl-2, Apoptosis rate	Cartilaginous tissue of the femoral condyle
Wang D. et al., 2021	New Zealand rabbits	Male, 10/group	Extension fixation of right hind limb	Warm Acupuncture	4 weeks	Bax, Bcl-2, mankin	Tibial plateau cartilage tissue
Qin et al., 2022	New Zealand rabbits	Male, 6/group	Videman	Acupotomy	3 weeks	Mankin, BV/TV	Cartilage and subchondral bone
Zhou et al., 2018	SD rat	Female, 10/group	Ovariectomy	Electroacupuncture	12 weeks	Mankin, BV/TV, Tb.sp, Tb.Th, Tb.N	Cartilage and subchondral bone
Zhu S. Q. et al., 2021	New Zealand rabbits	Un-limited, 10/group	Hulth-Telhag	Needling	4 times	Tb.sp, Tb.Th, Tb.N	Tibial plateau cartilage tissue

acupuncture, electroacupuncture, acupuncture knife, and warm acupuncture.

3.4. Meta-analysis results

3.4.1. p38MAPK pathway

p38MAPK was utilized as an outcome measure in four investigations (Fu et al., 2016a; Liao et al., 2016; Chen et al., 2020; Zhu D. Y. et al., 2021). Acupuncture substantially lowered p38MAPK levels when compared to the control group (FEM, SMD −2.12, 95% CI: [−3.43,−0.81], $P < 0.01$; $X^2 = 11.38$, $I^2 = 74\%$, **Figure 2**). At Revman, we ran a sensitivity analysis of p38MAPK by single exclusion and found that the effect size was steady and that removing one study had no influence on its significance. Similarly, five studies on IL-1β (Wu et al., 2019; Wang, 2020; Wang et al., 2020; Chen, 2021; Liu D. et al., 2021) and three on TNF-α (Wu et al., 2019; Wang et al., 2020; Liu H. et al., 2021) showed that all were significantly reduced in acupuncture intervention compared with model

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groups (P < 0.001, see **Figure 2**). One on p-p38MAPK (Zhu D. Y. et al., 2021) found significantly lower levels in acupuncture than in model groups (P = 0.01, **Figure 2**).

MMP-13 was used as an outcome indicator in nine studies (Xi et al., 2016; Liu D. et al., 2017; Wu et al., 2018; Lin and Xu, 2019; Zhang et al., 2019a; Wang et al., 2020; Chen, 2021; Jie et al., 2021; Liu D. et al., 2021), and pooled analysis showed that acupuncture significantly reduced MMP-13 compared to model groups (P < 0.001, I^2 = 85%, **Figure 2**). The single exclusion method showed a stable effect. In two studies on MMP-1 (Bao et al., 2011; Liu D. et al., 2017) and two on ADAMTS5 (Jie et al., 2021; Liu H. et al., 2021) levels were also significantly lower in acupuncture treatment than in model groups, their results were P = 0.03 and P < 0.001, respectively, see **Figure 2**. Conversely, five studies on collagen II (Liang et al., 2015; Xi et al., 2016; Yu, 2016; Liu H. et al., 2021; Zhu D. Y. et al., 2021) and five on aggrecan (Liang et al., 2015; Yu, 2016; Ma et al., 2017; Liu N. G. et al., 2018; Liu H. et al., 2021), found significantly higher levels in acupuncture than in model groups (P < 0.001, **Figure 2**), heterogeneity of

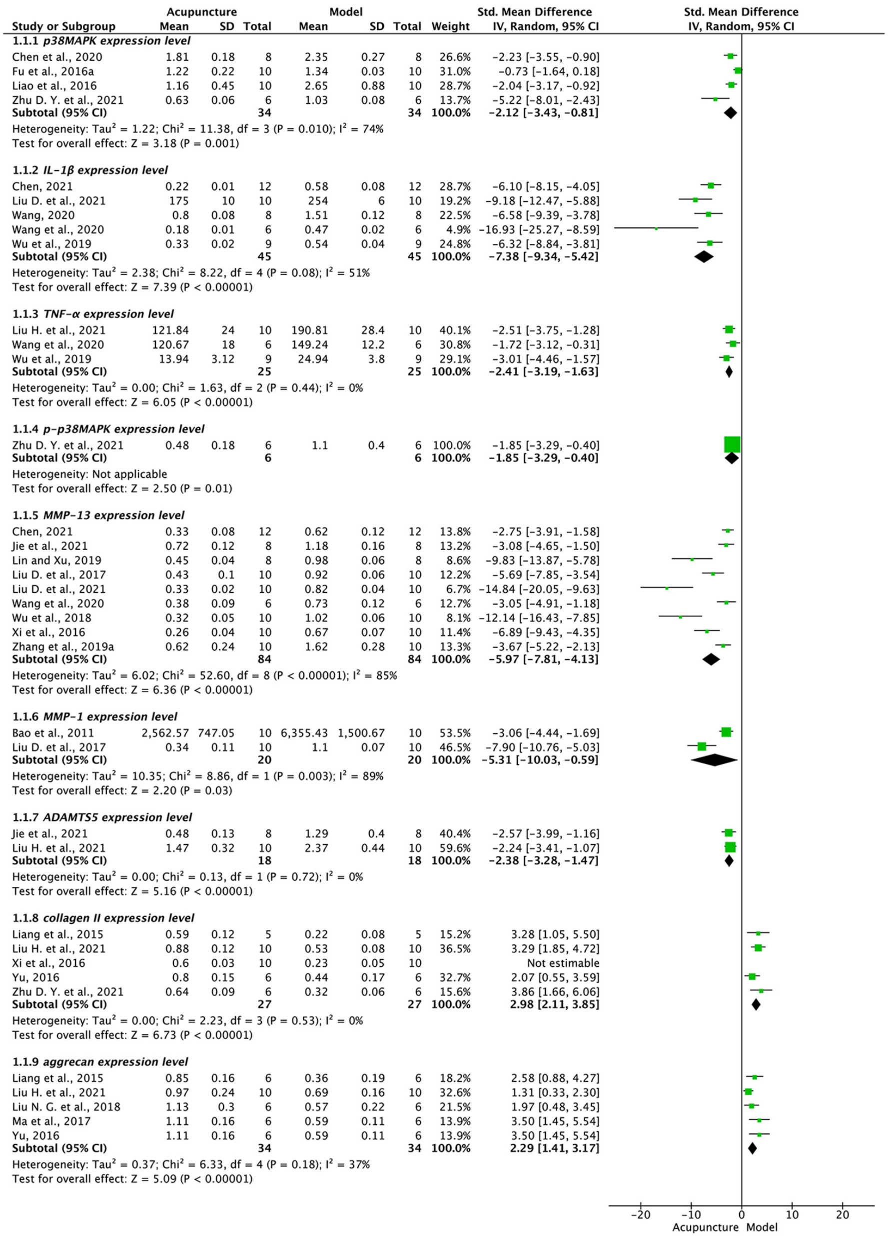

FIGURE 2
Forest plot of p38MAPK signaling regulators. p38MAPK, IL-1β, TNF-α, p-p38MAPK, MMP-13, MMP-1, ADAMST-5, collagen II, and aggrecan in acupuncture and model groups.

collagen II was significantly lower after exclusion of one study (Xi et al., 2016) perhaps due to sex distribution differences between studies(unrestricted in that study, all male or half male in others).

3.4.2. Mitochondrial pathway

3.4.2.1. mRNA expression of cytokines on the mitochondrial signaling pathway in cartilage

As shown by **Figure 3**, six publications (Liang, 2015; Liu, 2019; Zhang et al., 2019b; Liu J. W. et al., 2021; Wan et al., 2021; Wu et al., 2022) showed that Bax mRNA was significantly reduced in acupuncture compared to model groups ($P < 0.001$). However, in the same studies Bcl-2 mRNA was elevated in acupuncture groups compared to model groups. Sensitivity analysis showed that the heterogeneities of both Bax mRNA and Bcl-2 mRNA were significantly lower after excluding one study (Wan et al., 2021). The measured value in this study appeared small compared with other studies and this may be due to high RNA degradation rate or the concentration of internal reference genes of the samples sent for testing.

Six studies (Liang, 2015; Fu et al., 2016b; Liu, 2019; Wan et al., 2019; Liu J. W. et al., 2021; Zeng et al., 2021) on Caspase-3 mRNA and one (Wan et al., 2019) on Caspase-9 mRNA

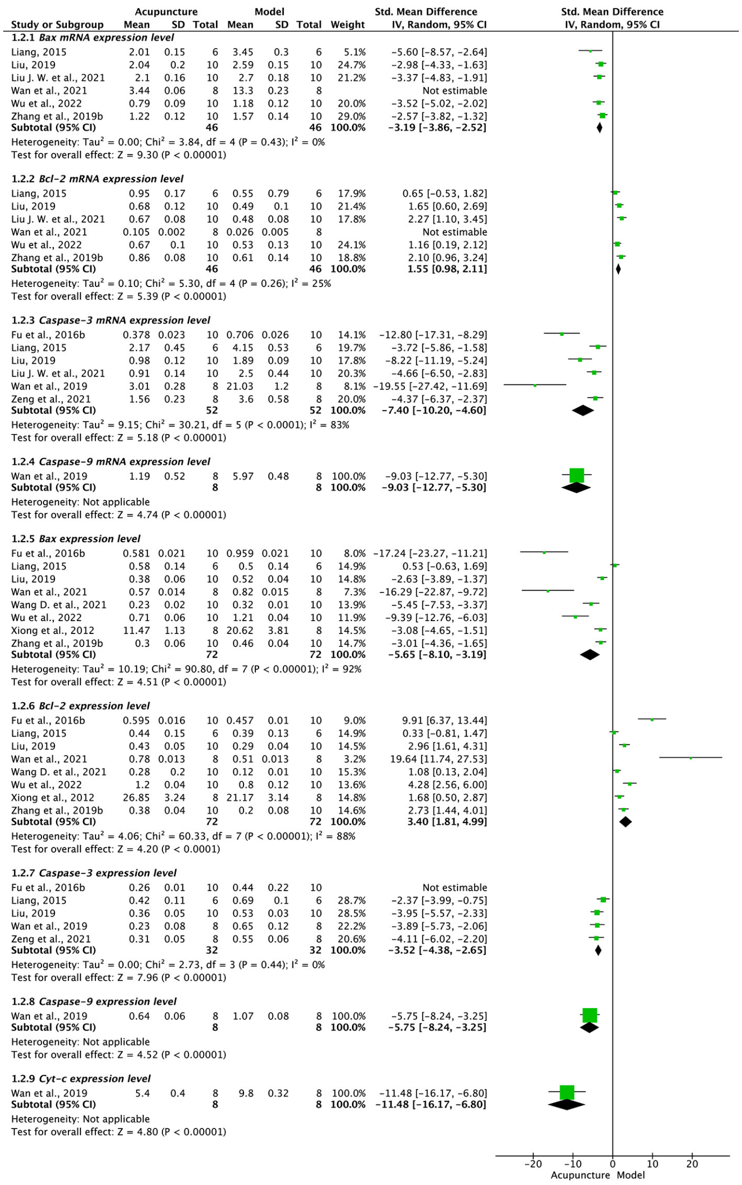

FIGURE 3

Forest plot of signaling regulator of mitochondria pathway. Bax mRNA, Bcl-2 mRNA, Caspase-3 mRNA, Caspase-9 mRNA, Bax, Bcl-2, Caspase-3, Caspase-9, Cyt-c in acupuncture and model groups.

were significantly lower in acupuncture than model groups ($P < 0.001$, **Figure 3**). Single exclusion method shows stable results in Caspase 3.

3.4.2.2. Protein expression of cytokines on the mitochondrial signaling pathway in cartilage

Figure 3 shows that pooled data from eight studies (Xiong et al., 2012; Liang, 2015; Fu et al., 2016b; Liu, 2019; Zhang et al., 2019b; Wan et al., 2021; Wang D. et al., 2021; Wu et al., 2022) found reduced Bax and increased Bcl-2 in acupuncture compared to model groups ($P < 0.001$). The single exclusion method showed a stable effect.

Pooled analysis from five studies (Liang, 2015; Fu et al., 2016b; Liu, 2019; Wan et al., 2019; Zeng et al., 2021) shows that Caspase-3 is significantly reduced in acupuncture compared to model groups ($P < 0.001$, **Figure 3**). Sensitivity analysis showed a significant reduction in heterogeneity after excluding one study (Fu et al., 2016b). This may be due to the unrestricted sex distribution of the animals used in that study, while other studies were all-male (Liang, 2015; Wan et al., 2019; Zeng et al., 2021) or half-male (Liu, 2019).

One study (Wan et al., 2019) found reduced Caspase-9 and Cytochrome-c (Cyt-c) levels in acupuncture compared with a model group ($P < 0.001$, **Figure 3**).

3.4.3. Effect of acupuncture intervention on cartilage phenotype in KOA

3.4.3.1. Chondrocyte apoptosis rate

Pooled data from seven studies (Xiong et al., 2012; Fu et al., 2016a; Wan et al., 2019; Liu H. et al., 2021; Liu J. W. et al., 2021; Zeng et al., 2021; Wu et al., 2022) showed that chondrocyte apoptosis rate was significantly lower in acupuncture than model groups ($P < 0.001$, $I^2 = 88\%$, **Figure 4**). The single exclusion method showed a stable effect.

3.4.3.2. Mankin's score

Cartilage damage is the gold standard for KOA assessment, and the Mankin's score as revised by the Osteoarthritis Research Society International (OARSI) (Moskowitz, 2006) is the most commonly used system to gauge cartilage destruction. Higher scores indicate more severe cartilage breakdown, lower chondrocyte counts, and worse pathological staining. As shown by **Figure 4**, data from 15 studies (Liang, 2015; Liang et al., 2015; Liao et al., 2016; Yu, 2016; Zhou et al., 2018; Wu et al., 2019, 2022; Zhang et al., 2019a,b; Jie et al., 2021; Liu D. et al., 2021; Liu J. W. et al., 2021; Wang D. et al., 2021; Zeng et al., 2021; Qin et al., 2022) show significantly lower score in acupuncture than model groups ($P < 0.001$).

3.4.3.3. Cartilage morphometrics

To assess the extrinsic effects of acupuncture on the regulation of matrix-degrading enzymes and extracellular matrix molecules in cartilage, we included the following values that quantify cartilage morphometry:

Data from three studies (Zhou et al., 2018; Jie et al., 2021; Qin et al., 2022) showed that BV/TV scores did not differ significantly between the acupuncture and model groups ($P = 0.75$, **Figure 5**). Further pooled data from three studies (Zhou et al., 2018; Jie et al., 2021; Zhu S. Q. et al., 2021) showed

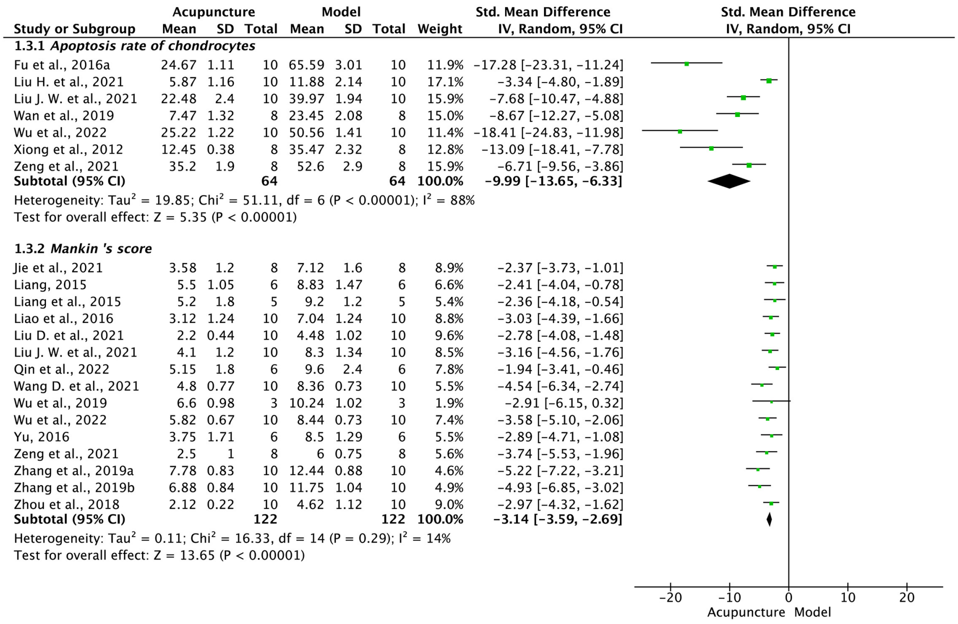

FIGURE 4
Forest plot of apoptosis rate and Mankin's score.

significant reduction in Tb.sp scores ($P < 0.01$, Figure 5) and significant increase in both Tb,N ($P < 0.001$, Figure 5)and Tb.Th ($P < 0.05$, Figure 5) in acupuncture compared with model groups. Sensitivity analysis showed a significant decrease in Tb.sp and Tb.N heterogeneity after excluding one study (Jie et al., 2021). We found that the values of the outcome indicators varied considerably among studies, probably due to the different magnifications of the light microscope and the software used for the calculation.

3.5. Subgroup analysis

Sources of a high level of heterogeneity ($I^2 = 85\%$) among studies on MMP-13 were explored from two subgroup analyses differing according to clinical characteristics, as follows.

(1) Articles were allocated to subgroups according to animal species (rabbit and rat). Results of analysis presented in Figure 6 show that the expression of MMP-13 in the acupuncture group was all significantly lower than that in the model group ($P < 0.001$), species factors don't influence acupuncture to reduce MMP-13 expression. However, the combined forest plot effect shows a more pronounced reduction in the leftward shift of the effector amount of MMP-13 in the cartilage of rabbits compared to rats. Furthermore, the difference between subgroups reached statistical significance ($P = 0.004$), with a greater reduction in the rabbit subgroup. These results suggest that the magnitude of the efficacy of acupuncture may be species dependent and that rabbits may be relatively more sensitive to the effects of acupuncture.

(2) Study data were allocated to subgroups according to sex selection (sex-unlimited and male), and the results of the analysis in Figure 7 show that the effect on MMP-13 was significantly greater in acupuncture than model groups in both forms of sex selection, providing further evidence of the generalizability of acupuncture for KOA. The decline of MMP-13 in male ($P < 0.001$) is more prominent than in sex-unlimited ($P = 0.004$), however, the differences between subgroups didn't reach statistical significance ($P = 0.41$).

3.6. Sensitivity analysis

To evaluate the stability of the results of acupuncture studies on KOA animal models, studies with significant differences but high heterogeneity (containing p38MAPK, MMP-13, Caspase-3 mRNA, Bax, Bcl-2 expression levels, and chondrocyte apoptosis rates) were subjected to sensitivity analysis using Stata 17.0 to explore the sources of heterogeneity and the degree of influence on the

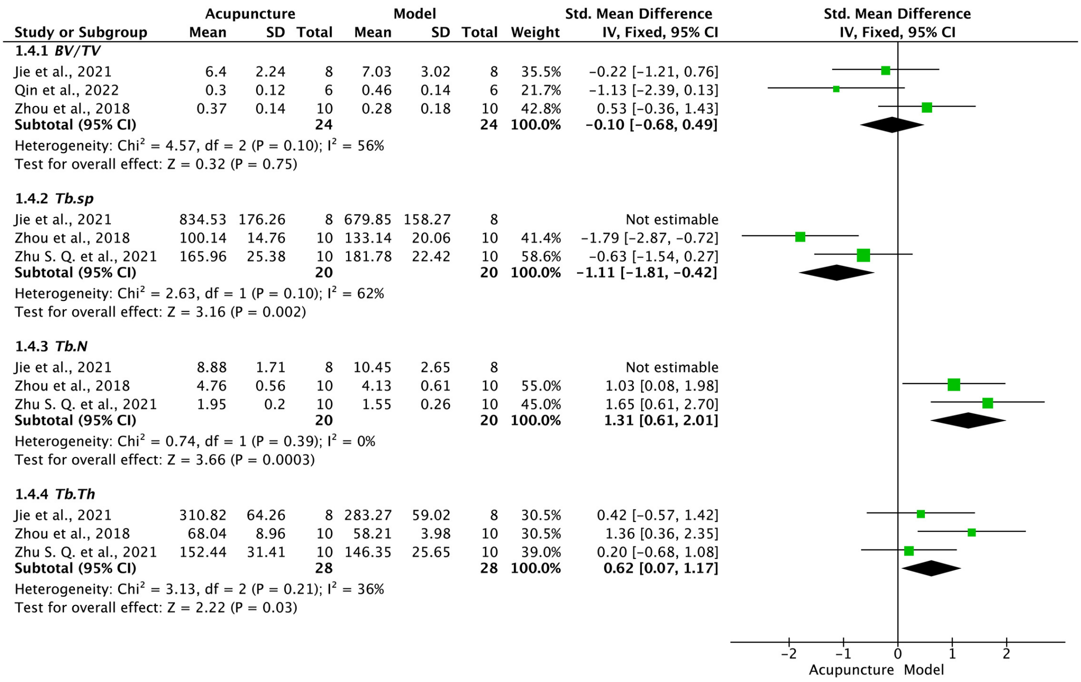

FIGURE 5
Forest plot of morphometry of cartilage.

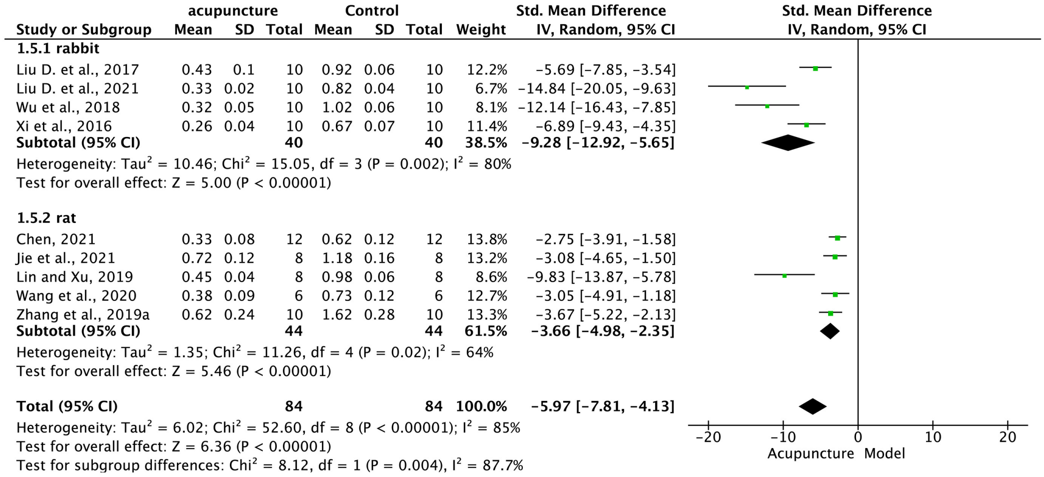

FIGURE 6
Subgroup analysis of effects of acupuncture on MMP-13 in KOA cartilage in different animal models (rabbit and rat).

combined effect sizes. The results of this analysis showed that data from all studies were evenly distributed around the line of no difference, and the MD, confidence interval, and heterogeneity did not change significantly with each excluded study, indicating that the results were relatively robust (**Figure 8**).

3.7. Publication bias

The funnel plot and the Egger test were used to compensate for publication bias; if $P < 0.05$ in the both Egger's test and Begg's test indicate potential bias. In this study, funnel plots for the effect of acupuncture on the Mankin's score of cartilage were created. The Egger's test, $P = 0.051$, close to 0.05, combined with the results of Begg's test ($P = 0.018$) and the asymmetry of the funnel plot, prefers to consider a slight publication bias, indicating a possible bias. This is depicted in **Figure 9**.

4. Discussion

4.1. Summary of main findings

In this review, we systematically analyzed 40 acupuncture studies on cytokines relevant to p38MAPK and mitochondrial pathways in cartilage samples from animal models. We found that in cartilage, acupuncture significantly inhibited two important KOA-inducing mediators, IL-1β and TNF-α, attenuating their effects on the cartilage environment. It also significantly blocked their activation of p38MAPK, preventing activation of the MAPK signaling pathway in cartilage and allowing increased P38MAPK phosphorylation (p-p38MAPK) (Park et al., 2018). Acupuncture also significantly attenuates IL-1β and TNF-α activation of MAPK and inhibits the expression of p-p38 MAPK. Reduced p-p38MAPK limits the production of enzymes such as MMP and ADAMTS that degrade and cause phenotypic change in cartilage matrix (Wang et al., 2013; Lieberthal et al., 2015). MMP-13, the main MMP involved in cartilage degradation (Mehana et al., 2019), has the specific ability to cleave collagen II and degrade aggrecan molecules, playing a dual role in matrix destruction, which makes it an attractive target for the treatment of OA. The ADAMTS protein family has also been associated with cartilage degradation of KOA, particularly ADAMTS5 (Kapoor et al., 2011). Therefore, MMP13 and ADAMTS5 were used as catabolic markers, while collagen II and aggrecan were used as anabolic markers of cartilage metabolism (He et al., 2020). The regulated synthesis or activity of these enzymes is essential to inhibit cartilage degeneration and catabolism of the cartilage matrix, and we found that acupuncture intervention significantly inhibited the expression of MMP-13 and ADAMTS5 thereby significantly reversing the reduction of collagen and aggrecan proteins in the extracellular matrix of cartilage during KOA progression.

In addition, the catabolism of cartilage matrix in KOA leads to chondrocyte apoptosis and a decrease in chondrocyte survival signals (Sun et al., 2019). Bcl-2 and Bax protein levels are directly related to apoptosis. Elevated Bcl-2 can inhibit apoptosis by moderating mitochondrial permeability. Conversely, elevated Bax can promote apoptosis by increasing mitochondrial membrane permeability via activated oligomers and Cyt-C release into the cytoplasm. The latter activates key enzymes of the mitochondria-dependent apoptotic pathway, triggering the Caspase cascade, with sequential activation of Caspase-9 and Caspase-3, leading to apoptosis (Vakifahmetoglu-Norberg et al., 2017). In the present study, acupuncture significantly

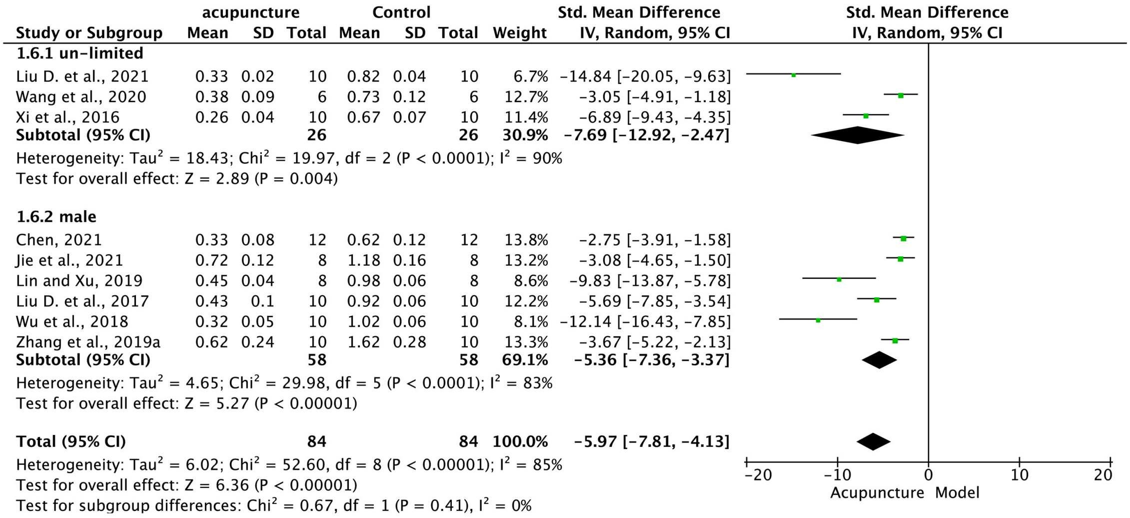

FIGURE 7
Subgroup analysis of MMP-13 in KOA cartilage treated with acupuncture in animal models of different gender distributions (male and un-limited).

modulated the mRNA and protein expression levels of Bcl-2, Bax, Caspase-9, and Caspase-3, inhibited the expression of Cyt-c, and reduced the chondrocyte apoptosis rate, suggesting that acupuncture achieved this by inhibiting the activation of mitochondrial pathways.

We also reviewed relevant phenotypes of cartilage to verify the effectiveness of the acupuncture effect. To verify cartilage improvement, chondrocyte apoptosis rates from Tunnel or cell flow tests, the Mankin score (which uses electron microscopy and pathological staining to assess cartilage gross morphological structure), and indicators of morphometric changes in cartilage and subchondral bone observed using light microscopy (BV/TV, Tb.sp, Tb.N, Tb.Th) were included. The results showed that acupuncture significantly improved the apoptosis of chondrocytes and the repair of cartilage morphological structures, especially the mean thickness of trabecular column structures (Tb.Th), the mean number of trabeculae per unit length (Tb.N), and the mean distance between trabeculae (column structures; Tb.Sp), providing strong evidence for cartilage remodeling. The exceptions were cartilage and BV/TV, which did not differ significantly, a surprising finding which may be due to the small number of included studies and the range of modeling methods, and needs to be verified by further study.

Species factors have significant effects on the mechanistic study of acupuncture. In the subgroup analysis of species differences, we found that acupuncture was effective across species, providing further evidence for the generalizability of acupuncture for KOA. The relevant forest plot (**Figure 9**) showed that acupuncture may be relatively sensitive in rabbits, consistent with a study (Vina et al., 2021) which found treatment differences in acupuncture management of KOA between African American and white participants, possibly due to cognitive selection bias by race or differences in response to mind-body feedback.

Furthermore, acupuncture performed effectively for persons with KOA regardless of gender, which is consistent with a secondary analysis of a multicenter randomized controlled study revealing that the efficacy of acupuncture for KOA is independent of gender (Hao et al., 2022). While we discovered in the forest plot that acupuncture may work more sensitively in men, some studies have examined gender differences in the efficacy of acupuncture management for KOA and the cost-effectiveness of treatment (Reinhold et al., 2008; Vina et al., 2021), indicating that acupuncture is more effective in women with osteoarthritis and that women are more favorable to acupuncture, the underlying reasons for this gender difference remain unknown. The fact that acupuncture engages distinct active brain regions in men and women may explain the gender disparities in acupuncture benefits (Li et al., 2018).Thus, demographics and gender demand additional investigation and emphasize the necessity for thorough control of these factors in mechanistic research.

4.2. Strengths and limitations

To our knowledge, this is the first systematic review of the effects of acupuncture on KOA pathway mechanisms and related phenotypes in animal studies and the first study to evaluate acupuncture interventions in KOA animal experiments, providing a reference for future KOA mechanism studies and animal experiments. We conducted as comprehensive a search as possible for the full text of all articles (in any language) in nine databases. The CAMARADES

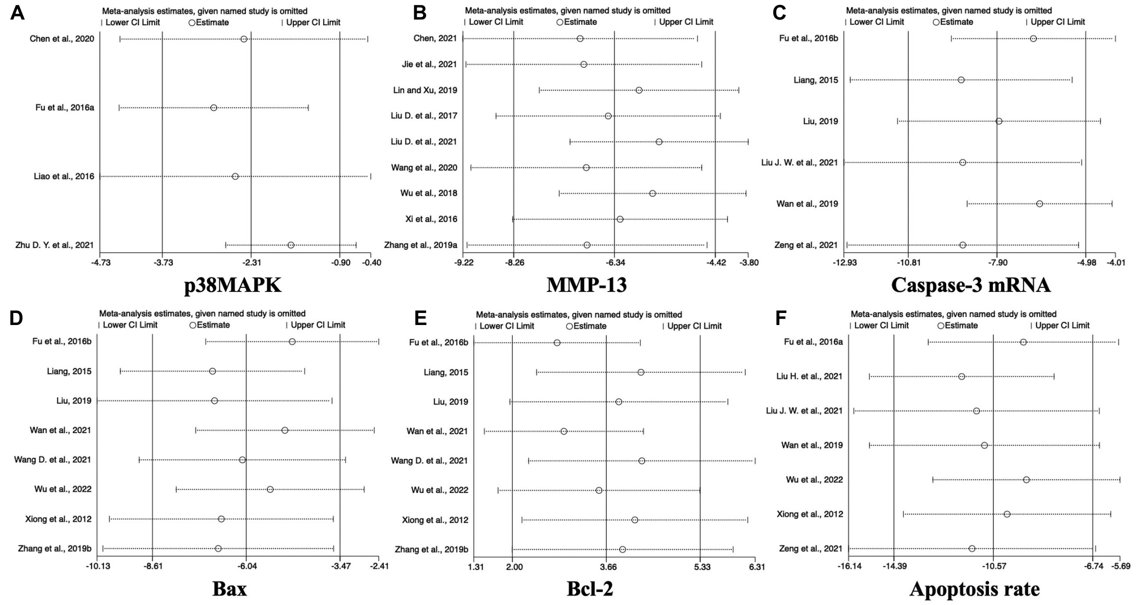

FIGURE 8
Sensitivity analysis of acupuncture effects on p38MAPK, MMP-13, Caspase-3 mRNA, Bax, and Bcl-2 in KOA cartilage.

inventory was used to assess the quality of the studies and to extract data for analysis to validate our findings. The present study was conducted to provide a theoretical basis for revealing the mechanism of acupuncture action in the future.

However, there are some limitations to this research. The studies we included did not perform p38MAPK and mitochondrial pathway silencing experiments, which should be conducted in future studies on acupuncture mechanisms. Secondly, acupuncture is a traditional Chinese therapy, and the included literature is from China, which may have an unavoidable publication bias. Moreover, the small amount and poor quality of the selected literature meant that no firm conclusions could be drawn. We look forward to higher quality studies on the mechanisms of acupuncture and hope that the present review provides a useful reference in the field.

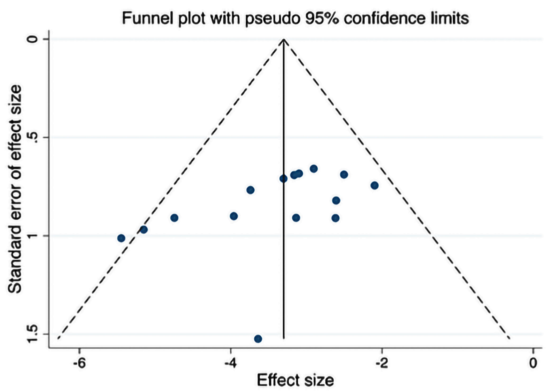

FIGURE 9
Funnel plots of Mankin's score in the KOA animal model of acupuncture intervention.

5. Conclusion

In conclusion, our analysis shows that acupuncture treatments might minimize cartilage extracellular matrix breakdown by inhibiting cytokine production in the p38MAPK pathway and regulating cytokines in the mitochondrial route to limit chondrocyte death. It also appears to enhance cartilage tissue morphologies, preventing cartilage degradation.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

J-NY took responsibility for the integrity of the data and the accuracy of the data analysis. J-NY and C-GS drafted the manuscript and performed statistical analysis. Y-QJ, YZ, W-XS, X-XZ, J-TM, and X-YL made critical revision of the manuscript for important intellectual content. JZ supervised the study.

All authors conceptualized, designed the study, analyzed, and interpreted data.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1098311/full#supplementary-material

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Acupuncture combined with balloon dilation for post-stroke cricopharyngeal achalasia: A meta-analysis of randomized controlled trials

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Background: The purpose of this study was to systematically evaluate the effectiveness of acupuncture combined with balloon dilatation in patients with post-stroke cricopharyngeal achalasia (CPA) according to the effective rate, videofluoroscopy swallowing study (VFSS) score and standardized swallowing function assessment scale (SSA) score through Meta-analysis.

Methods: English and Chinese language literature published before July 24,2022 were searched in ten electronic databases. The identified articles were screened, data were extracted, and the methodological quality of the included trials was assessed. Using RevMan 5.4.1 software to perform Meta-analysis.

Results: 10 studies with 517 patients with post-stroke CPA were included. Meta-analysis showed that the effective rate of the experience group was higher than that of the control group [OR = 0.62; 95% CI (2.32, 13.05); I^2 = 0%; p = 0.0001]. Compared to the control group, the SSA score was lower in the experience group [MD = −4.22; 95% CI (−4.57, −3.87); I^2 = 42%; p < 0.00001]. In terms of VFSS scores, the experience group showed greater efficacy differences than control group [MD = 1.53; 95% CI (1.32, 1.75); I^2 = 0%; p < 0.00001]. The subgroup analysis of VFSS score based on the average course of disease (<1 month vs. ≥1 month) showed no significant difference. The subgroup analysis based on average age (>60 years vs. ≤60 years) showed the VFSS score of the experience group was significantly higher than that of the control group, and the effect may be better in the subgroup older than 60 years. The subgroup analysis based on the treatment course (>30 days vs. ≤30 days) showed the VFSS score of the experience group was significantly higher than that of the control group, and the effect may be better in the subgroup the treatment course>30 days.

Conclusion: Acupuncture combined with balloon dilatation may be an effective method for treating post-stroke CPA. Compared with balloon dilatation, acupuncture combined with balloon can significantly improve the swallowing function of patients, and it is also effective for patients of different courses, ages, and treatment course, while patients over 60 years old and the treatment course over 30 days may have better clinical outcomes.

KEYWORDS

acupuncture, balloon dilation, stroke, cricopharyngeal achalasia, meta-analysis

Introduction

Post-stroke dysphagia (PSD) is a common complication after stroke (Takizawa et al., 2016), and on the verge 5.7% of them are attributable to cricopharyngeal achalasia (CPA) (Regan et al., 2014; Yang et al., 2018). CPA usually cause severe dysphagia, with serious complications which could lead to an increase in medical expenses and mortality, a decrease in quality of life, etc (Kocdor et al., 2016). Currently, balloon dilation is a regular treatment of post-stroke CPA (Dou et al., 2012; Dewan et al., 2020). Through repeated mechanical traction and dilation, balloon dilation can relax the cricopharyngeal muscle (CPM) and improve swallowing (Suntrup et al., 2015). However, simple balloon dilatation involves a long period, which is not always effective at solving the problems of delayed swallowing, weak swallowing, poor swallowing endurance and aspiration. Simple balloon dilatation is difficult to achieve satisfactory results, especially for severe ones.

Being a relatively simple, inexpensive, and safe treatment (Yang et al., 2016), acupuncture has been recommended by the World Health Organization (WHO) as an alternative and complementary method for treating stroke (Belskaya et al., 2020). A systematic review of 6,010 patients also showed that acupuncture could improve post-stroke dysphagia (Ye et al., 2017). In addition, combination of acupuncture and rehabilitation provides a novel strategy for the clinical rehabilitation of stroke (Tang et al., 2022). Le Peng et al. found that compared to rehabilitation therapy alone, the combined therapy is more effective (Peng et al., 2018). In recent years, clinical studies have reported better results of acupuncture combined with balloon dilation than simple balloon dilation in treating post-stroke CPA. However, no reliable objective evidence exists to support its exact efficacy. Therefore, we conducted this systematic analysis of randomized controlled trial (RCT) studies to assess the clinical efficacy of acupuncture combined with balloon dilation on post-stroke CPA and try to provide evidence for the clinical treatment of post-stroke CPA.

Abbreviations: CPA, cricopharyngeal achalasia; PSD, Post-stroke dysphagia; RCT, Randomized controlled trial; VFSS, Videofluoroscopy Swallowing Study; SSA, standardized swallowing function assessment scale; RR, risk ratios; OR, odds ratio; MD, mean difference; CI, confidence interval; NMES, Neuromuscular Electrical Stimulation; CPM, cricopharyngeal muscle; UES, upper esophageal sphincter.

Materials and methods

Search strategies

Between the establishment and July 24, 2022, PubMed, Embase, Web of Science, The Journal of Alternative and Complementary Medicine, Medline, The Cochrane Library, CBM, CNKI, VIP and WanFang Data were systematically searched in both Chinese and English. We searched acupuncture combined with balloon dilatation in the treatment of post-stroke CPA with the search term "swallow disturbance" or "cricopharyngeal achalasia" and "Balloon Dilatation" and "acupuncture" and "stroke." A "randomized controlled trial" search was conducted. As an example, the search strategy for PubMed is shown in Figure 1. References and review articles with potential relevance studies were manually examined. A PROSPERO registration number (CRD42022350411) was assigned to this study.

Inclusion and exclusion criteria

To select the studies for inclusion in this meta-analysis, the following criteria were used: (1) RCTs; (2) Post-stroke patients with CPA (confirmed by videofluoroscopy swallowing study); (3) Patients enrolled in studies with age <80 years; (4) Acupuncture combined with balloon dilatation was used in the experimental group, while simple balloon dilatation was used in the control group, and the researchers provided original data or sufficient information about dysphagia that occurred pre- and posttreatment in experimental trials and control trials. Exclusion criteria: (1) Identical publications; (2) The original research data was not provided and cannot be obtained by contacting the original author; (3) A control group did not receive simple balloon dilation (acupuncture and other measures were also included); (4) Inclusion criteria were not met by some publications.

Outcome measures

According to this study, the outcome measures were: effective rate, standardized swallowing function assessment scale (SSA), and Videofluoroscopy Swallowing Study (VFSS).

#1	(acupuncture) OR (acupuncture therapy) OR (acupuncture analgesia) OR (acupuncture, ear) OR (electroacupuncture) OR (meridians) OR (acupuncture points) OR (trigger points) OR (acupuncture) OR (electroacupuncture) OR (electro-acupuncture) OR (acupoint) OR (meridians) OR (needling) OR (meridian) OR (non-meridian) OR (trigger)
#2	Balloon Dilatation OR (balloon AND (dilat OR dilatation OR inflat OR catheter OR tamponade))
#3	(cerebrovascular disorders) OR (basal ganglia cerebrovascular disease) OR (brain ischemia) OR (carotid arterydiseases) OR (cerebral small vessel diseases) OR (intracranial arterial diseases) OR (intracranial embolism and thrombosis) OR (intracranial hemorrhages) OR (stroke) OR (brain infarction) OR (stroke, lacunar) OR (vasospasm, intracranial) OR (vertebral artery dissection) OR (stroke) OR (poststroke) OR (post-stroke) OR (cerebrovasc) OR (brain next vasc) OR (cerebral next vasc) OR (cva) OR (apoplex) OR (SAH) OR (brain) OR (cerebr) OR (cerebell) OR (intracran) OR (intracerebral) OR (infarct) OR (thrombo) OR (emboli) OR (occlus) OR (brain) OR (cerebr) OR (cerebell) OR (intracerebral) OR (intracranial) OR (subarachnoid) OR (haemorrhage) OR (hemorrhage) OR (haematoma) OR (hematoma) OR (bleed) OR (hemipleg) OR (hemipar) OR (paresis) OR (paretic) OR (brain injuries) OR (brain injury, chronic)
#4	((((Deglutition) OR (Deglutition Disorders)) OR (((swallow or deglutit or dysphag) AND (disturbance or disorder or difficult or dysfunction or impair or condition or abnormal or damage or injur)))) OR (Pharynx or pharyngeal muscles)) OR (((pharyn or oropharyn) AND (disturbance or disorder or difficult or dysfunction or impair or condition or abnormal or damage or injur)))
#5	cricopharyngeal achalasia OR crico-pharyngeal muscle OR achalasia
#6	#4 OR #5
#7	(randomized controlled trial) OR (controlled clinical trial) OR (randomized) OR (placebo) OR (random) OR (trial) OR (groups)
#8	#1 AND #2 AND #3 AND #6 AND #7

FIGURE 1
PubMed retrieval strategy.

Data extraction and quality assessment

Data were independently extracted by two well-trained evaluators to review the original text. The disagreements were solved by the third author's assistance. A study's publication year and first author were included in its characteristics. Among the patient characteristics were age, sample size, intervention measures, treatment course and average course of disease. The efficiency rate, SSA score, and VFSS score were also calculated. The study's methodological quality was assessed according to the risk of bias tool described in the Cochrane system evaluator's handbook 5.1.0 (Jpt, 2011). The risk of bias was assessed by random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessors, selective reporting, incomplete outcome data, and other potential risks.

Statistical analysis

For all statistical analyses, Rev Man 5.4.1 was used. For dichotomous variables, risk ratios (RR) or odds ratio (OR) and 95% confidence interval (CI) were used as statistical tools for efficacy analysis and effect sizes, respectively. There were mean difference (MD) and 95% CI for continuous variables. I^2 statistic was used as a measure of heterogeneity indicating the percentage of total variability in a set of effect sizes caused by true heterogeneity (Huedo-Medina et al., 2006). For high, moderate, and low heterogeneity, I^2 values of 75, 50, and 25% were used (Ampt et al., 2018). A fixed-effects model for data pooling was used if the I^2 statistic was below 50%, which meant that the included studies displayed acceptable heterogeneity. Whenever the I^2 statistic was above 50%, the random-effects model was employed, followed by subgroup analysis or sensitivity analysis (Qiao et al., 2022).

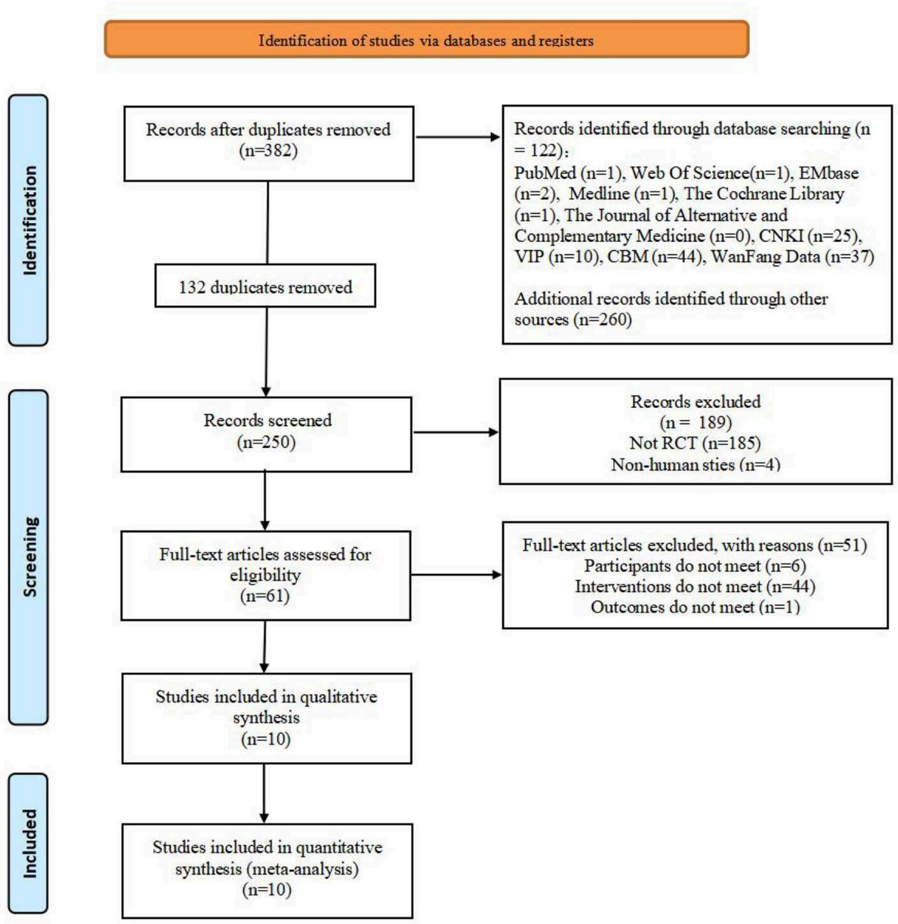

FIGURE 2
PRISMA flowchart of the study selection process. RCT, randomized controlled trials; acupuncture combined with balloon dilation: Cricopharyngcal achalasia.

Results

Characteristics of studies

In the initial retrieval, 382 articles totally were found. After layer-by-layer screened, 10 articles were finally included in the meta-analysis (He, 2017; Yang and Lei, 2017; Zhang, 2017, 2019; Cao et al., 2019; Li et al., 2019; Fan et al., 2020; Gao, 2020; Luo et al., 2020; Long et al., 2021). Study selection, literature screening and reasons for exclusion are shown in the PRISMA diagram (Figure 2). According to Table 1, the primary characteristics of the included studies are listed.

The effective rate

Five studies were included in total. The findings of the fixed effect model analysis revealed that the efficacy rate of acupuncture combined with balloon dilatation was statistically significantly greater than that of simple balloon dilatation [OR = 5.50, 95%CI (2.32, 13.05), $p = 0.0001$] (Figure 3).

Standardized swallowing function assessment scale (SSA)

Four studies were included in total. The fixed effect model analysis revealed that in the combination of acupuncture with balloon dilatation group, the SSA score was statistically significantly lower than in the simple balloon dilatation group [MD = −4.22, 95%CI (−4.57, −3.87), $p < 0.00001$] (Figure 4).

Videofluoroscopy swallowing study (VFSS)

7 studies were included in total. The findings of the fixed effect model analysis revealed that the VFSS score of

TABLE 1 Characteristics of the randomized controlled studies.

Study	N (T/C)	Average age ± SD (T/C, YrS)	Average course of disease ± SD (T/C)	Interventions		Treatment course	Outcomes
				T	C		
Cao et al. (2019)	30/30	61 ± 5/61 ± 5	30.86 ± 0.52/30.57 ± 0.64 (d)	Acupuncture + Balloon Dilation	Balloon Dilation	4 wks	②
Fan et al. (2020)	33/33	67.31 ± 5.36/66.58 ± 5.83	1.35 ± 0.59/1.29 ± 0.42 (mo)	Acupuncture + Balloon Dilation	Balloon Dilation	2 mo	③
Gao (2020)	24/24	52.68 ± 4.75/50.85 ± 4.69	4.82 ± 0.24/4.45 ± 0.16 (wks)	Acupuncture + Balloon Dilation	Balloon Dilation	4 wks	①-③
He (2017)	31/31	59.65 ± 8.58/59.00 ± 8.72	133.65 ± 29.52/131.55 ± 28.34 (d)	Acupuncture + Balloon Dilation	Balloon Dilation	1 mo	① ③
Li et al. (2019)	15/15	56 ± 8/57 ± 8	2.5 ± 1.6/2.5 ± 1.4 (mo)	Acupuncture + Balloon Dilation	Balloon Dilation	6 wks	③
Long et al. (2021)	30/30	60.53 ± 10.61/59.93 ± 12.89	21.73 ± 18.07/22.07 ± 16.74 (d)	Electroacupuncture + Balloon Dilation	Balloon Dilation	4 wks	① ②
Luo et al. (2020)	34/33	63.3 ± 7.3/62.6 ± 8.1	28.2 ± 6.8/29.4 ± 5.8 (d)	Acupuncture + Balloon Dilation	Balloon Dilation	4wks	① ③
Yang and Lei (2017)	24/24	60 ± 8/60 ± 5	4.57 ± 0.64/4.86 ± 0.52 (wks)	Tongue Acupuncture + Balloon Dilation	Balloon Dilation	4 wks	②
Zhang (2017)	20/20	63.56 ± 8.03/65.06 ± 11.09	2.72 ± 2.44/3.01 ± 2.88 (mo)	Acupuncture + Balloon Dilation	Balloon Dilation	-	③
Zhang (2019)	18/18	61 ± 9/59.3 ± 10.1	23.9 ± 16.1/25.3 ± 18.7 (d)	Acupuncture + Balloon Dilation	Balloon Dilation	20 d	① ③

①clinical treatment effects; ②SSA; ③VFSS.
T, experimental group; C, control group; min, minutes; d, days; wk, weeks; m, months; y, years.

the acupuncture combined with balloon dilatation group was statistically significantly higher than that of the simple balloon dilatation group [MD = 1.53, 95%CI (1.32, 1.75), $p < 0.00001$] (Figure 5).

Subgroup analyses

Based on VFSS scores, we performed analysis of 2 subgroups, including the average course of disease (<1 month vs. ≥1 month) and the average age (>60 years vs. ≤60 years).

The average course of disease

A total of two studies were included in the subgroup with an average course of disease was <1 month, and analyzed by fixed model showed that the VFSS score of acupuncture combined with balloon dilatation group was higher than that of simple balloon dilatation group [MD = 1.66, 95%CI (1.02, 2.30), $p < 0.00001$]. However, a total of 5 studies were included in subgroups with an average course of disease was ≥1 month, and analyzed by fixed effect model showed that the VFSS score in acupuncture combined with balloon dilatation group was also higher than that of simple balloon dilatation group [MD = 1.52, 95%CI (1.30, 1.74), $p < 0.00001$]. And acupuncture combined with balloon dilation showed a greater significant effect in patients whose course of disease is <1 month, with low heterogeneity between groups ($I^2 = 0\%$, $p = 0.69$) (Figure 6).

The average age

A total of four studies were included for subgroup with an average age over 60, and analyzed by fixed effect model. Average age subgroup analysis demonstrated that the VFSS score in acupuncture combined with balloon dilatation group was higher than that in the simple balloon dilatation group [MD = 1.84,95%CI (1.35, 2.33), $p < 0.00001$]. And three studies for subgroup with an average age ≤60 years showed the same result [MD = 1.47, 95%CI (1.23, 1.70), $p < 0.00001$]. However, the result in the >60 years group revealed a higher effect size than the control conditions. Among groups, there is moderate heterogeneity ($I^2 = 45.7\%$, $p = 0.17$) (Figure 7).

The treatment course

A total of two studies were included for the subgroup with the treatment course over 30 days, and analyzed by fixed effect model. Treatment course analysis demonstrated

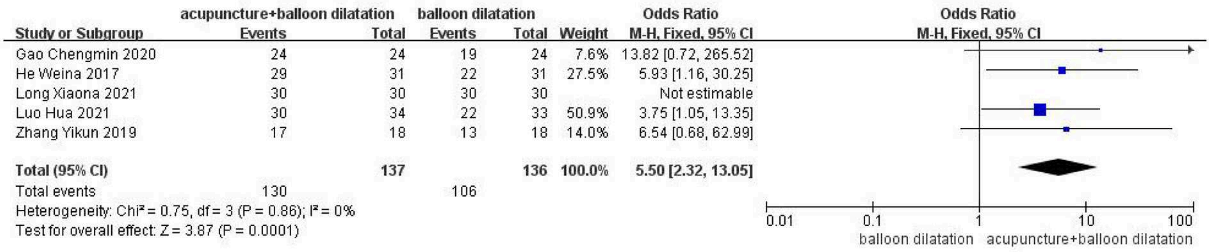

FIGURE 3
Forest plot for the effective rate.

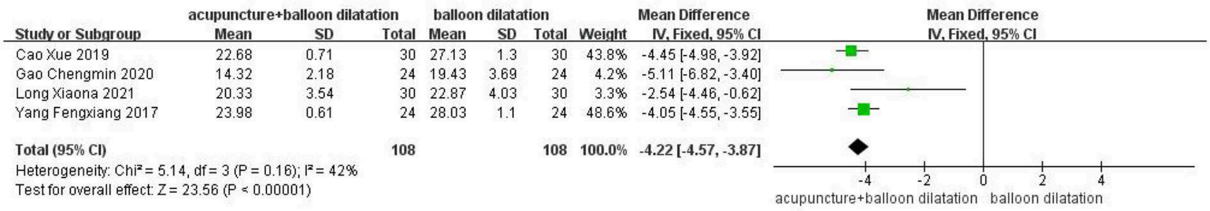

FIGURE 4
Forest plot for the SSA score.

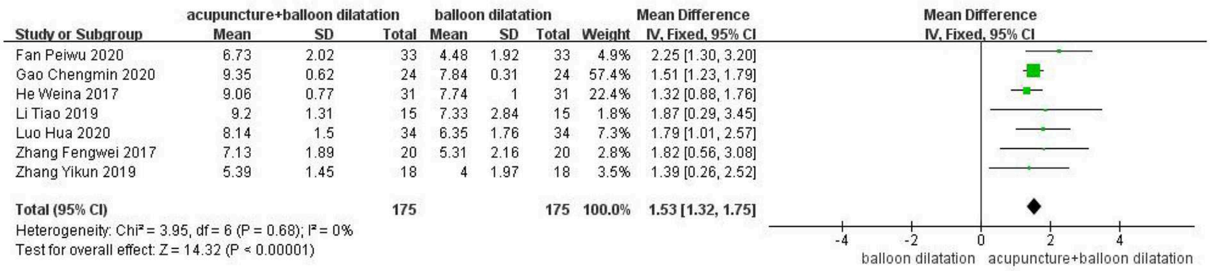

FIGURE 5
Forest plot for the VFSS score.

that the VFSS score in acupuncture combined with balloon dilatation group was higher than that in the simple balloon dilatation group [MD = 2.15, 95%CI (1.33, 2.96), $p < 0.00001$]. And 4 studies for subgroup with the treatment course ≤30 days showed the same result [MD = 1.48, 95%CI (1.26, 1.70), $p < 0.00001$]. However, the >30 days group result revealed a higher effect size than the control conditions. Among groups, there is moderate heterogeneity ($I^2 = 58.5\%$, $p = 0.12$) (Figure 8).

Risk of bias for independent studies

Bias risk assessment results are shown in Figures 9, 10.

Discussion

Post-stroke CPA is currently treated mainly with balloon dilatation, acupuncture neuromuscular electrical stimulation (NMES) through the skin, cricopharyngeal myotomy, taking botulinum toxin injections, etc. However, the clinical efficacy of the monotherapy is not satisfactory (Mason et al., 1998; Freed et al., 2001; Brigand et al., 2007; Bülow et al., 2008; Gallas et al., 2010; Kos et al., 2010; Rofes et al., 2013; Kocdor et al., 2016; Knigge and Thibeault, 2018; Lin, 2018). It is often argued that combined therapies might be more effective (Xie et al., 2021). Currently, balloon dilatation has become a commonly used method for treating post-stroke CPA (Dou et al., 2012). Patients suffering from post-stroke CPA can also benefit from

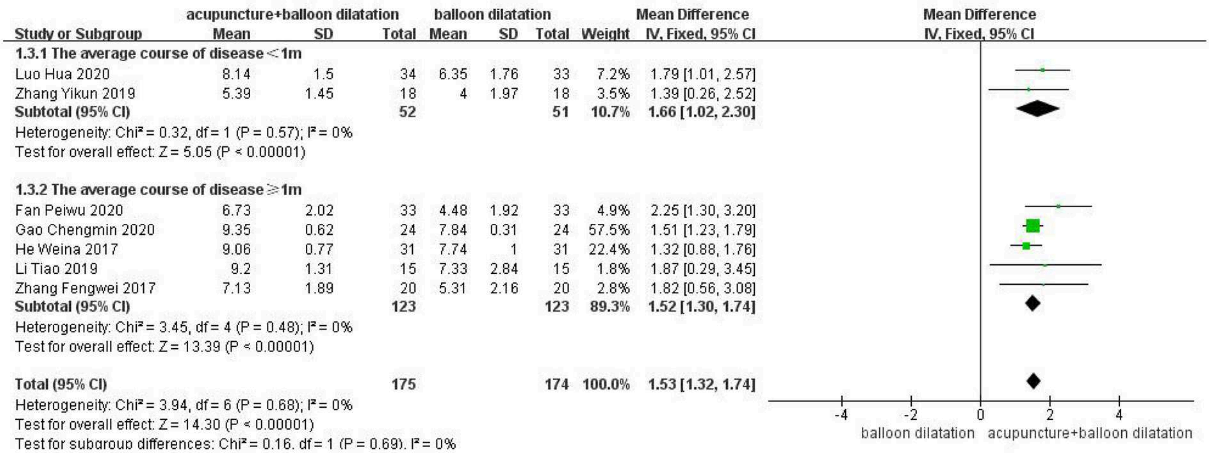

FIGURE 6
Forest plot for subgroup analysis for the average course of disease: the average course of disease <1 m vs. the average course of disease ≥1 m.

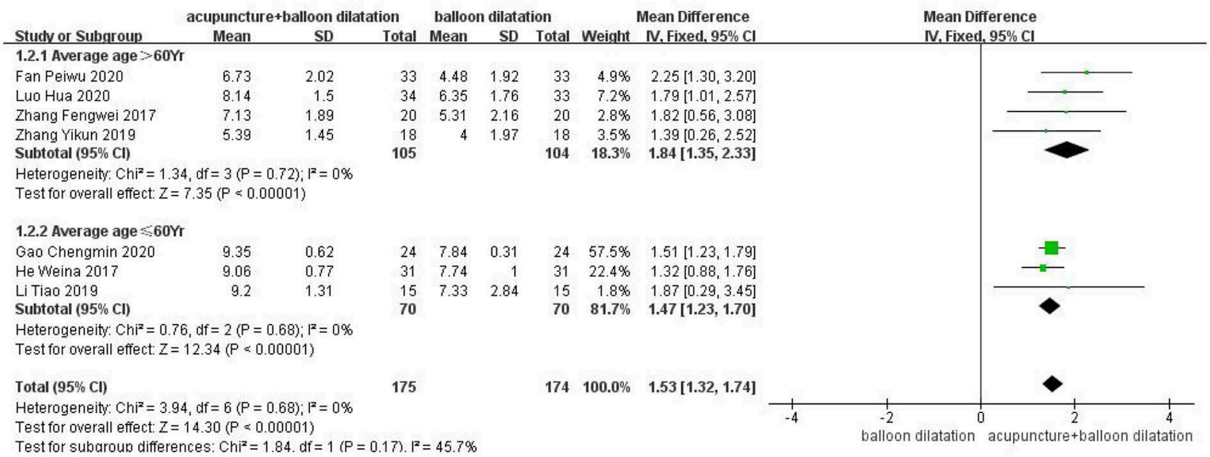

FIGURE 7
Forest plot for subgroup analysis for the average age: the average age >60 Yr vs. the average age ≤60 Yr.

acupuncture in terms of swallowing function, and acupuncture has fewer adverse reactions than other treatments (Jia et al., 2009; Dou et al., 2013; Arnold et al., 2016; Han and Gao, 2017; Rajahthurai et al., 2022). But there is no high-quality evidence for the effect of acupuncture combined with balloon dilation. Therefore, we conducted this Meta-analysis with different subgroups to explore the efficacy of acupuncture combined with balloon dilatation and simple balloon dilatation on post-stroke CPA, trying to provide more effective treatment for clinic. The results of this meta-analysis showed that acupuncture combined with balloon dilatation is a superior treatment comparing to simple balloon dilatation in treating post-stroke CPA. It is also effective for patients at different courses of the disease (less than one month or longer than one month), different ages (over 60 years old and under 60 years old) and different treatment course (over 30 days and under 30 days), while patients over 60 years old, and the treatment course over 30 days may have the better clinical outcome.

Acupuncture combined with balloon dilation may play their respective advantages. Post-stroke CPA manifests as tonic contraction or incoordination of the CPM (Luan et al., 2021). CPM is a significant component of the upper esophageal sphincter (UES) and it is innervated by the recurrent laryngeal nerve and the pharyngeal plexus vagus nerve (Lierse, 1992). Balloon dilatation provides sensory input to the swallowing center while expanding the CPM, strengthens the damaged cortical and subcortical connection, promotes nerve remodeling, as well as improving swallowing abilities

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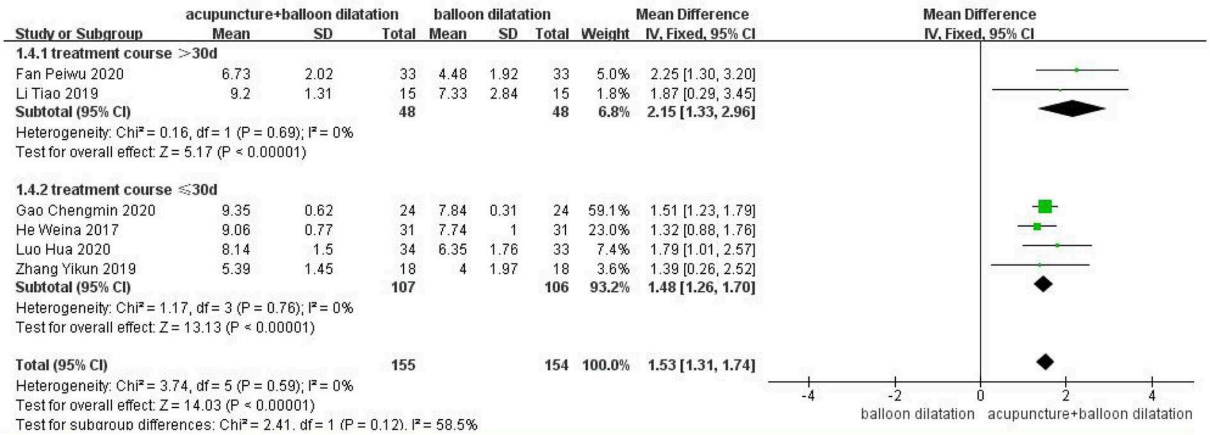

FIGURE 8
Forest plot for subgroup analysis for the treatment course: the treatment course >30 d vs. the treatment course ≤30 d.

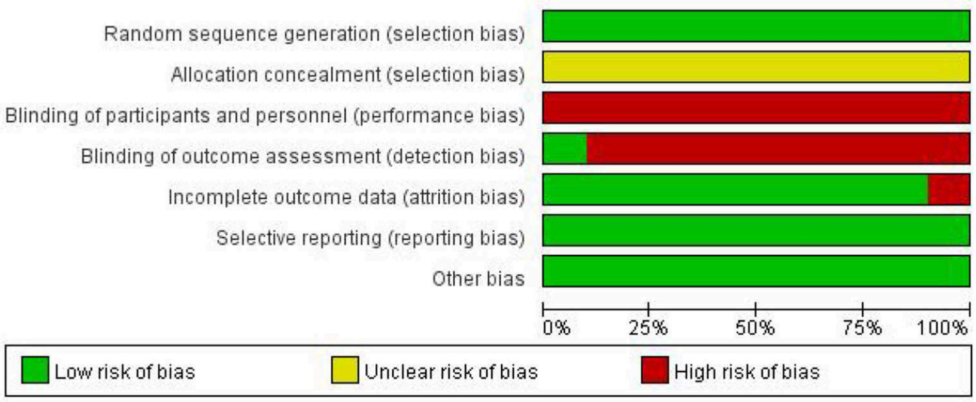

FIGURE 9
Performance of each type of bias in all studies.

(Dou et al., 2012). It is reported that, balloon dilatation has a certain effect in the early stage of the disease. However, the effect in the late follow-up gradually declines as time goes on, only 36% of the patients' symptoms have been relieved (Müller et al., 2018). Moreover, research had shown that, Simple balloon dilatation has poor effect on aspiration and dysphagia of some refractory post-stroke CPA patients with long course of the disease. It is difficult to solve the problems such as delayed start of swallowing, weakness of swallowing muscles, poor swallowing tolerance and aspiration. Many patients still need to rely on nasogastric tube to eat (Li et al., 2019). Guo and Malik (2019) found that acupuncture could stimulate glossopharyngeal, sublingual, and vagus nerves, regulate the excitability of the swallowing-related cerebral center, enhance brain plasticity and promote swallowing function. In addition, acupuncture can stimulate swallowing related muscles and regulate the tension of the CPM (Huang et al., 2020; Chen et al., 2022). Yao et al. (2022). found that acupuncture could improve the movement and sensory function of the pharynx, improve swallowing activation, and reducing the incidence of infiltration-misaspiration. This may be why acupuncture combined with balloon dilatation is superior to simple balloon dilatation for treating post-stroke CPA.

In the assessment of dysphagia, the VFSS is regarded as the gold standard. Based on VFSS assessment, subgroup analysis for different courses of the disease (<1 month or longer than 1 month) both revealed that there was a statistically significant difference between acupuncture combined with balloon dilatation group and simple balloon dilatation group. In comparison with balloon dilatation alone, acupuncture combined with balloon dilatation group showed a larger effect in improving the swallowing function of patients. It indicates that acupuncture combined with balloon dilatation may be a more effective treatment for different courses of post-stroke CPA. After the stroke, the patient's brain structure and connectivity have changed. Related studies have found that, the plasticity of the brain provides a basis for rehabilitation after stroke (Xie et al., 2022), as time goes on, the brain tissue has a certain ability to repair itself (Hermann and Chopp, 2012). Acupuncture combined with balloon dilatation may promote this compensation and repair mechanism, and reorganize the brain function of stroke patients (Zhang et al., 2021), thus improving swallowing function, promoting rapid recovery of patients, and shortening the disease's course. At present, research on the various stages of post-stroke CPA is still insufficient. Due to data limitations, we were unable to complete the detailed analysis of acupuncture combined with balloon dilatation in the acute phase, recovery phase, and sequelae phase.

According to the subgroup analysis of average ages, regardless of whether they were older or younger than 60, there was no difference between the two groups, the VFSS score of the acupuncture combined with balloon dilatation group was significantly higher than the balloon dilatation group (I^2= 45.7%, $p = 0.17$). Wilmskoetter et al. (2019). found that age is a negative predictor of the recovery for PSD. Interestingly, our meta-analysis found that acupuncture combined with balloon dilation had a larger effect size in the subgroup of older adults (MD = 1.84 > MD = 1.47). Acupuncture could promote the recovery of neuromuscular function, which may overcome the adverse effects of age on the repair of nerve injury, so that the damaged function could be better repaired. Shi et al. (1995) found the same effect in acupuncture treating for other diseases.

The subgroup analysis of the treatment course indicated a possible cumulative benefit of the combined therapy, with the prolongation of treatment duration, this suggested the dose-effect relationship of acupuncture combined with balloon dilation, and consistent with the previous study (Peng et al., 2018; Li et al., 2022; Xu et al., 2022). However, we cannot judge the best treatment course because of the limited literature. An implication of our result is that, in treating CPA, the treatment course of acupuncture combined with balloon dilation is preferably greater than 30 days.

Safety is a significant indicator in acupuncture studies, and we should have included it in our research. However, in extracting data from the original article, we found that only one piece mentioned safety indicators (adverse events), and its statistical adverse events were 0. In other articles, we did not mention to extract relevant data on security. Therefore, we cannot conduct further data analysis. This also reminds us to pay attention to the observation of safety indicators when doing research about acupuncture in the future.

Nonetheless, we should concede that this study has a few restrictions. First, in addition to age, disease duration, and treatment course, the patient's lesion location, stroke severity, and etiology can significantly impact on the prognosis of these patients. We should have included them in our research. However, in the original articles, the baseline data collection for this disease was primarily biased toward various functional evaluation tables. Most of the above specific vital factors were not mentioned or differentiated. We tried to contact the original author, but they have not replied. This meta-analysis may be affected by differences in the etiology, location of lesions, and stroke severity among the studies. Second, among the included articles, only one was in English, suggesting a bias in language selection. Finally, although the included articles had a good homogeneity, it should be noted that the evidence strength was still low due to the high risk of bias in the included studies, and the example size was small. Therefore, the conclusions should be interpreted with more caution, and more high-quality large-sample RCT literature analyses are urgently needed to confirm the conclusions.

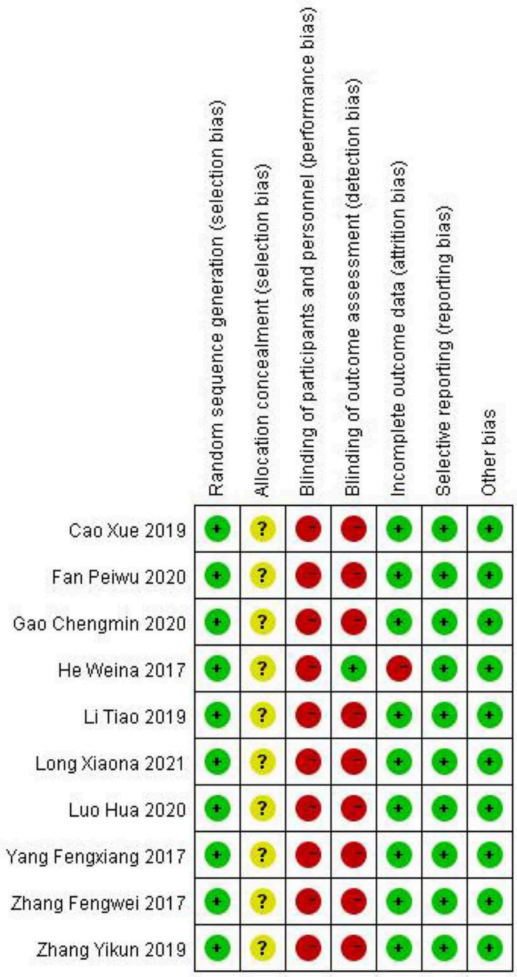

FIGURE 10
Summary plot of bias in all studies.

Conclusion

Post-stroke CPA may be treated effectively with acupuncture combined with balloon dilatation. In comparison with balloon dilatation alone, acupuncture combined with balloon dilatation can significantly improve the gulping capability of patients, and it is also effective for patients at different courses of the disease (less than one month or longer than one month), different ages (over 60 years old and under 60 years old) and different treatment course (over 30 days and under 30 days), while patients over 60 years old and the treatment course over 30 days may have the better clinical outcome.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JL responsible for article retrieval and writing. BH and HZ responsible for literature screening, data extraction, and statistical analysis. JL, BH, and HZ are joint first authors and contributed equally. ZY assists BH and HZ in their work. RL, ZF, WM, and MW responsible for bias risk assessment. MX and ZX responsible for the guidance on modification of this paper. SC responsible for the review of articles and ensuring that all listed authors have approved the manuscript before submission. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A systematic review with meta-analysis: Traditional Chinese tuina therapy for insomnia

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Background: With changes in the way of life and work, an increasing number of people are suffering from insomnia. In China, a traditional Chinese medicine method tuina is widely used for the treatment of insomnia. However, the evidence for tuina therapy for insomnia remains controversial. Therefore, this systematic review aimed to evaluate the effect of tuina therapy on the symptoms of patients with primary insomnia.

Methods: From establishment to January 2022, a comprehensive literature search was conducted using seven electronic databases to identify randomized controlled trials of tuina therapy for insomnia. We used RevMan 5.4 software and the GRADEpro Guideline Development Tool to evaluate the quality of the included randomized controlled trials and perform the meta-analysis. The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool. Subgroup analysis was performed according to the different intervention methods. The I2 statistic was used to assess the heterogeneity.

Results: Eighteen studies conducted from 2011 to 2021 were included, with a total of 1,471 patients. In terms of efficacy, tuina alone was superior to other treatments [odds ratio (OR), 3.46; 95% confidence interval (CI), 2.15, 5.55; $P < 0.00001$]; tuina combined with other treatments (acupuncture, scraping, auricular acupuncture, Suanzaoren decoction, estazolam) was more effective than other single therapies (OR, 3.99; 95% CI, 2.84, 5.61; $P < 0.00001$). In terms of Pittsburgh Sleep Quality Scale score, the improvement in insomnia patients by tuina alone was better than that of other treatments [standardized mean difference (SMD), −2.57; 95% CI, −2.98, −2.17; $P < 0.00001$], and tuina combined with other treatments (acupuncture, scraping, auricular point pressing, Suanzaoren decoction, estazolam) was better than other single therapies (SMD, −2.83; 95% CI, −2.98, −2.68; $P < 0.00001$).

Conclusion: This meta-analysis revealed that tuina can significantly improve the clinical efficacy and sleep quality of patients with primary insomnia. This study provides a theoretical basis and treatment guidance for patients with primary insomnia.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42022355742.

KEYWORDS

tuina, insomnia, randomized controlled trial, meta-analysis, effective rate, Pittsburgh Sleep Quality Scale

1. Introduction

Insomnia is a common sleep problem in modern society. It is also called "insomnia" or "blindness" in traditional Chinese medicine (TCM). It mainly manifests in a lack of sleep time and depth of sleep for various reasons. It may include dizziness, forgetfulness, fatigue, and other symptoms. Insomnia can be divided into two categories: primary and secondary. Primary insomnia refers to those who have insomnia symptoms despite lack of a clear cause or exclusion of what may be the cause of insomnia. The main causes of secondary insomnia include: (1) somatic organic diseases that affect the central nervous system; (2) alcohol, caffeine, or drugs that increase the excitability of the central nervous system; and (3) mental disorders, especially anxiety and depression, which are generally accompanied by insomnia. This review only focused on primary insomnia. Insomnia not only seriously affects the physical and mental health, and quality of life, of patients but also causes a variety of cardiovascular diseases (such as hypertension, coronary heart disease, and atherosclerosis), mental and psychological diseases (such as Alzheimer's disease, anxiety, and depression), and is an important risk factor for cognitive impairment (Chen and Yuan, 2021). According to statistics, 45.5% of Chinese people have sleep problems, and the risk factors include age, sex, family history, genetic factors, and drugs. Age is an important risk factor for insomnia, and insomnia increases with age. The prevalence of insomnia in China has gradually increased (Zhang et al., 2012). TCM believes that the pathogenesis of insomnia always involves the decline of yang and yin, the loss of yin and yang, the disharmony of qi and blood, and the dysfunction of the viscera.

At present, Western medicine, such as benzodiazepines and antidepressants, is the main treatment for insomnia. However, long-term application of these medicines has certain side effects. For example, benzodiazepines are not only associated with drug dependence and tolerance, but also contribute to the incidence of Alzheimer's disease, and some antidepressants may cause weight gain (Ye et al., 2017). TCM has a long history in treating insomnia, and it has been recorded in books such as "The Yellow Emperor's Classic of Internal Medicine," "On the Origin and Symptoms of Various Diseases," and "Puji Fang." Among them, tuina, as an important part of traditional medicine, has received attention in the treatment of insomnia owing to its advantages of simple administration, high safety, and good social and economic benefits. Tuina, a non-pharmacological intervention using fingers and strength, was developed from ancient therapeutic art. Tuina is a treatment based on TCM Zang-Fu organ and meridian theories, and integrates modern scientific knowledge (such as biomechanical function, anatomy, pathology, and physiology) with traditional practice. However, there is currently a lack of randomized controlled comparisons of the effectiveness of tuina compared with other intervention methods. This article uses a meta-analysis to comprehensively evaluate the effectiveness and safety of tuinas compared with other intervention methods to provide reliable evidence for clinical practice.

2. Methods

2.1. Trial registration

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (number: CRD42022355742).

2.2. Search strategy

The following Chinese databases were searched: China National Knowledge Infrastructure, Wanfang, VIP, China Biomedical Literature Database; the international databases included PubMed, Embase, Cochrane Library, and Web of Science. The retrieval period was from the establishment of the database to August 2022. The search adopted the method of subject words + free words. Chinese search terms included: "insomnia," "tuina," "tuinas," and "random control." English search terms included: "insomnia," "sleeplessness," "agrypnia," "tuina," "massage," "manipulation," "randomized controlled trial," and "RCT."

2.3. Study selection

Literature screening was performed independently by two reviewers according to the inclusion and exclusion criteria. The inclusion criteria for this review were as follows. (1) Type of study: randomized controlled trial (RCT). (2) Participant type: Participants with a clinical diagnosis of insomnia, age, sex, course of disease, race, nationality, and TCM syndrome were not limited. (3) Types of intervention: The experimental group was treated with simple tuina therapy, while the control group was treated with treatments other than tuina therapy, such as acupuncture, moxibustion, and drugs. The experimental group received tuina + other therapy, and the control group received another therapy. There were no restrictions on the operation time, specific techniques, parts, acupoint selection, and treatment course of the tuina. (4) Outcome types: The total clinical response was the primary outcome, and the Pittsburgh Sleep Quality Index (PSQI) was the secondary outcome. We excluded (1) quasi-randomized RCT and non-randomized trials, (2) duplicate publications, and (3) studies without the full text available or missing data. Any disagreements were resolved through discussions between the two reviewers.

2.4. Data extraction

Two researchers independently searched the literature, performed preliminary screening according to the title and abstract, read the full text of the studies meeting the inclusion criteria, screened again according to the inclusion and exclusion criteria, and conducted a reference search for the included studies. Data extraction was performed for the included literature, including literature title, first author, publication year, sample size, intervention method, patient baseline data, outcome indicators, and the occurrence of adverse conditions. Any disagreement was discussed by all those involved in the audit.

2.5. Quality assessment

Two investigators evaluated the methodological quality of the included studies using the Cochrane risk bias assessment tool. According to the evaluation criteria, the following five items were rated as low, unclear, and high risk: ① generation of random allocation sequence; ② allocation concealment; ③ blinding of investigators and participants; ④ blind evaluation of study outcomes; and ⑤ completeness of outcome data. Any disagreements were resolved by obtaining consensus from all reviewers.

2.6. Data synthesis and analysis

First, a heterogeneity Q-test was performed. For results with $p > 0.10$, multiple similar studies were considered to be homogenous. If $p > 0.10$, and $0 \leq I^2 \leq 50\%$, the combined analysis between the study results used a fixed effect model; if $p \leq 0.10$, or $I^2 > 50\%$, the results of multiple similar studies were considered heterogeneous, and sensitivity analysis was performed first. A random effect model was used for combined analysis. Continuous variables used the standardized mean difference (SMD) with 95% confidence interval (CI), and dichotomous variables used the odds ratio (OR) with 95% CI to indicate the effect size; the test results were listed in a forest plot. Subgroup analysis was performed according to the different intervention methods. If more than 10 articles were included in the analysis, a funnel plot was drawn to analyze publication bias. Statistical significance was set at $p < 0.05$. Statistical analysis and the meta-analysis were performed using Review Manager version 5.4 (The Cochrane Collaboration, London, England).

3. Results

3.1. Search and selection

A total of 941 related articles were obtained, and 673 articles remained after the software was deduplicated. According to the inclusion and exclusion criteria, 20 articles were finally included. The inclusion process is illustrated in **Figure 1**.

3.2. Characteristics of the included studies

The included studies (Ye et al., 2017) were all Chinese RCTs, with a total of 1,713 insomnia patients, 858 in the treatment group and 855 in the control group. Ten studies used tuina alone to treat insomnia. The intervention methods in the control group included estazolam, acupuncture, Longdan Xiegan pills, Jieyu Anshen granules, Guipi decoction, and auricular point sticking. Eight studies used tuinas in combination with other therapies to treat insomnia. The control group received acupuncture, scraping, estazolam, Suanzaoren decoction, and auricular acupuncture. The course of tuina therapy was 14–30 days, and the majority were 20 days. Each tuina treatment time was 20–40 min, and the frequency was mostly once per day. Primary outcomes included the overall response rate and PSQI. The basic characteristics of the included studies are shown in **Table 1**.

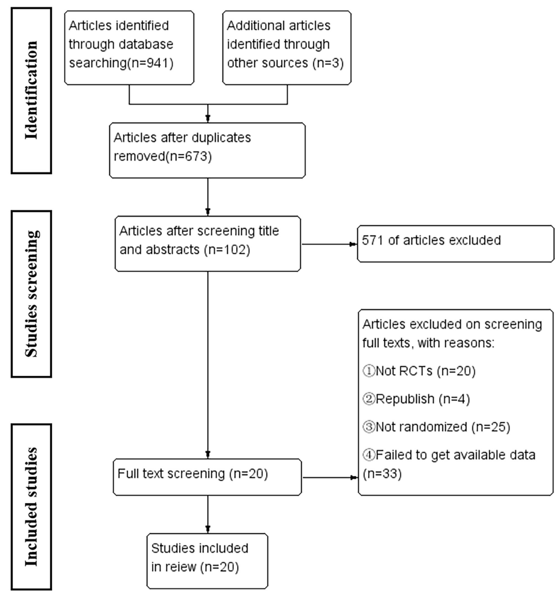

FIGURE 1
Flow chart for the review.

3.3. Methodological quality

The 20 included studies applied the principle of randomization and most of the studies had good methodological quality. Among them, eight (Zhang et al., 2011; Luo, 2012; Xu, 2012; Pang et al., 2015; Wu, 2019; Wang, 2019, 2020; Zhuang, 2020) studies used the random number table method, two (Pan, 2018; Zhang et al., 2020) studies were randomly assigned according to the order of visits, one (Liu, 2019) study used the envelope random method, and one [4] study used computer-generated random numbers. Other studies did not describe the randomized methods used. Only four (Luo, 2012; Pan, 2018; Liu, 2019; Wu, 2019) studies had detailed hidden assignments. All of the included RCTs were free of subject blinding and treatment. One study (Yu, 2013) described the reasons for dropout in detail, and another study (Pan, 2018) only mentioned the number of people who were compared for efficacy or the intervention effect, and the report with an incomplete outcome was judged as "low risk." In three studies (Pang et al., 2015; Shi et al., 2017; Pan, 2018), although cases were dropped, the reasons were not described, and it was not possible to determine whether they were selective outcome reports. No other biases were evident in the included studies. See **Figures 2**, **3**.

3.4. Synthesis of the results

3.4.1. Overall efficacy

In terms of the total effective rate, 20 studies reported that tuina can significantly improve the clinical symptoms of insomnia patients better than the control group (OR, 3.98; 95% CI, 2.91, 5.45; $P < 0.00001$, $I^2 < 50\%$, **Figure 4**). The sensitivity analysis showed that the above results were similar and not significantly different.

In the subgroup analysis, as an independent treatment, tuina therapy improved insomnia better than the other treatments (OR, 3.57; 95% CI, 2.37, 5.37; $P < 0.00001$, **Figure 5A**). In studies of tuina combined with other therapies, the efficacy was better than that of

TABLE 1 Randomized controlled trials evaluating the effects of tuina for insomnia.

References	Sample size	Duration (year)	Follow-up (months)	Experimental group intervention	Control group intervention	Main outcomes
Feng, 2017	100 100	3.1 ± 0.5 3.2 ± 0.8	/	Acupuncture (30 min, 1/day, 21 days)	Tuina + Acupuncture (1/day, 21 days)	Overall efficiency, PSQI
Liu, 2019	30 30	/	/	Longdan Xiegan Pills (2/day, 10 days)	Tuina (30 min, 1/day, 10 days)	Overall efficiency, PSQI
Luo, 2012	30 30	1.21 ± 0.52 1.19 ± 0.56	/	Acupuncture (20 min, 1/day, 15 days)	Tuina (30 min, 1/day, 15 days)	Overall efficiency, PSQI
Pan, 2018	29 28	/	/	Estazolam (1/day, 14 days)	Tuina (1/day, 14 days)	Overall efficiency, PSQI
Pang et al., 2015	77 73	2.25 ± 1.31 2.42 ± 1.15	/	Estazolam (1/day, 30 days)	Tuina (20 min, 1/day, 30 days)	Overall efficiency, PSQI
Shi et al., 2017	45 42	4.78 ± 4.56 4.56 ± 4.23	/	Acupuncture (20 min, 1/day, 20 days)	Tuina + Acupuncture (1/day, 20 days)	Overall efficiency, PSQI
Tang et al., 2015	38 38	1.75 ± 1.47 1.67 ± 1.30	/	Estazolam (1/day, 30 days)	Tuina (1/day, 30 days)	Overall efficiency, PSQI
Wang, 2019	40 40	3.4 ± 1.1 3.3 ± 0.8	/	Acupuncture (30 min, 1/day, 21 days)	Tuina + Acupuncture (1/day, 21 days)	Overall efficiency, PSQI
Wang, 2020	44 44	/	/	Scraping (1/day, 20 days)	Tuina + Scraping (1/day, 20 days)	Overall efficiency, PSQI
Wang, 2021	30 30	2.93 ± 0.79 2.98 ± 0.76	/	Acupuncture (30 min, 1/day, 30 days)	Tuina + Acupuncture (1/day, 21 days)	Overall efficiency, PSQI
Wei et al., 2013	40 40	2.18 ± 1.15 2.2 ± 1.12	/	Estazolam (1/day, 20 days)	Tuina (1/day, 20 days)	Overall efficiency, PSQI
Wu, 2019	30 30	/	/	Guipi Tang (1/day, 4 weeks)	Tuina (25 min, 3/week, 4 weeks)	Overall efficiency, PSQI
Xu, 2012	30 30	1.43 ± 1.07 1.59 ± 1.38	/	Auricular pressure (1/3 days, 30 days)	Tuina (30 min, 1/day, 30 days)	Overall efficiency, PSQI
Yu, 2013	28 31	/	/	Guipi Tang (3/day, 28 days)	Tuina (30 min, 1/day, 14 days)	Overall efficiency, PSQI
Zhang et al., 2011	30 36	/	/	Jieyu Anshen Granules (2/day, 21 days)	Tuina (1/day, 15 days)	Overall efficiency, PSQI
Zhang et al., 2020	30 30	2.4 ± 1.2 1.8 ± 0.9	/	Estazolam (1/day, 20 days)	Tuina (20 min, 1/2 days, 20 days)	Overall efficiency, PSQI
Zhang, 2021	35 35	0.56 ± 0.28 0.55 ± 0.29	/	Auricular pressure (1/2days, 20 days)	Tuina + Auricular pressure (1/day, 18 days)	Overall efficiency, PSQI
Zhou et al., 2007	84 82	/	/	Guipi Pills (3/day, 15 days)	Tuina (3/day, 15 days)	Overall efficiency, PSQI
Zhou et al., 2017	37 37	3.6 ± 2.1 3.7 ± 2.2	/	Suanzaoren Tang (2/day, 20 days)	Tuina + Suanzaoren Tang (1/day, 20 days)	Overall efficiency, PSQI
Zhuang, 2020	50 50	4.04 ± 0.57 4.03 ± 0.56	/	Estazolam (1/day, 20 days)	Tuina + Estazolam (1/day, 20 days)	Overall efficiency, PSQI

PSQI, Pittsburgh Sleep Quality Index.

other therapies alone (OR, 4.63; 95% CI, 2.83,7.57; P < 0.00001; Figure 5B). The sensitivity analysis showed that the above results were similar and not significantly different.

The subgroup analysis also showed that the use of tuina alone improved clinical symptoms in insomnia patients better than herbal treatment alone (OR, 4.34; 95% CI, 2.33, 8.08; P < 0.00001, Figure 6A) and eszopiclone treatment alone (OR, 3.03, 95% CI, 1.66,5.54; P = 0.0003; Figure 6B). Among the combination therapies, tuina combined with acupuncture was superior to acupuncture alone (OR, 3.91, 95% CI, 2.20,6.93; P < 0.00001; Figure 6C). The sensitivity analysis yielded similar and non-significant differences in these results.

3.4.2. PSQI

The combined results of the PSQI score showed that tuina therapy could improve the sleep status of patients with insomnia (SMD, −1.55; 95% CI, −1.97, −1.13; P < 0.00001; I^2 > 50%, Figure 7). The sensitivity analysis showed that the above results were similar and not significantly different.

In the subgroup analysis, tuina alone was lower than other treatments in the total PSQI score and could better improve the PSQI score of insomnia patients (SMD, −0.92; 95% CI, −1.26, −0.58; P < 0.00001, Figure 8A). Tuina combined with other therapies in the treatment of insomnia could significantly improve the PSQI score of patients compared to other therapies alone (SMD, −2.57; 95%

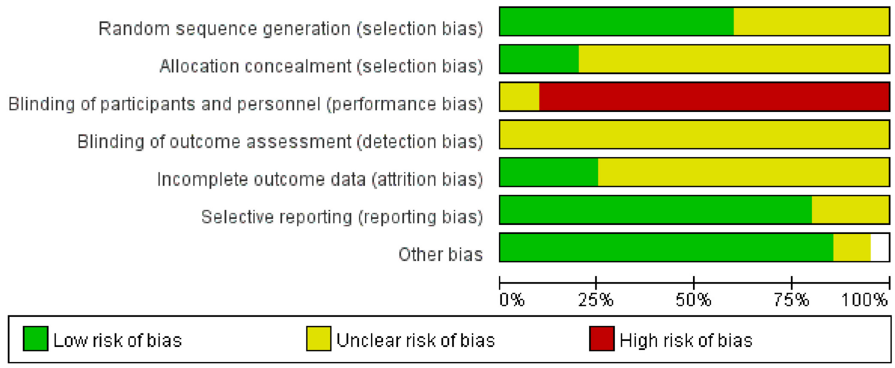

FIGURE 2
Risk of bias in included studies.

CI, −3.28, −1.87; $P < 0.00001$, **Figure 8B**). The sensitivity analysis showed that the above results were similar and not significantly different.

The subgroup analysis showed that the use of tuina alone improved the PSQI scores of insomnia patients better than herbal treatment alone (SMD; −0.89; 95% CI, −1.65, −0.13; $P < 0.00001$, **Figure 9A**) and eszopiclone treatment alone (SMD, −1.69; 95% CI, −2.53, −0.86; $P < 0.00001$, **Figure 9B**). Among the combination therapies, tuina combined with acupuncture was more effective than acupuncture alone (SMD, −2.65; 95% CI, −3.50, −1.79; $P < 0.00001$; **Figure 9C**). The sensitivity analysis yielded similar and non-significant differences in these results.

3.4.3. Publication bias

The funnel plot of tuina in improving patients with primary insomnia included 20 RCTs (**Figure 10A**). The funnel plot was somewhat biased because the blobs were asymmetrical. Sensitivity analysis was carried out by excluding literature one by one, and it was found that the bias after excluding three studies (Zhou et al., 2017; Zhuang, 2020; Zhang, 2021) was low, and the spots were basically symmetrical, as shown in **Figure 10B**. The comprehensive analysis results after exclusion were relatively stable (OR, 3.70; 95% CI, 2.68,5.11; $P < 0.00001$; **Figure 11**). Reevaluation of the three studies revealed that the source of heterogeneity was possibly related to intervention frequencies, inconsistent times, and different indicator measures among institutions.

3.4.4. Quality of evidence

The GRADEpro Guideline Development Tool was employed to assess the quality of all the outcomes from five aspects, including the risk of bias, inconsistency, indirectness, imprecision, and other considerations. The included studies have some defects in randomization, allocation concealment, and blinding, which were downgraded one level because of risk of bias. One outcome was downgraded one level in terms of consistency due to the high heterogeneity of the results. The final results revealed that five outcomes were of medium quality and six were of low quality, as shown in **Table 2**.

3.4.5. Adverse events

None of the included studies reported whether there were adverse events or not.

4. Discussion

This systematic review and meta-analysis evaluated the efficacy of tuinas in the treatment of primary insomnia. The results show that tuina therapy can significantly improve the clinical symptoms and PSQI scores of patients with primary insomnia. The curative effect of pure tuina in treating insomnia is better than that of acupuncture, estazolam, TCM, and other treatments, and the curative effect of tuina combined with acupuncture, Suanzaoren decoction, estazolam, and other treatments is better than that of acupuncture alone. However, there is not enough evidence to support that tuina alone is superior to acupuncture and auricular sticking alone in improving the efficacy in insomnia patients. There is also insufficient evidence to prove the efficacy of tuina combined with estazolam and TCM in the treatment of insomnia, which is better than that of estazolam and TCM alone. Moreover, there is insufficient evidence on the long-term efficacy of tuina in insomnia patients, which may be related to the lack of included studies and the lack of follow-up in most studies.

In the included studies, other combined therapies included acupuncture, TCM, estazolam, scraping, and auricular sticking; however, due to the limited number of included studies, only subgroup analyses were performed on studies of tuina combined with acupuncture. Furthermore, the effect of tuina therapy on the mental health of patients with primary insomnia has not been addressed in any study. We found that tuina therapy has a certain effect on improving anxiety and depression in patients with insomnia (Luo, 2012; Pan, 2018; Wu, 2019). Tuina manipulation may act on the body surface and produce a stimulating effect by touching the tactile receptors on the skin, causing the excitation of tactile receptors, baroreceptors, and deep tissue pulling receptors, forming action potentials of different frequencies and numbers, and then through the complex ascending pathway of afferent nerves, reaching different nerve centers (Fang and Fang, 2013). Finally, the nerve-endocrine-endocrine pathway, one of the three intermediary pathways of the immune system, plays an extensive and effective role in regulation and treatment (Guo, 2009). In these three studies (Luo, 2012; Pan, 2018; Wu, 2019), the intervention methods of the experimental group were tuinas alone, and the combined therapy of tuinas was not included. Therefore, our review provides strong evidence for tuina therapy in the improvement of anxiety and depression in patients with primary insomnia.

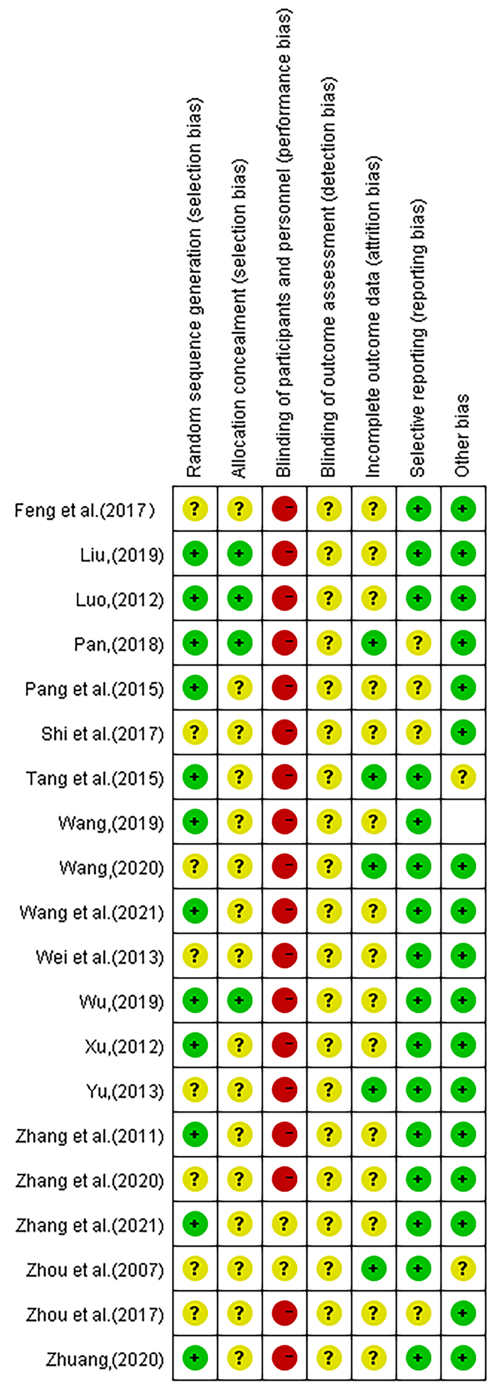

FIGURE 3
Risk of bias in included studies.

In China, tuina is often used as adjunct therapy for neck pain. Our review included studies that used tuina plus acupuncture, herbal remedies, or medications to treat insomnia. Therefore, we reviewed the complementary and independent effects of tuina in the treatment of insomnia and conducted a subgroup analysis in the meta-analysis according to whether tuina was combined with other treatments. A previous systematic review (Yang et al., 2019) was consistent with the results of our review. Therefore, there is strong evidence in our review that tuinas can effectively treat insomnia.

Progress has also been made in the study of tuina for the treatment of insomnia by modulating neural circuitry. Current studies show that the anterior cingulate, amygdala, hippocampus, thalamus, and nucleus accumbens are involved in sleep-wake regulation in humans (Liu et al., 2020). When the body is in a state of arousal or when the ability to fall asleep is impaired, studies have identified associations between cognitive functions and dysregulation of the loops located in the limbic cortical system, which is closely associated with the formation of insomnia (Perrier et al., 2015). Gamma-aminobutyric acidergic neurons within the ventral lateral preoptic area of the hypothalamus (ventrolateral preoptic area) are considered to be the sleep nuclei, while neurons within the nuclei such as the nucleus "blue spot" and nodal papillary nuclei are referred to as the nuclei of arousal (Yi and Zhang, 2019). Many multifunctional nuclei are present in the lateral hypothalamic area involved in the sleep-wake cycle, eating, and metabolism (Stuber and Wise, 2016), and dysfunction of these nuclei can trigger insomnia symptoms. In a further study of brain mechanisms, the hypothalamic paraventricular nucleus-paraventricular nucleus neural circuit was identified as necessary for sleep-wake regulation (Liu, 2021). Researchers (Zhi et al., 2022) found that abdominal thrusting in an insomnia rat model significantly improved the neurotransmitters 5-HT and β-EP in the hypothalamus. They hypothesized that, through the observation of electroencephalogram activity, the information generated by abdominal thrusting could be transmitted to the hypothalamus through the lower centers of the brain to regulate secretion of the related neurotransmitters by altering the functional changes of sleep-wake nuclei, such as the nucleus blue spot and nodal papillary nucleus within the hypothalamus, thereby regulating excessive arousal and improving insomnia. Zhang (2022) used the vibration abdominal ring kneading method to intervene in PI model rats, and the results showed that the behavioral scores of rats improved while the number of corticotropin-releasing hormone receptors 1 and 2 and gamma-aminobutyric acid levels decreased in the hypothalamus after the tuina intervention. These findings suggest the key role of regulating the hypothalamic corticotropin-releasing hormone-receptor pathway in the treatment of insomnia using the vibration abdominal ring kneading method. Another study found (Hu, 2018) that the occipitofrontal neural circuit had an influential role in the process of tuina treatment in PI patients, with a positive correlation to improved sleep indicators.

Research has shown that the main causes of insomnia are hypothalamic-pituitary-adrenal axis dysfunction, changes in vagal tone, and central neurotransmitter disorders (Cheng et al., 2016). Tuina, as a non-drug therapy for insomnia, may exert pressure through tactile receptors, improve blood circulation, regulate the excitation and inhibition of the central system and cerebral cortex, increase the level of serotonin in patients with insomnia, and improve health. Sleep status (Yao, 2014), may be related to the improvement in patients' clinical symptoms and PSQI scores. Tuina manipulation is gentle and deep, which can effectively relieve pressure on patients and relax skeletal muscles. Simultaneously, tuina manipulation can further regulate the central nervous system by stimulating the meridians and acupoints. This may be the potential mechanism by which tuina improves the anxiety and depression scores of patients with insomnia. However, its specific mechanism of action remains unclear.

According to the theory of TCM, the secretion of yang-ping is an important condition for the normal realization of the function of the viscera, and TCM believes that the loss of communication

Study or Subgroup	Tuina Events	Tuina Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Feng et al.(2017)	93	100	75	100	11.9%	4.43 [1.82, 10.80]
Liu,(2019)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Luo,(2012)	28	30	21	30	3.2%	6.00 [1.17, 30.72]
Pan,(2018)	26	28	24	29	3.8%	2.71 [0.48, 15.29]
Pang et al.(2015)	68	73	60	77	9.1%	3.85 [1.34, 11.08]
Shi et al.(2017)	36	42	30	45	9.4%	3.00 [1.04, 8.69]
Tang et al.(2015)	35	38	32	38	5.7%	2.19 [0.50, 9.48]
Wang,(2019)	37	40	29	40	4.9%	4.68 [1.19, 18.34]
Wang,(2020)	41	44	34	44	5.3%	4.02 [1.02, 15.79]
Wang et al.(2021)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Wei et al.(2013)	38	40	34	40	3.9%	3.35 [0.63, 17.74]
Wu,(2019)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Xu,(2012)	28	30	25	30	3.8%	2.80 [0.50, 15.73]
Yu,(2013)	28	31	22	28	5.1%	2.55 [0.57, 11.34]
Zhang et al.(2011)	31	36	21	30	7.2%	2.66 [0.78, 9.05]
Zhang et al.(2020)	26	30	24	30	7.2%	1.63 [0.41, 6.47]
Zhang et al.(2021)	35	35	28	35	0.9%	18.68 [1.02, 341.22]
Zhou et al.(2007)	81	84	60	82	4.9%	9.90 [2.83, 34.61]
Zhou et al.(2017)	37	37	33	37	1.0%	10.07 [0.52, 194.16]
Zhuang,(2020)	49	50	43	50	1.9%	7.98 [0.94, 67.46]
Total (95% CI)		**858**		**855**	**100.0%**	**3.98 [2.91, 5.45]**
Total events	801		667			

Heterogeneity: Chi² = 8.01, df = 19 (P = 0.99); I² = 0%
Test for overall effect: Z = 8.62 (P < 0.00001)

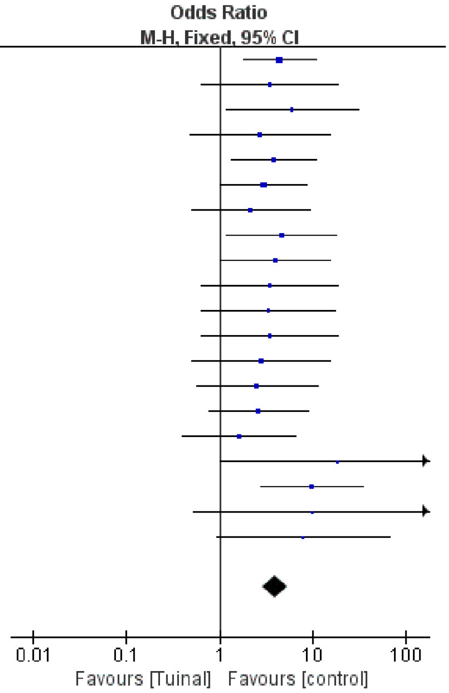

FIGURE 4
Meta-analysis of objective response rate (ORR).

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
A 3.1.1 Tuina vs Other therapies						
Liu,(2019)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Luo,(2012)	28	30	21	30	3.2%	6.00 [1.17, 30.72]
Pan,(2018)	26	28	24	29	3.8%	2.71 [0.48, 15.29]
Pang et al.(2015)	68	73	60	77	9.1%	3.85 [1.34, 11.08]
Tang et al.(2015)	35	38	32	38	5.7%	2.19 [0.50, 9.48]
Wei et al.(2013)	38	40	34	40	3.9%	3.35 [0.63, 17.74]
Wu,(2019)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Xu,(2012)	28	30	25	30	3.8%	2.80 [0.50, 15.73]
Yu,(2013)	28	31	22	28	5.1%	2.55 [0.57, 11.34]
Zhang et al.(2011)	31	36	21	30	7.2%	2.66 [0.78, 9.05]
Zhang et al.(2020)	26	30	24	30	7.2%	1.63 [0.41, 6.47]
Zhou et al.(2007)	81	84	60	82	4.9%	9.90 [2.83, 34.61]
Subtotal (95% CI)		**480**		**474**	**61.1%**	**3.57 [2.37, 5.37]**
Total events	445		371			
Heterogeneity: Chi² = 5.24, df = 11 (P = 0.92); I² = 0%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
B 3.1.2 Tuina+other therapies vs Other therapies						
Feng et al.(2017)	93	100	75	100	11.9%	4.43 [1.82, 10.80]
Shi et al.(2017)	36	42	30	45	9.4%	3.00 [1.04, 8.69]
Wang,(2019)	37	40	29	40	4.9%	4.68 [1.19, 18.34]
Wang,(2020)	41	44	34	44	5.3%	4.02 [1.02, 15.79]
Wang et al.(2021)	28	30	24	30	3.6%	3.50 [0.65, 18.98]
Zhang et al.(2021)	35	35	28	35	0.9%	18.68 [1.02, 341.22]
Zhou et al.(2017)	37	37	33	37	1.0%	10.07 [0.52, 194.16]
Zhuang,(2020)	49	50	43	50	1.9%	7.98 [0.94, 67.46]
Subtotal (95% CI)		**378**		**381**	**38.9%**	**4.63 [2.83, 7.57]**
Total events	356		296			
Heterogeneity: Chi² = 2.19, df = 7 (P = 0.95); I² = 0%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Total (95% CI)		**858**		**855**	**100.0%**	**3.98 [2.91, 5.45]**
Total events	801		667			

Heterogeneity: Chi² = 8.01, df = 19 (P = 0.99); I² = 0%
Test for overall effect: Z = 8.62 (P < 0.00001)
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%

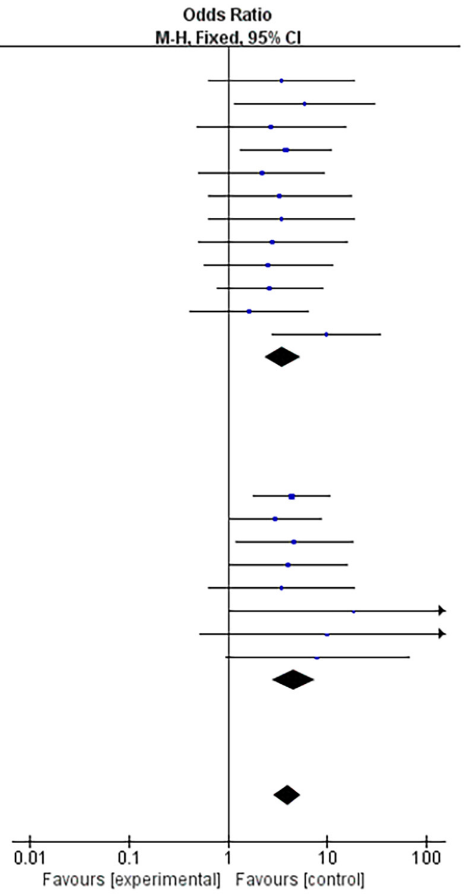

FIGURE 5
Forest plot of tuina for objective response rate (ORR). **(A)** Tuina vs. Other therapies. **(B)** Tuina + Other therapies vs. Other therapies.

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Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
A 3.3.1 Tuina vs Traditional Chinese medicine						
Liu,(2019)	28	30	24	30	4.3%	3.50 [0.65, 18.98]
Wu,(2019)	28	30	24	30	4.3%	3.50 [0.65, 18.98]
Yu,(2013)	28	31	22	28	6.0%	2.55 [0.57, 11.34]
Zhang et al.(2011)	31	36	21	30	8.6%	2.66 [0.78, 9.05]
Zhou et al.(2007)	81	84	60	82	5.9%	9.90 [2.83, 34.61]
Subtotal (95% CI)		**211**		**200**	**29.1%**	**4.34 [2.33, 8.08]**
Total events	196		151			
Heterogeneity: Chi² = 2.90, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 4.63 (P < 0.00001)						
B 3.3.2 Tuina vs Estazolam						
Pan,(2018)	26	28	24	29	4.5%	2.71 [0.48, 15.29]
Pang et al.(2015)	68	73	60	77	10.8%	3.85 [1.34, 11.08]
Tang et al.(2015)	35	38	32	38	6.8%	2.19 [0.50, 9.48]
Wei et al.(2013)	38	40	34	40	4.6%	3.35 [0.63, 17.74]
Zhang et al.(2011)	31	36	21	30	8.6%	2.66 [0.78, 9.05]
Subtotal (95% CI)		**215**		**214**	**35.3%**	**3.03 [1.66, 5.54]**
Total events	198		171			
Heterogeneity: Chi² = 0.46, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 3.60 (P = 0.0003)						
C 3.3.3 Tuina+acupuncture vs Acupuncture						
Feng et al.(2017)	93	100	75	100	14.2%	4.43 [1.82, 10.80]
Shi et al.(2017)	36	42	30	45	11.2%	3.00 [1.04, 8.69]
Wang,(2019)	37	40	29	40	5.9%	4.68 [1.19, 18.34]
Wang et al.(2021)	28	30	24	30	4.3%	3.50 [0.65, 18.98]
Subtotal (95% CI)		**212**		**215**	**35.5%**	**3.91 [2.20, 6.93]**
Total events	194		158			
Heterogeneity: Chi² = 0.40, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 4.66 (P < 0.00001)						
Total (95% CI)		**638**		**629**	**100.0%**	**3.72 [2.64, 5.26]**
Total events	588		480			
Heterogeneity: Chi² = 4.26, df = 13 (P = 0.99); I² = 0%						
Test for overall effect: Z = 7.47 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%						

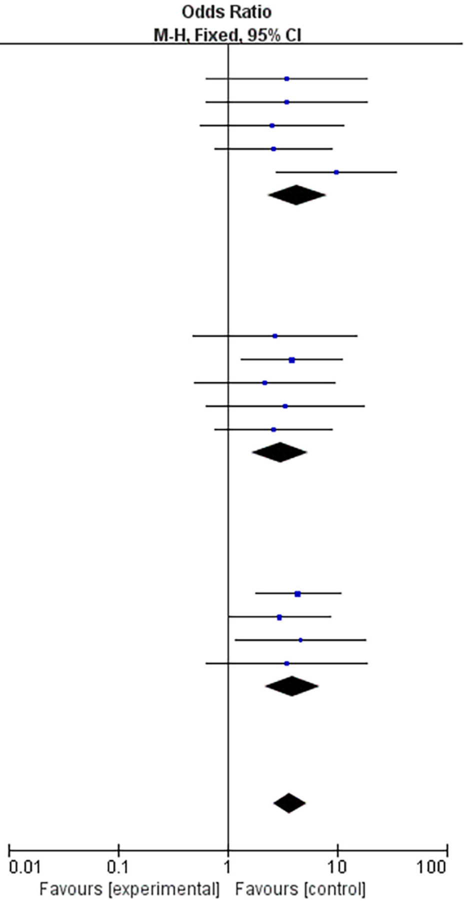

FIGURE 6
Subgroup analysis of tuina and different interventions in ORR. **(A)** Traditional Chinese Medicine (TCM). **(B)** Estazolam. **(C)** Acupuncture.

Study or Subgroup	Tuina Mean	Tuina SD	Tuina Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Feng et al.(2017)	5.39	0.51	100	7.71	1.19	100	5.2%	-2.52 [-2.90, -2.15]
Liu,(2019)	6.3	2.76	30	8.97	3.34	30	5.0%	-0.86 [-1.39, -0.33]
Luo,(2012)	5.7	2.31	30	7.93	2.59	30	5.0%	-0.90 [-1.43, -0.36]
Pan,(2018)	5.5	2.37	28	9.6	3.84	29	5.0%	-1.26 [-1.83, -0.69]
Pang et al.(2015)	5.32	1.65	73	8.31	2.28	77	5.2%	-1.49 [-1.85, -1.13]
Shi et al.(2017)	4.82	2.71	42	8.63	2.44	45	5.1%	-1.47 [-1.94, -0.99]
Tang et al.(2015)	3.32	2.65	38	6.58	3.98	38	5.1%	-0.95 [-1.43, -0.48]
Wang,(2019)	5.4	0.5	40	7.9	1.1	40	4.9%	-2.90 [-3.53, -2.26]
Wang,(2020)	4.37	1.14	44	7.01	1.27	44	5.0%	-2.17 [-2.70, -1.64]
Wang et al.(2021)	5.22	0.46	30	7.99	0.87	30	4.4%	-3.93 [-4.81, -3.04]
Wei et al.(2013)	3.1	2.77	40	5.1	2.38	40	5.1%	-0.77 [-1.22, -0.31]
Wu,(2019)	7.6	4.2	30	8.83	4.49	30	5.1%	-0.28 [-0.79, 0.23]
Xu,(2012)	5.2	2.93	30	6.37	3.99	30	5.1%	-0.33 [-0.84, 0.18]
Yu,(2013)	5.1	4.62	31	7.56	4.21	28	5.0%	-0.55 [-1.07, -0.03]
Zhang et al.(2011)	5.8	3.03	36	7.73	3.97	30	5.1%	-0.55 [-1.04, -0.05]
Zhang et al.(2020)	4.4	4.05	30	6.9	4.14	30	5.0%	-0.60 [-1.12, -0.08]
Zhang et al.(2021)	5.24	1.23	35	10.54	1.17	35	4.4%	-4.37 [-5.25, -3.49]
Zhou et al.(2007)	5.29	2.64	84	11.23	2.81	82	5.2%	-2.17 [-2.55, -1.78]
Zhou et al.(2017)	6.7	2.9	37	9.6	4	37	5.1%	-0.82 [-1.30, -0.35]
Zhuang,(2020)	6.22	1.15	50	9.67	1.27	50	5.0%	-2.83 [-3.39, -2.27]
Total (95% CI)			**858**			**855**	**100.0%**	**-1.55 [-1.97, -1.13]**
Heterogeneity: Tau² = 0.86; Chi² = 270.02, df = 19 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 7.17 (P < 0.00001)								

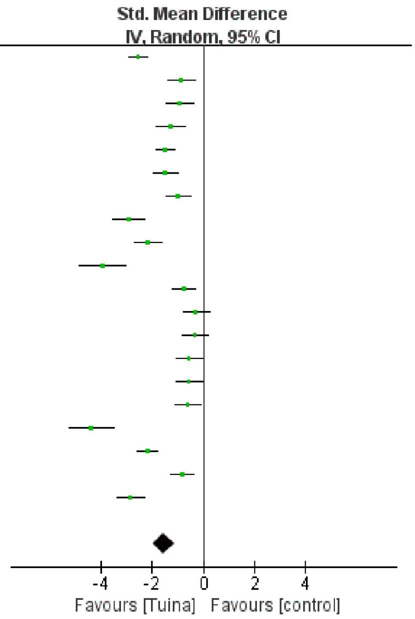

FIGURE 7
Meta-analysis of Pittsburgh Sleep Quality Index (PSQI).

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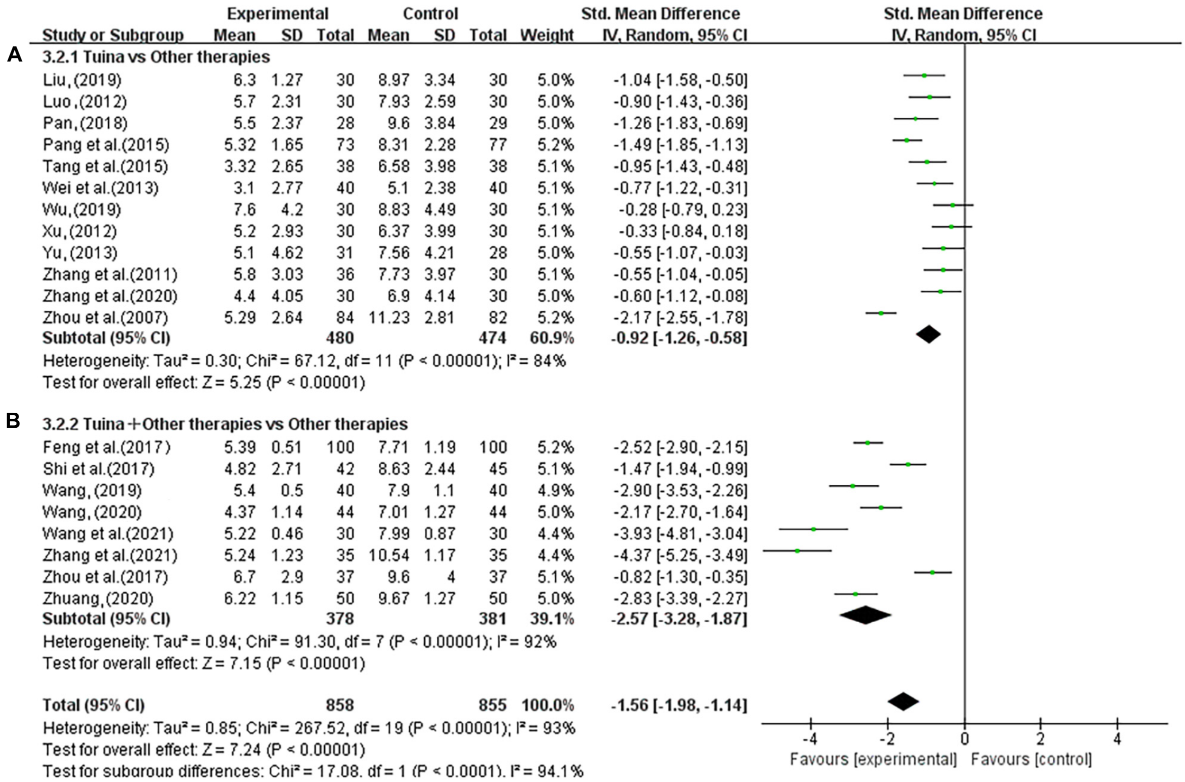

FIGURE 8

Forest plot of tuina for Pittsburgh Sleep Quality Index (PSQI). **(A)** Tuina vs. Other therapies. **(B)** Tuina + Other therapies vs. Other therapies.

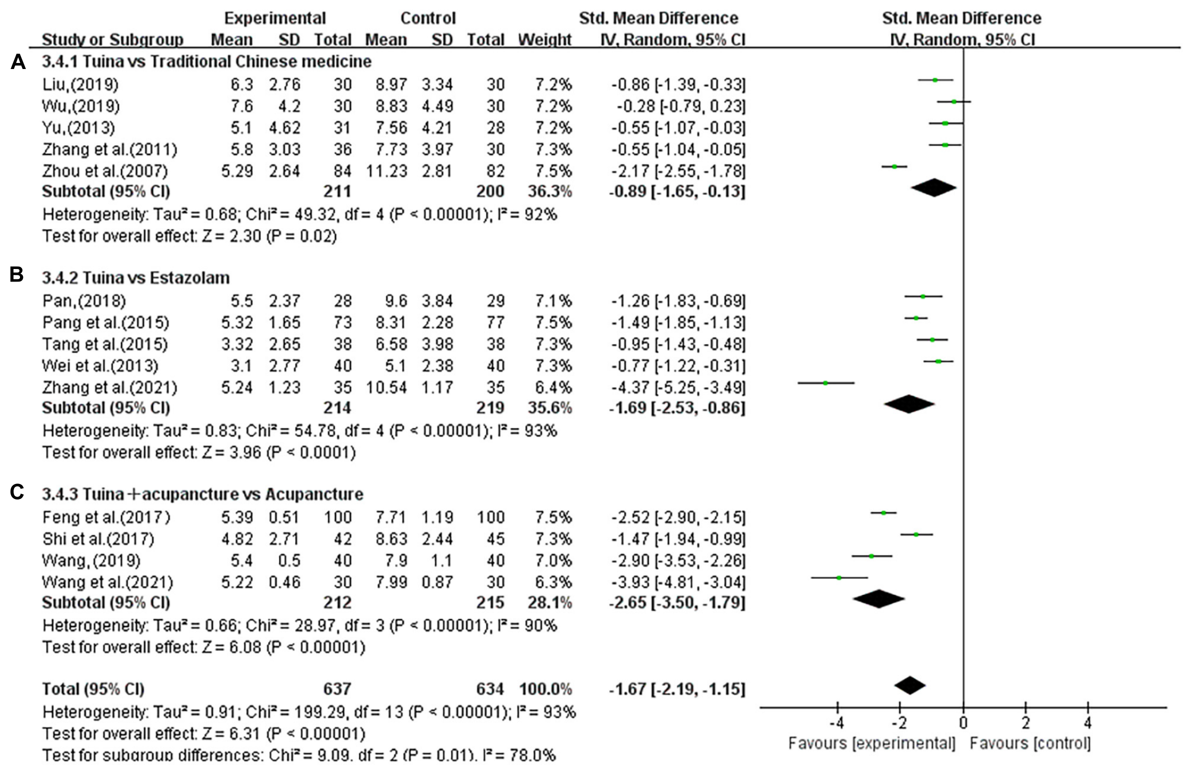

FIGURE 9

Subgroup analysis of tuina and different interventions in Pittsburgh Sleep Quality Index (PSQI). **(A)** Traditional Chinese Medicine (TCM). **(B)** Estazolam. **(C)** Acupuncture.

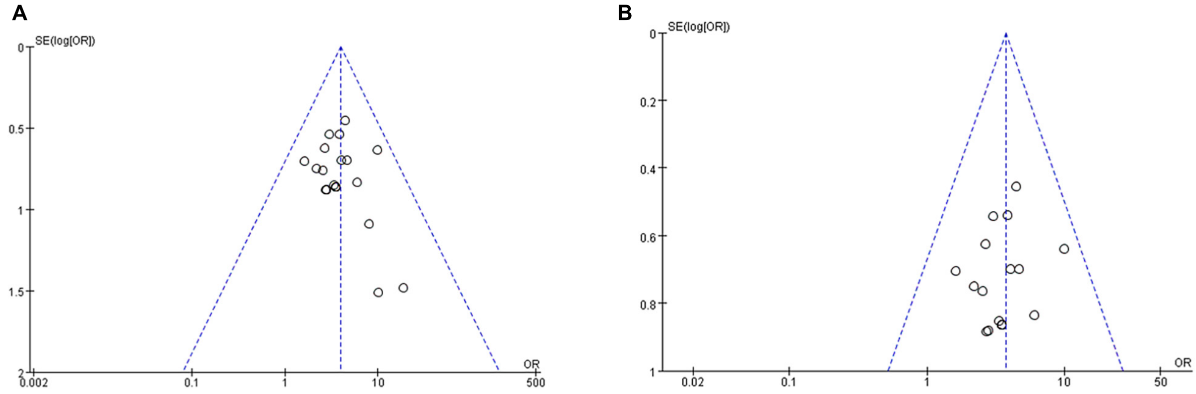

FIGURE 10
The funnel plots for tuina for primary insomnia. **(A)** Before sensitivity analysis. **(B)** After sensitivity analysis.

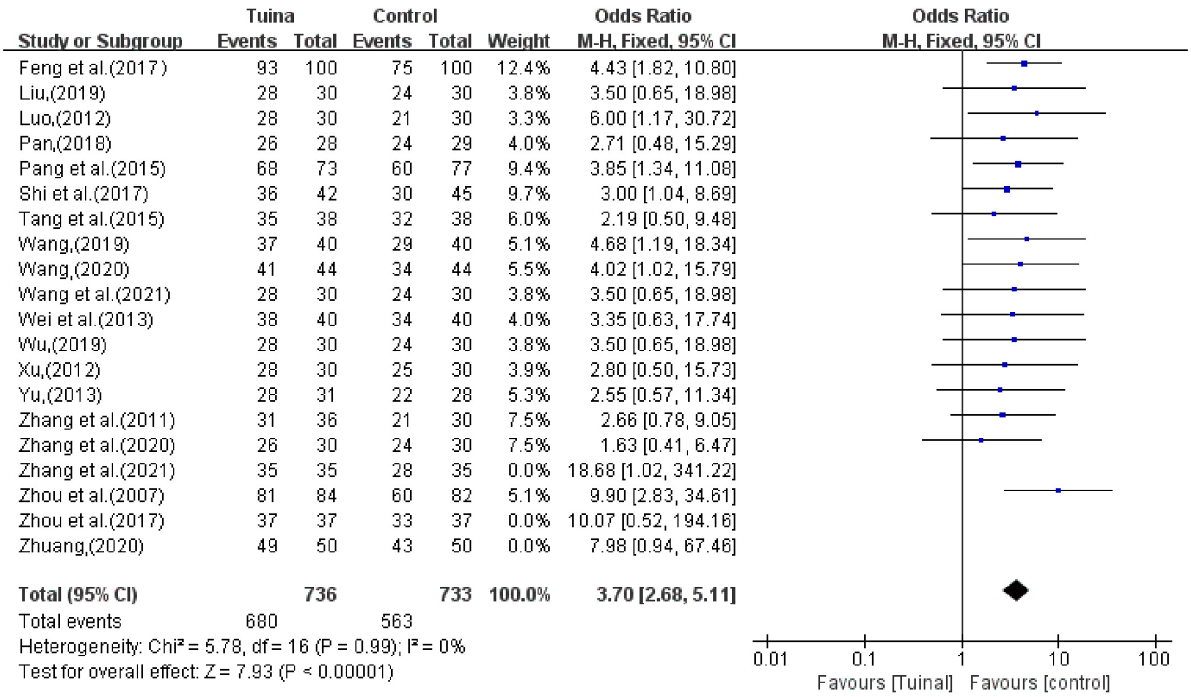

FIGURE 11
Forest plot of tuina for objective response rate (ORR) after sensitivity analysis.

TABLE 2 GRADE evidence profile.

Outcomes (Trials)	Quality assessment					Group		Clinical efficacy and safety		Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Experiment	Control	Relative ratio (95% CI)	Absolute (95% CI)	
ORR (20)	Serious[1]	No	No	No	Strongly suspected[2]	801/858 (93.1%)	667/855 (78.5%)	3.98 (2.91 to 5.45)	154 more per 1,000 (from 132 more to 171 more)	• ⊕⊕ ○○ low
PSQI (20)	Serious[2]	No	No	No	None	858	855	No	1.55 (1.97 to 1.13)	⊕⊕⊕○ Moderate

ORR, objective response rate; PSQI, Pittsburgh Sleep Quality Scale.
[1]The included studies have certain defects in randomization, allocation concealment and blinding.
[2]There is evidence of publication bias, Egger's test, $p < 0.05$.

between yin and yang is the basic pathogenesis of insomnia. Under the influence of a variety of pathogenic factors, yang qi in the body does not meet with yin, and yang is prosperous and yin is weakened, resulting in dysfunction of the viscera and meridians, and sleep disturbance. Tuina acts on the meridians and acupoints of the human body through different manipulations, which can regulate blood circulation, balance yin and yang, accelerate blood circulation, promote the recovery of blood vessel walls, dilate capillaries, rebuild capillary networks, reduce blood viscosity, and improve cardiac function and blood pressure. This slows down gastrointestinal motility, promotes the secretion of digestive juice, regulates qi and blood, and balances yin and yang to achieve the purpose of treatment (Fan, 2015). According to the theory of TCM, the secretion of yang-ping is an important condition for the normal realization of the function of the viscera, and TCM believes that the loss of communication between yin and yang is the basic pathogenesis of insomnia. Under the influence of a variety of pathogenic factors, yang qi in the body does not meet with yin, and yang is prosperous and yin is weakened, resulting in dysfunction of the viscera and meridians, and sleep disturbance. Tuina acts on the meridians and acupoints of the human body through different manipulations, which can regulate blood circulation, balance yin and yang, accelerate blood circulation, promote the recovery of blood vessel walls, dilate capillaries, rebuild capillary networks, reduce blood viscosity, and improve cardiac function and blood pressure. This slows down gastrointestinal motility, promotes the secretion of digestive juice, regulates qi and blood, and balances yin and yang to achieve the purpose of treatment (Fan, 2015).

4.1. Limitations

This review had several limitations. First, only a few of the included studies mentioned the long-term efficacy, and the follow-up time did not exceed 6 months; therefore, there is still no direct and favorable evidence for the long-term efficacy of tuina in the treatment of insomnia. Second, the studies included were insufficient in terms of methodology and sample size, with large inconsistencies and precision, which had an impact on the outcome indicators; that is, the quality of evidence on tuina therapy for insomnia was low. Third, our review only included RCTs, but it is difficult to blind patients and therapists in tuina studies, which directly affects the quality of the final body of evidence. Implementing opaque outcome raters and implicit assignments could partially remedy these deficiencies, but only four studies used implicit assignments and two studies blinded outcome reviews. Fourth, the results may be influenced by the TCM syndrome types of insomnia, but subgroup analyses could not be performed due to the small number of included studies. Fifth, the results may be influenced by the genre, frequency, duration, and course of treatment of the different tuina manipulations. If there are enough eligible studies in the future, further review should focus on these parameters of tuina. Sixth, the results of the included studies were all positive, and there is a possibility of omission of negative results, which has an impact on publication bias. Finally, the included studies were all published in Chinese, suggesting that tuina therapy has limited use outside of China, hence more research on tuina therapy for insomnia is necessary.

5. Conclusion

Altogether, tuina can effectively improve the clinical efficacy and sleep quality of patients with primary insomnia, which is worthy of further promotion and application in clinical practice. However, considering the poor quality of the included studies, we need to carry out large-scale, multi center, high-quality rct to further confirm the results of this study.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ZW, HX, YW, and YZ designed the study and drafted the manuscript. HZ and LY performed literature searches. ZW and HZ identified and selected studies. LY and YL assessed methodological quality and extracted the data. ZW and HX performed data synthesis and analysis, respectively. ZW, HX, HZ, LY, and JG wrote the manuscript. All authors contributed to the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effects of acupuncture therapy in migraine: An activation likelihood estimation meta-analysis

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Background: Previous functional magnetic resonance imaging studies indicated that acupuncture could activate the brain regions in patients with migraine. However, these studies showed inconsistent results. This activation likelihood estimation (ALE) meta-analysis aimed to investigate the consistent activated change of brain regions between pre- and post-acupuncture treatment in migraineurs.

Methods: We conducted a literature search in PubMed, Embase, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure, the Chinese Science and Technology Periodical Database, the Wanfang Database, and the Chinese Biomedical Literature Database from their inception to 18 August, 2022, to obtain articles assessing the functional magnetic resonance imaging changes of acupuncture for migraine. Two investigators independently performed literature selection, data extraction, and quality assessment. The methodological quality was assessed with a modified version of the checklist. The reporting quality of interventions among included studies was evaluated by the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). Our meta-analysis was conducted according to the GingerALE software. The Jackknife sensitivity analysis was used to assess the robustness of the results.

Results: 14 articles were finally included according to the eligible criteria. Regarding the immediate effect of acupuncture on migraine, the ALE meta-analysis demonstrated that the deactivation regions were mainly located in the superior frontal gyrus, and middle frontal gyrus (uncorrected $P < 0.001$). The ALE meta-analysis of the cumulative effect showed that the activation regions were the thalamus, superior frontal gyrus, posterior lobe of the cerebellum, insula, middle frontal gyrus, precentral gyrus, anterior cingulate, and the deactivation brain regions were located in the transverse temporal gyrus, postcentral gyrus, superior temporal gyrus, anterior cingulate, parahippocampal gyrus, inferior parietal lobule, and inferior occipital gyrus (uncorrected $P < 0.001$).

Conclusion: Acupuncture could activate multiple brain areas related with the regulation of pain conduction, processing, emotion, cognition, and other brain regions in patients with migraine. In the future, the combination of multiple imaging technologies could be a new approach to deeply investigate the central mechanism of acupuncture for migraine.

KEYWORDS

acupuncture, migraine, functional magnetic resonance imaging, meta-analysis, activation likelihood estimation

1. Introduction

Migraine is a chronic paroxysmal neurological disorder, along with multiphase attacks of headache and a myriad of neurological symptoms (Dodick, 2018). According to epidemiological statistics (Safiri et al., 2022), the global age-standardized point prevalence and annual incidence rate of migraine were 14,107.3 and 1,142.5 per 100,000 in 2019, and migraine prevalence peaks in 40 to 44 age group. Migraine sufferers have a variety of problems that can lead to decreased productivity at school, at home, and in society. Globally, migraine is the leading cause of years lived with disability (YLDs) accounting for 45.1 million YLDs annually (Gbd 2016 DALYs and Hale Collaborators, 2017). The economic costs of migraine are substantial. The high prevalence and societal burden of migraine have contributed to the acknowledgment of migraine as a serious public health concern. At present, pharmaceutical treatment for migraine is the most basic and common treatment. However, the efficacy of most existing drugs for migraine is limited, and long-term use may produce significant side effects, such as addiction, and overdose deaths (Hagemeier, 2018). For the management of migraine, safe, effective, and acceptable non-pharmacological treatments are crucial to solve this problem.

Mounting evidence supports the application of acupuncture to prevent and treat migraines, due to its long-term effectiveness, good tolerance, and fewer side effects. A Cochrane review from Germany concluded that acupuncture was effective and safe for episodic migraine prophylaxis when compared with prophylactic drug treatment (Linde et al., 2016). Apart from reducing pain, acupuncture may be beneficial for migraineurs with co-morbid problems such as anxiety, insomnia, and muscle tension (Liao et al., 2020; Natbony and Zhang, 2020). Acupuncture imaging studies have confirmed that the anti-migraine mechanism of acupuncture is closely related to the regulation of cerebral activities, which can modulate the functional and structural brain in patients with migraine (Ma et al., 2021). Li et al. (2017) found that acupuncture could normalize the decreased amplitude of low-frequency fluctuation (ALFF) of the rostral ventromedial medulla/trigeminocervical complex in migraineurs. Liu S. et al. (2021) observed that the region homogeneity (ReHo) values in the cerebellum and angular gyrus increased significantly after 12 sessions of acupuncture treatment in patients with migraine. Zhang et al. (2016) discovered that acupuncture could increase the functional connectivity (FC) of brain regions in patients with migraine. Nevertheless, the underlying central mechanism of acupuncture for migraine is still not completely studied.

The resting-state fMRI (functional magnetic resonance imaging) is used to measure the spontaneous activity of neurons by enabling the recording of the blood oxygenation level dependent (BOLD) signals. Three indicators are commonly used to determine spontaneous brain activity: ALFF, fractional ALFF (fALFF), and ReHo (Zang et al., 2004; Liu S. et al., 2022). ALFF and fALFF reflect the regional intensity of spontaneous fluctuations in the BOLD signal (Zang et al., 2007; Zou et al., 2008). ReHo indicates the synchronization and consistency of the BOLD signal between a single voxel and neighboring voxels (Zang et al., 2004). Therefore, the combination of ALFF, fALFF, and ReHo can fully present spontaneous activity of the local brain. Activation likelihood estimation (ALE) is an effective method for meta-analysis of brain neuroimaging, which is a brain region localization analysis method based on voxel coordinates, and the brain region localization can be achieved by carrying out 3D Gaussian smoothing and permutation tests of the relevant coordinates in the included studies. Previous reviews narratively summarized the functional brain changes of acupuncture in patients with migraine (Liu L. et al., 2021; Ma et al., 2021), while quantitative meta-analyses were not performed. Therefore, the purpose of this study was to explore the acupuncture-related brain regions in migraineurs with ALE algorithm.

2. Methods

The protocol of this ALE-meta analysis has already been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY)[1] (registration number: INPLASY2022110026). The present study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

2.1. Literature search

We performed a comprehensive search in the following databases from their inception to August 18, 2022: PubMed, EMBASE, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), the China Science and Technology Journal Database (VIP), Wanfang Database, and the China Biology Medicine (CBM). Both Medical Subject Headings (MeSH) and free-text words related to acupuncture, migraine, and fMRI were used to retrieve relevant studies. We additionally searched the references of the

1 https://inplasy.com/inplasy-2022-11-0026/

included studies. We consulted the specialists for possible eligible studies. The full search strategies for all databases are shown in **Supplementary Table 1**.

2.2. Inclusion criteria

We included studies that met the following criteria:

1) The patients were diagnosed with migraine by any internationally recognized or accepted clinical guideline or consensus like The International Classification of Headache Disorders, 3rd edition (beta version) (Headache Classification Committee of the International Headache Society (IHS), 2013);
2) The intervention involved electro-acupuncture or manual acupuncture; no limitations on manipulation methods of acupuncture, acupoint selection, and duration of acupuncture;
3) The studies reported neuroimaging results (ReHo, ALFF, or fALFF) of pre- and post-acupuncture treatment *via* fMRI using the standard anatomical template;
4) Both randomized controlled trials and clinical controlled trials were included.

2.3. Exclusion criteria

We excluded studies that fulfilled the following criteria:

1) No detailed description of the diagnostic criteria;
2) Full texts were unavailable through extensive search;
3) Coordinates could not be obtained through various approaches;
4) The results were based on the region of interest.

2.4. Study selection

The retrieved records were imported into Endnote (X9). After removing duplicates, two researchers (X-BL and X-YG) independently eliminated irrelevant records by reading the titles and abstracts, then screened the rest records in full text to identify eligible studies. After selection, two reviewers cross-checked, and disagreements were settled through team discussion or consultation with the third reviewer (JL).

2.5. Data extraction

Two independent reviewers (X-BL and X-YG) extracted the following information: (1) publication information: title, first author, year of publication; (2) demographic characteristics: types of migraine, diagnostic criteria, sample size, characteristics of the study population (age, gender); (3) intervention details: manipulation methods of acupuncture, frequency, duration, and sessions; (4) neuroimaging data: MRI acquisition, processing parameters, analysis parameters, activation coordinates (POST > PRE), and deactivation coordinates (PRE > POST), along with their associated standard anatomical template. If a study observed the neuroimaging results of different acupoints or needle stimulations, we extracted data separately. After extraction, two reviewers cross-checked to ensure accuracy. Any disagreement was resolved through discussion or arbitration by a third reviewer (JL).

2.6. Assessment of methodological quality

A modified version of checklist (Iwabuchi et al., 2015; Pan et al., 2017) was used to assess the methodological quality of individual functional neuroimaging studies. The checklist contains two domains (Category 1: Sample characteristics, Category 2: Methodology and reporting) with 13 items. The overall score is 20 points. The higher the score, the better the methodological quality. Before the formal evaluation, two reviewers intensively discussed the checklist to achieve consensus. Then two independent reviewers (X-BL and X-YG) assessed and cross-checked the results. Discrepancies were resolved by team discussion.

2.7. Evaluation of reporting quality of interventions in controlled trials of acupuncture

The Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) was used to appraise the reporting quality of interventions in controlled trials of acupuncture (Macpherson et al., 2010). The STRICTA consists of six items (17 sub-items), including acupuncture rationale, details of needling, treatment regimen, co-interventions, practitioner background, and control or comparator interventions. Then the two independent reviewers (X-BL and X-YG) assessed and cross-checked the results. Discrepancies were resolved by a third reviewer (JL).

2.8. Statistical analysis

The ALE meta-analysis was performed with the Ginger ALE software (version 2.3.6)[2]. The data analysis process was as follows: (1) Data organization: 3D (X, Y, Z) coordinates in the standard space included were organized into text files. (2) Convert coordinate format: Talairach space coordinates were converted into Montreal Neurological Institute (MNI) space coordinates using Ginger ALE software. (3) Parameter settings: uncorrected $P < 0.001$, and Min.Volume 150 mm^3 (Yuan et al., 2022). (4) Viewing results: the results were presented in an Excel spreadsheet, and the ALE maps were overlaid onto the MNI template and viewed with MRIcron[3]. The process of data analysis is presented in **Figure 1**.

2.9. Sensitivity analysis

The reproducibility of the ALE meta-analysis results was assessed using the Jackknife sensitivity analysis method. That is, all studies were excluded one by one, and the remaining studies were re-analyzed.

2 http://brainmap.org/ale/
3 https://www.nitrc.org/projects/mricron

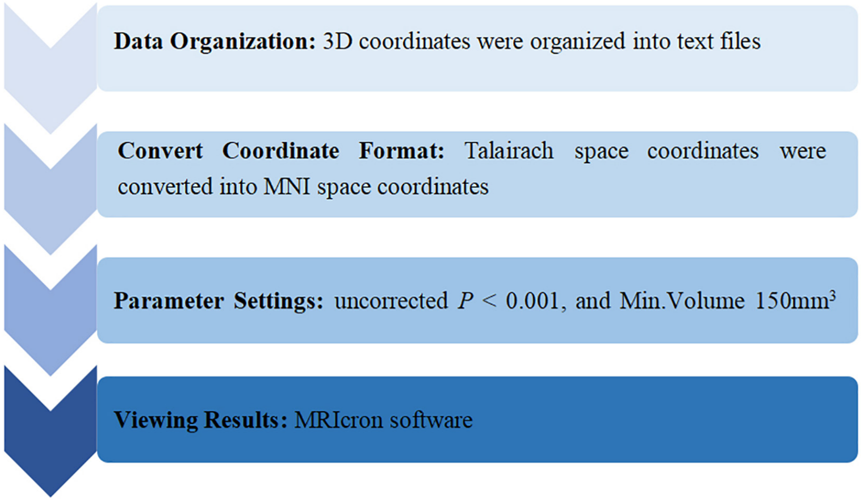

FIGURE 1
The process of ALE analysis.

3. Results

3.1. Search selection

The flow diagram of study selection is shown in Figure 2. A total of 338 records were retrieved in the literature search. Following the removal of 112 duplicates, 212 irrelevant records were eliminated based on their titles and abstracts, and 20 records were excluded based on full-text screening. Finally, we identified 14 eligible studies. The list of excluded records with reasons is provided in Supplementary Table 2.

3.2. Study overview

We identified 14 eligible studies (Peng, 2013; Zhao et al., 2014; Xie, 2016; Zhang, 2016; Cai, 2017; Li et al., 2017; Ning et al., 2017; Du, 2019; Wang, 2019; Zhang, 2019; Fan, 2020; Jia, 2021; Liu S. et al., 2021; Zhang Y. et al., 2021) for this ALE meta-analysis, of which 9 were in Chinese and 5 in English. There were 9 randomized controlled trials and 5 non-randomized controlled trials. With regards to the subtypes of migraine patients, 4 studies included patients with menstrual migraine, 4 studies enrolled migraine patients without aura, and 6 studies did not describe the subtypes of migraine. As for the analytical method, 3 studies used both the ALFF and ReHo, 8 studies adopted the ReHo, and 3 studies applied the ALFF. The details of all the included studies are presented in Table 1.

The needle stimulations were manual acupuncture (13 studies) and electro-acupuncture (1 study). There were 11 studies focused on the long-term efficacy of acupuncture for migraine and 5 studies on the immediate efficacy of acupuncture for migraine. Four studies included acupuncture with different acupoint protocols. The details of acupuncture treatment are shown in Table 2.

Neuroimaging data was acquired at either 1.5 T (1 study) or 3 T (12 studies), while one study did not specify the magnetic field strength. Most of the studies used the Siemens MRI scanner (8 studies), others included General Electric (4 studies), United Imaging Medical Systems (1 study), and 1 study did not report the scanner. Most of the structural images were obtained using fast spoiled gradient sequence (9 studies), magnetization-prepared rapid acquisition with gradient echo sequence (MPRAGE) (2 studies), and 3 studies did not specify the T1. T2-functional images were mainly from the echo-planar imaging (EPI) sequence (12 studies). Statistical analysis was conducted in either statistical parametric mapping (SPM) (13 studies) or data processing assistant for resting-state fMRI (DPARSF) (1 study). The details of MRI acquisition and analysis are demonstrated in Table 3.

3.3. Assessment of methodological quality

The methodological quality of included studies ranges from 16 to 19 points. In Category 1 (Sample characteristics), the patients from all included studies were evaluated with specific standardized diagnostic criteria (item 1), and all the important demographic data (item 2) were reported. While only 6 studies (Peng, 2013; Zhang, 2016; Li et al., 2017; Ning et al., 2017; Wang, 2019; Liu S. et al., 2021) recruited healthy comparison subjects and provided demographic data (item 3), only 1 study (Jia, 2021) reported important clinical variables (item 4), and the sample size per group of 11 studies (Peng, 2013; Zhao et al., 2014; Xie, 2016; Zhang, 2016; Cai, 2017; Li et al., 2017; Ning et al., 2017; Zhang, 2019; Jia, 2021; Liu S. et al., 2021; Zhang Y. et al., 2021) were > 10 (item 5). In Category 2 (Methodology and reporting), all the items were adequately reported. The detailed information of the methodological quality of included studies are shown in Supplementary Table 3. The modified version of checklist is provided in Supplementary Table 4.

3.4. STRICTA checklist for the included studies

According to the STRICTA checklist, the items with 70% of reporting rates were item 1a (style of acupuncture, 100%), item 1b (reasoning for treatment provided, 88.2%), item 2b

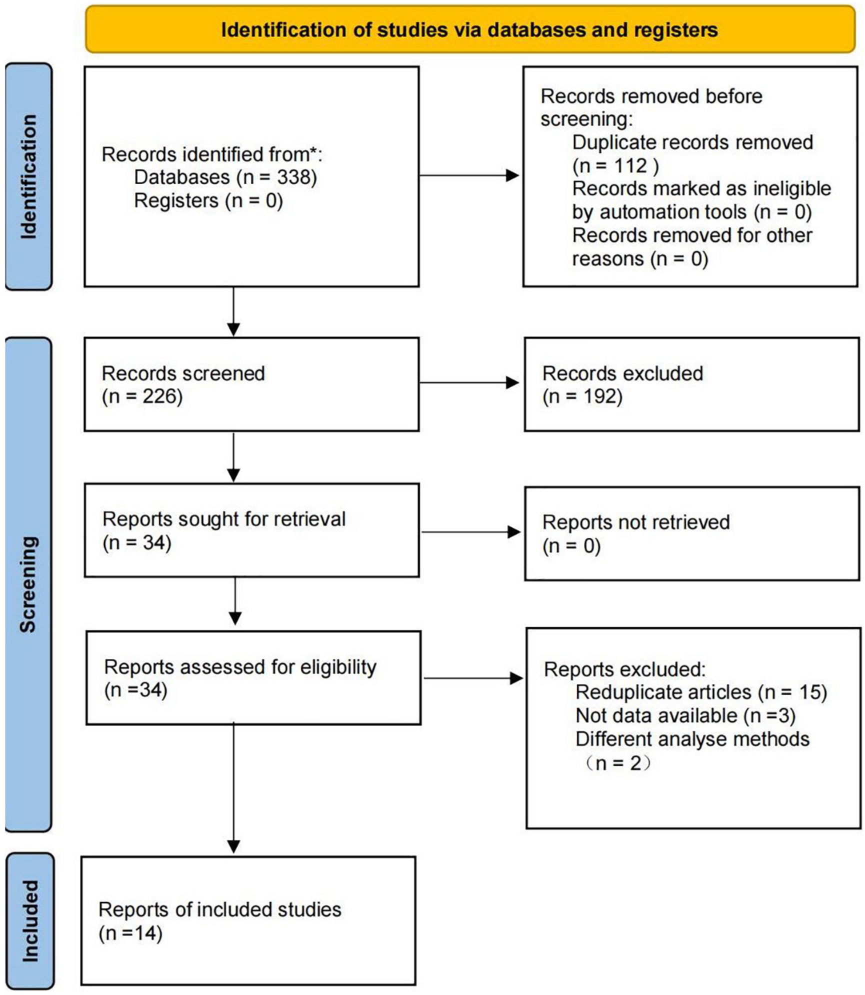

FIGURE 2
Flow diagram of literature search.

(points used, 100%), item 2c (depths of insertion, 100%), item 2d (response sought, 76.5%), item 2e (needle stimulation, 100%), item 2f (needle retention time, 100%), item 2g (needle type, 94.1%), item 3a (number of treatment sessions, 100%), and item 3b (frequency and duration of treatment sessions, 100%). While, item 1c (the extent to which treatment was varied), item 2a (number of needle insertions per subject per session), and item 4a (details of other interventions) were not mentioned in the included studies. The STRICTA checklist is shown in **Supplementary Table 5**.

3.5. ALE meta-analysis results

3.5.1. The immediate effect of acupuncture

Five studies evaluated the immediate effects of acupuncture on migraine (Peng, 2013; Xie, 2016; Ning et al., 2017; Fan, 2020; Liu S. et al., 2021). We extracted 82 foci with brain activation regions from 6 experiments, and 61 foci with brain deactivation regions from 5 experiments in patients with migraine after acupuncture treatment. No significant clusters with activation brain were detected between pre-acupuncture and post-acupuncture treatment. One significant cluster with deactivation brain was found between pre-acupuncture and post-acupuncture treatment: the left superior frontal gyrus (SFG, 168 mm^3, BA9). The specific analysis results are presented in **Table 4** and **Figure 3**.

3.5.2. The cumulative effect of acupuncture

The data from 11 studies were pooled to investigate the cumulative effect of acupuncture on migraine (Zhao et al., 2014; Xie, 2016; Zhang, 2016; Cai, 2017; Li et al., 2017; Du, 2019; Wang, 2019; Zhang, 2019; Jia, 2021; Liu S. et al., 2021; Zhang Y. et al., 2021). We extracted the 77 foci with brain activation regions from 13 experiments and 83 foci with brain deactivation regions from 12 experiments in patients with migraine after acupuncture treatment. Seven activated clusters were found between pre-acupuncture and post-acupuncture treatment: (1) the right thalamus (THA, 976 mm^3); (2) the right superior frontal gyrus (SFG, 400 mm^3, BA8); (3) the left posterior lobe (376 mm^3); (4) the right insula (INS, 344 mm^3, BA13); (5) the right middle frontal gyrus (MFG, 272 mm^3, BA8); (6) the right precentral gyrus (PreCG, 224 mm^3, BA6); (7) the left anterior cingulate (ACC, 208 mm^3, BA24). Five deactivated clusters were detected between pre-acupuncture and post-acupuncture treatment: (1) the right transverse temporal gyrus (TTG, 744 mm^3, BA41); (2) the left anterior cingulate (ACC, 328 mm^3, BA32); (3) the left parahippocampal gyrus (PHG, 192 mm^3); (4) the left inferior parietal

TABLE 1 Characteristics of included studies.

References	Disease	Study type	Sample size		Age (years ± SD)		Gender (M/F)		Experiments	Analytical method	Standard anatomical template
			AG	CG (Patient/HC)	Patient	HC	Patient	HC			
Peng, 2013	Migraine	Non-RCT	32	18 (0/18)	37.91 ± 5.354	37.5 ± 5.272	16/16	9/9	1	ReHo	Talariach
Zhao et al., 2014	Migraine	RCT	20	20 (20/0)	AG:32.90 ± 10.99 CG: 37.25 ± 9.68	–	14/26	–	1	ReHo	Talariach
Xie, 2016	Migraine without aura	RCT	19	19 (19/0)	AG:29.58 ± 6.26 CG: 30.52 ± 6.85	–	8/30	–	2	ReHo	MNI
Zhang, 2016	Migraine	Non-RCT	20	20 (0/20)	21.70 ± 2.29	21.40 ± 0.82	6/14	6/14	1	ReHo	Talariach
Cai, 2017	Menstrual migraine without aura	RCT	15	13 (13/0)	AG:31.80 ± 6.70 CG: 34.69 ± 7.51	–	0/28	–	1	ReHo	Talariach
Li et al., 2017	Migraine without aura	RCT	35	69 (27/42)	21.29 ± 0.44	21.21 ± 0.28	48/14	34/8	1	ALFF	MNI
Ning et al., 2017	Migraine without aura	Non-RCT	16	(0/16)	28.3 ± 6.0	27.1 ± 4.8	3/13	3/13	1	ALFF	MNI
Du, 2019	Menstrual migraine without aura	Non-RCT	PMM:10 MRM:29	–	PMM: — MRM: 32.59 ± 7.15	–	PMM:0/10 MRM:0/29	–	2	ALFF ReHo	Talairach
Wang, 2019	Menstrual migraine	RCT	AG1:8 AG2:7	12 (0/12)	–	28.22 ± 8.524	0/15	0/12	2	ALFF ReHo	Talairach
Zhang, 2019	Migraine without aura	RCT	20	20 (20/0)	AG:38.95 ± 12.61 CG:36.30 ± 9.56:	–	4/36	–	1	ReHo	MNI
Fan, 2020	Migraine	RCT	AG1:6 AG2:6	–	AG1: 37.00 ± 8.81 AG2: 43.83 ± 12.09	–	2/10	–	2	ALFF	MNI

(Continued)

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TABLE 1 (Continued)

References	Disease	Study type	Sample size		Age (years ± SD)		Gender (M/F)		Experiments	Analytical method	Standard anatomical template
			AG	CG (Patient/HC)	Patient	HC	Patient	HC			
Jia, 2021	Migraine	RCT	AG1:16 AG2:19	–	AG1: 38.88 ± 14.77 AG2: 33.45 ± 10.81	–	8/27	–	2	ReHo	MNI
Liu S. et al., 2021	Migraine Without Aura	Non-RCT	37	15 (0/15)	37.97 ± 9.82	34.88 ± 6.66	6/31	2/13	2	ReHo	MNI
Zhang Y. et al., 2021	Menstrual migraine	RCT	24	20 (20/0)	AG:33.04 ± 6.43 CG: 35.30 ± 9.43	–	0/44	–	1	ALFF ReHo	Talairach

MNI, Montreal Neurological Institute; RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial; ALFF, amplitude of low-frequency fluctuation; fALFF, fractional amplitude of low-frequency fluctuation; ReHo, regional homogeneity; AG, acupuncture group; CG, control group; MA, manual acupuncture; EA, electro-acupuncture; SA, sham acupuncture; HC, health control; PMM, pure menstrual igraine; MRM, menstrually related migraine; F/M: female/male.

lobule (IPL, 192 mm^3, BA40); (5) the left inferior occipital gyrus (IOG, 160 mm^3, BA19). The specific analysis results are provided in Table 4 and Figure 4.

3.6. Sensitivity analysis

We conducted a sensitivity analysis on the immediate effect and cumulative effect of acupuncture, and the details are shown in Supplementary Table 6. Leave-one-out analysis of the immediate effect (post-acupuncture < pre-acupuncture) showed that the repeatability of the left SFG was up to 3/5 times of analysis, and MFG was up to 4/5 times of analysis. Leave-one-out analysis of the cumulative effect (post-acupuncture > pre-acupuncture) revealed that right THA, MFG was up to 12/13 times of analysis; right SFG, INS, PreCG, and left posterior lobe of the cerebellum, ACC was up to 11/13 times of analysis. Leave-one-out analysis of the cumulative effect (post-acupuncture < pre-acupuncture) showed that the repeatability of the right TTG, Postcentral gyrus (PoCG), Superior Temporal Gyrus (STG), and left ACC, PHG, IPL, IOG was up to 10/12 times of analysis.

4. Discussion

In the present study, we used the ALE method to perform a quantitative integration analysis of previously published original research and to identify the cerebral responses to acupuncture for migraine. The ALE analysis results of immediate acupuncture treatment showed that the deactivation regions located in the SFG and MFG. The ALE analysis results of cumulative acupuncture treatment revealed that the activation regions were the THA, SFG, posterior lobe of the cerebellum, INS, MFG, PreCG, ACC and the deactivation brain regions were the TTG, PoCG, STG, ACC, PHG, IPL, and IOG. The consistent results of immediate and cumulative change were the THA, INS, frontal lobe, parietal lobe, temporal lobe, occipital lobe, limbic system, and cerebellum. Pain is a multidimensional subjective experience generally including sensory (intensity, location), affective (unpleasantness, fear), and cognitive factors (memory, attention) (Schnitzler and Ploner, 2000). The brain processing network of pain can be divided into the medial and lateral pain systems, which are respectively involved in processing the affective-cognitive-evaluative aspects of pain, and the sensory-discriminative aspects (Friebel et al., 2011). Based on our findings, we found that several regions of the lateral and medial pain systems (including the THA, INS, ACC, SFG, MFG, and PoCG) participated in the cerebral responses to acupuncture for migraine.

The medial and ventrobasal parts of THA are separately involved in the medial and lateral pain pathways. In migraine pathogenesis, THA is considered as the relay center of ascending nociceptive information (Younis et al., 2019). Kim et al. (2021) observed that the regional fALFF values of the bilateral ventral posteromedial thalamus was positively correlated with the duration of migraine. Gu et al. (2018) discovered N-acetylaspartate/creatine increased in bilateral THA of migraineurs after acupuncture, which was significantly related with the headache intensity. The anterior part of the INS encodes the emotional processing of pain, and the posterior part encodes the intensity and lateralization of pain. Thus, the INS plays an integrative role in nociceptive processing. Zhang et al. (2022)

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TABLE 2 Intervention details of included studies.

References	Study type	Interventions		Needle sessions	Needle duration	Needle frequency	Acupoints
		AG	CG				
Peng, 2013	Non-RCT	MA	–	Instant	–	–	Qiuxu (GB40)
Zhao et al., 2014	RCT	MA	SA	32	8 weeks	4 times per week	Fengchi (GB20), Yanglingquan (GB34), Qiuxu (GB40), Waiguan (SJ5)
Xie, 2016	RCT	MA	SA	20	4 weeks	5 times per week	Headache point
Zhang, 2016	Non-RCT	MA	HC	20	4 weeks	once per day	Yanglingquan (GB34), Qiuxu (GB40), Waiguan (SJ5)
Cai, 2017	RCT	MA	SA	27	3 months	Before menses (1 week):3 times per week; Onset of menses and after menses (2 weeks): 2 times per week	Fengchi (GB20), Shuaigu (GB8), Sanyinjiao (SP6), Neiguan (PC6), Taichong (LR3)
Li et al., 2017	RCT	MA	SA, WA, HC	20	4 weeks	5 times per week	AG1: Yanglingquan (GB34), Qiuxu (GB40), Waiguan (SJ5). AG2: Xiyangguan (GB33), Diwuhui (GB42), Sanyangluo (SJ8) AG3: Zusanli (ST36), Chongyang (ST42), Pianli (L16)
Ning et al., 2017	Non-RCT	MA	HC	Instant	–	–	Zulinqi (GB41)
Du, 2019	Non-RCT	MA	–	27 ± 6	3 menstrual cycles	Before menses (1 week):3 times per week; Onset of menses and after menses (2 weeks): 2 times per week	Fengchi (GB20), Shuaigu (GB8),Sanyinjiao (SP6), Neiguan (PC6),Taichong (LR3)
Wang, 2019	RCT	MA	HC	27 ± 6	3 menstrual cycles	Before menses (1 week):3 times per week; Onset of menses and after menses (2 weeks): 2 times per week	AG1: Fengchi (GB20), Shuaigu (GB8), Taichong (LR3) AG2: Fengchi (GB20), Shuaigu (GB8), Neiguan (PC6)
Zhang, 2019	RCT	MA	SA	12	4 weeks,	3 times per week	Benshen (GB13), Shuaigu (GB8), Fengchi (GB20), Baihui (DU20), Shenting (DU24)
Fan, 2020	RCT	MA	–	Instant	–	–	AG1: Naokong (GB19), Fengchi (GB20), Naohu (DU17), Fengfu (DU16) AG2: Shenting (DU24), Yintang (EX-HN3), Meichong (BL3), Cuanzhu (BL2), Toulinqi (GB15),Yuyao (EX-HN4),Touwei (ST8), Sizhukong (SJ23), Hanyan (GB4), Xuanli (GB6)
Jia, 2021	RCT	MA	–	12	4 weeks	3 times per week	AG1:Zuqiaoyin (GB44), Lidui (ST45), Zhiyin (BL67), ashi point AG2: ashi point
Liu S. et al., 2021	Non-RCT	EA	HC	12	6 weeks	2 times per week	Baihui (DU20), Taiyang (EX-HN5), Fengchi (GB20), Shuaigu (GB8), Xuanlu (GB5), Toulinqi (GB15), Hegu (LI4), Taichong (LR3)
Zhang Y. et al., 2021	RCT	MA	SA	27 or 27 ± 6	3 months	Before menses (1 week):3 times per week; Onset of menses and after menses (2 weeks): 2 times per week	Fengchi (GB20), Shuaigu (GB8), Neiguan (PC6), Sanyinjiao (SP6), Taichong (LR3)

RCT, randomized controlled trial; Non-RCT, non-randomized controlled trial; MA, manual acupuncture; EA, electro-acupuncture; SA, sham acupuncture; HC, health control; AG, acupuncture group; CG, control group.

TABLE 3 The details of MRI acquisition and analysis.

References	MRI acquisition				T1				T2				Analysis	
	Teslas	MRI-system	MRI-model	Head-coil	Sequence	TR (ms)	TE (ms)	Voxel size (mm)	Sequence	TR (ms)	TE (ms)	Voxel size (mm)	Software	Method
Peng, 2013	3T	Siemens	Trio	–	FSPGR	1900	2.26	1 × 1 × 1	–	2000	30	–	SPM5	ReHo
Zhao et al., 2014	3T	Siemens	Allegra	8	–				EPI	2000	30	–	SPM5	ReHo
Xie, 2016	1.5T	Siemens	Sonata	standard	MPRAGE	24	6	–	EPI	2000	30	–	SPM8	ReHo
Zhang, 2016	3T	Siemens	–	–	FSPGR	1900	2.26	–	EPI	2000	30	–	SPM8	ReHo
Cai, 2017	3T	GE	MR750	12	FSPGR	2530	3.4	–	GRE-EPI	2000	30	3.75 × 3.75 × 4	SPM8	ReHo
Li et al., 2017	3T	Siemens	Trio Tim	8	FSPGR	1900	2.26	1 × 1 × 1	EPI	2000	30	–	SPM12	ALFF
Ning et al., 2017	3T	Siemens	Sonata	–	–	1900	2.52	–	–	2000	30	–	SPM8	ALFF
Du, 2019	3T	GE	MR750	–	FSPGR	–	–	–	GRE-EPI	2000	25	3.75 × 3.75 × 4	SPM8	ALFF/ReHo
Wang, 2019	3T	GE	MR750	32	FSPGR	2530	3.4	1 × 1 × 1	GRE-EPI	2000	25	3.75 × 3.75 × 4	SPM12	ALFF/ReHo
Zhang, 2019	3T	Siemens	Skyra	20	–	–	–	–	EPI	3000	30	2.3 × 2.3 × 3	SPM8	ReHo
Fan, 2020	–	–	–	12	FSPGR	2530	3.4	–	GRE-EPI	2000	30	2.3 × 2.3 × 5	SPM12	ALFF
Jia, 2021	3T	Siemens	Skyra	–	MPRAGE	2530	2.98	1 × 1 × 1	EPI	2000	30	3.5 × 3.5 × 3.5	DPARSF	ReHo
Liu S. et al., 2021	3T	United Imaging Medical Systems	uMR780	12	FSPGR	7.2	3.1	1 × 1 × 1	EPI	2000	30	–	SPM12	ReHo
Zhang Y. et al., 2021	3T	GE	MR750	8	FSPGR	–	–	–	EPI	2000	25	3.44 × 3.44 × 4	SPM12	ALFF/ReHo

MRI, magnetic resonance imaging; GE, gradient echo pulse; FSPGR, fast spoiled gradient sequence; MPRAGE, magnetization-prepared rapid acquisition with gradient echo sequence; SPGR, spoiled gradient recalled sequence; SPM, statistical parametric mapping; fALFF, fractional amplitude of low-frequency fluctuation; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity; TR, repetition time for the whole pulse sequence in MRI; TE, echo time i.e., Time between middle of exciting RadioFrequency pulse and middle of spin echo production; data processing assistant for resting-state fMRI (DPARSF).

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TABLE 4 Changes of brain activation in patients with pre- to post- acupuncture.

Cluster number	Volume (mm^3)	MNI coordinates			Peak ALE value	Area	Hemisphere	Brodmann area
		X	Y	Z				
Post-acupuncture < Pre-acupuncture (Immediate effect)								
1	168	−2	58	26	0.009318931	Frontal Lobe, SFG	L	9
		2	54	32	0.008554844	Frontal Lobe, MFG	L	6
Post-acupuncture > Pre-acupuncture (Cumulative effect)								
1	976	16	−20	6	0.014990999	THA	R	—
		16	−16	2	0.01456283	THA	R	—
		8	−26	2	0.008749179	THA, Pulvinar	R	—
2	400	24	42	42	0.014283381	Frontal Lobe, SFG	R	8
3	376	−36	−44	−36	0.012764244	Posterior Lobe, Cerebellar Tonsil	L	—
4	344	38	−12	20	0.011733903	INS	R	13
5	272	38	44	36	0.009829718	Frontal Lobe, MFG	R	8
6	224	36	−4	54	0.009671894	Frontal Lobe, PreCG	R	6
		34	−8	52	0.009619225	Frontal Lobe, PreCG	R	6
7	208	−2	34	6	0.009718803	Limbic Lobe, ACC	L	24
Post-acupuncture < Pre-acupuncture (Cumulative effect)								
1	744	54	−24	14	0.010470914	Temporal Lobe, TTG	R	41
		54	−16	14	0.009503565	Parietal Lobe, PoCG	R	43
		62	−30	12	0.009446988	Temporal Lobe, STG	R	42
		56	−30	10	0.009303252	Temporal Lobe, STG	R	41
2	328	−8	46	−16	0.013347376	Limbic Lobe, ACC	L	32
3	320	−28	−20	−16	0.010965006	Limbic Lobe, PHG	L	—
4	192	−46	−62	48	0.00994727	Parietal Lobe, IPL	L	40
		−44	−58	46	0.009831539	Parietal Lobe, IPL	L	40
5	160	−38	−74	−2	0.009893779	Occipital Lobe, IOG	L	19

SFG, superior frontal gyrus; MFG, medial frontal gyrus; THA, thalamus; INS: insula; PreCG, precentral gyrus; ACC, anterior cingulate; TTG: transverse temporal gyrus; PoCG, postcentral gyrus; STG, superior temporal gyrus; PHG, parahippocampal gyrus; IPL, inferior parietal lobule; IOG, inferior occipital gyrus; L, left; R, right.

found that the duration of migraine was negatively associated with gray matter (GM) alterations in the left INS. Cao et al. (2019) revealed that the INS was activated to integrate sensory and affective information and to produce analgesic effects during acupuncture stimulation. Our ALE meta-analysis showed that the activity of ACC (BA24) increased, while the activity of ACC (BA32) decreased after acupuncture in migraineurs. The ACC is considered to be involved in the affective-motivational component of pain (Price, 2000). Chen et al. (2021) discovered that the dynamic ALFF values in the ACC were negatively correlated with pain intensity in migraine. The ACC plays a different role in pain processing. Vogt et al. (1996) found that the increased regional cerebral blood flow (rCBF) in area 24'

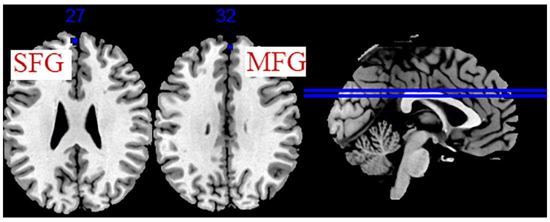

FIGURE 3
Regions of brain activation in patients with pre- to post- acupuncture (immediate effect). Blue represents brain deactivation regions.

of ACC may be involved in nocifensive reflex inhibition, and the reduced rCBF in area 32 of ACC may enhance pain perception in the surrounding cortex. Zhang et al. (2003) also discovered that the caudal part of the ACC (BA24) signal increased during the electrical acupoint stimulation, which positively related with the analgesic effect. Therefore, different parts of ACC may play different roles in the acupuncture-induced analgesic effect. The SFG is located at the superior part of the prefrontal cortex, which is responsible for emotion regulation (Cao et al., 2022). And the MFG is crucial to attention (Japee et al., 2015). The increased GM in the right SFG and the decreased GM in the left MFG were observed in migraineurs (Zhang et al., 2022). Zou et al. (2019) demonstrated that the decreased FC between the SFG and precuneus could restore to the healthy control level after acupuncture treatments. Russo et al. (2012) found that the FC between the MFG and the dorsal ACC reduced in migraineurs, and the decreased connectivity in the MFG was negatively related to the pain intensity of migraine attacks. The PoCG located in the primary somatosensory cortex (SI), which is involved in the adjustment of pain perception, including the positioning and recognition of pain intensity (Zhang S. et al., 2021). Wei et al. (2020) discovered that increased brain activity of the right PoCG is positively correlated with headache frequency in patients with migraine. Yang et al. (2012) also found that cerebral glucose metabolism decreased in the PoCG after acupuncture in migraine.

Besides, the TTG, STG, IPL, HPG, IOG, PreCG, and posterior lobe of the cerebellum are also involved in the analgesic effect of acupuncture. The temporal lobe is recognized as a region associated with multisensory integration. An analysis of voxel-based morphometric studies of migraine (Zhang et al., 2022) showed that GM increased in the bilateral temporal poles, the bilateral STG, the right SFG, and the left middle temporal gyrus (MTG) in migraine patients, and the frequency of migraine attacks was negatively associated with GM alteration in the left STG. This suggests that the temporal lobe is involved in pain regulation. Liu L. et al. (2022) revealed that the STG and MTG may be the key nodes linked to the multisensory processing of pain modulation in patients with migraine during acupuncture. It has been confirmed that the cerebellum plays an important role in pain processing and regulation (Moulton et al., 2010). Wang et al. (2016) observed that patients with migraine had significantly higher ALFF levels in the posterior lobe of the cerebellum in contrast with healthy controls. Zhang et al. (2022) revealed that the duration of migraine was negatively associated with GM alterations in the bilateral cerebellum (hemispheric lobule IX). Zhang et al. (2022) also found that GM increased in the PHG, and GM decreased in the IPL. Qin et al. (2020) discovered that reduced FC between the right IPL and right MFG, and the FC Z-scores between the ventral posterior nucleus (VPN) and right IPL were negatively related with pain intensity and disease duration in migraine. The PHG is involved in pain perception, pain modulation, and descending pain facilitation (Ruscheweyh et al., 2018). Yang et al. (2014) found that acupuncture could reduce brain glucose metabolism of PHG in migraine. Liu et al. (2012) observed that compared with healthy subjects, the PreCG exhibited abnormal centrality in both structural and FC networks in migraineurs, and negative correlations were observed between migraine duration and PreCG. Our results indicated that IOG also participated in acupuncture-induced analgesia, while few studies supported the finding.

There were 5 studies focused on the immediate effect of acupuncture and 11 studies on the cumulative effect. The results of ALE meta-analysis showed that both SFG and MFG were associated with immediate and cumulative effects, but the

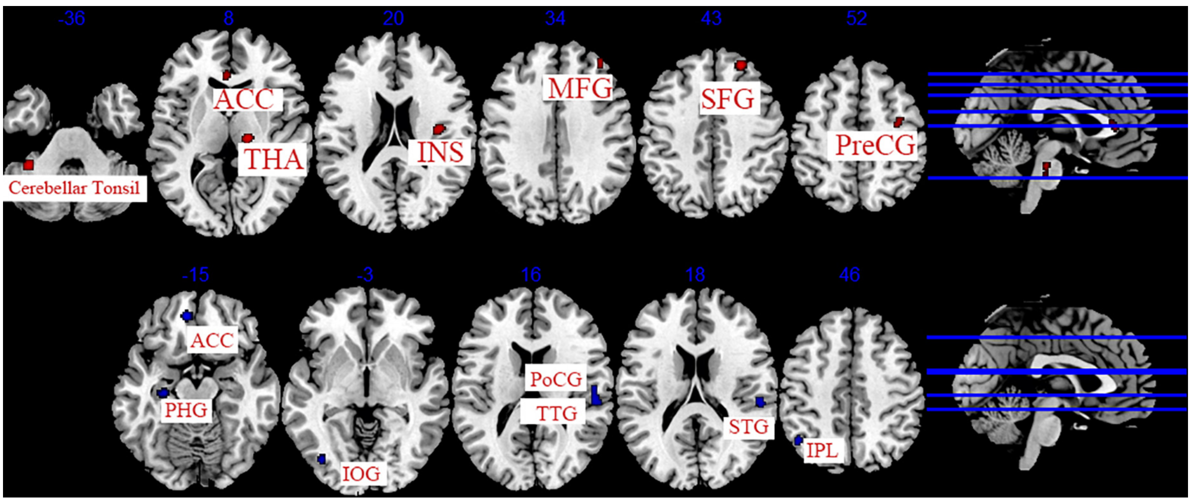

FIGURE 4
Regions of brain activation in patients with pre- to post- acupuncture (cumulative effect). Red represents brain activation regions; blue represents brain deactivation regions.

activity of SFG and MFG decreased after immediate acupuncture and increased after cumulative acupuncture. A possible explanation for the inconsistent results may be related to the number of included studies, which needs further investigation. Simultaneously, the neuroimaging results indicated that cumulative acupuncture treatment could induce a more extensive and remarkable cerebral response in contrast with single acupuncture treatment.

5. Strengths and limitations

In this meta-analysis, there are several strengths. First, instead of descriptive analysis, we used the ALE methodology to analyze the brain changes of acupuncture intervention in patients with migraine. Second, the present study analyzed the imaging studies on the immediate and cumulative effects of acupuncture in patients with migraine. Third, we comprehensively evaluated the methodological quality and the reporting quality of interventions with a modified version of checklist and STRICTA. Nevertheless, there are several limitations. First, due to the limitations of the analytical method, funnel plot was unavailable to detect the publication bias of the included studies. Second, we failed to compare the brain changes of patients with migraine after acupuncture with those in healthy individuals due to the incomplete information among included studies. Third, the STRICTA results showed that the protocol of acupuncture was not reported adequately, researchers should report in accordance with STRICTA to improve the reporting quality.

6. Conclusion

Acupuncture could activate multiple brain areas related with the regulation of pain conduction, processing, emotion, cognition, and other brain regions in patients with migraine. In the future, the combination of multiple imaging technologies might be a new approach to deeply investigate the central mechanism of acupuncture for migraine.

Author contributions

JZ designed the protocol, conducted this review, and drafted the manuscript. JL pointed out the research question, designed the protocol, and drafted the manuscript. X-YG and X-BL screened the articles, collected and assessed the data. YZ analyzed the data. Y-XL, D-LZ, YF, ZZ, and R-JJ revised this manuscript, and provided constructive suggestions for this review. Y-XL provided guidance on data analysis. L-XG and H-RL provided clinical knowledge support for this review. JL pointed out the research question, and guided the whole process of this review. All authors reviewed and approved this review.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1097450/full#supplementary-material

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Manual acupuncture for neuromusculoskeletal disorders: The selection of stimulation parameters and corresponding effects

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As a minimally invasive method of physical stimulation, manual acupuncture (MA) is used globally as a sort of therapy for neuromusculoskeletal disorders. In addition to selecting appropriate acupoints, acupuncturists should also determine the stimulation parameters of needling, such as the manipulation (lifting-thrusting or twirling), needling amplitude, velocity, and stimulation time. At present, most studies focus on acupoint combination and mechanism of MA, the relationship between stimulation parameters and their therapeutic effects, as well as the influence on mechanism of action are relatively scattered, and lack of systematic summary and analysis. This paper reviewed the three types of stimulation parameters of MA, their common options and values, corresponding effects and potential mechanisms of action. The purpose of such efforts is to provide a useful reference for the dose-effect relationship of MA and the quantification and standardization of its clinical treatment of neuromusculoskeletal disorders to further promote the application of acupuncture in the world.

KEYWORDS

manual acupuncture, stimulation parameters, therapeutic effects, review, mechanism of action

1. Introduction

As a minimally invasive method of physical stimulation, acupuncture is widely used globally as a sort of therapy of traditional Chinese medicine (TCM) and clinical skill; according to the statistics of the World Health Organization (WHO), it has been used in 183 countries or regions around the world (World Health Organization [WHO], 2013). Acupuncture has a wide range of indications and is also recommended by WHO because of its safety, simplicity and efficacy (World Health Organization [WHO], 2019). Among these indications, the use of manual acupuncture (MA) in neuromusculoskeletal disorders has been around for hundreds of years and is very prevalent. Some ancient Chinese medical books have records of MA for the relief of low back and leg pain and the improvement of limited mobility (Zhu et al., 2021). At the same time, many modern clinical randomized controlled trials (RCT) have also confirmed the therapeutic effects of MA on these diseases (Zhang X. et al., 2019; Chen L. et al., 2021).

During the treatment process of neuromusculoskeletal disorders, in addition to selecting appropriate acupoints according to the patient's condition and TCM theory, acupuncturists should also determine the stimulation parameters of needling, such as the selections of acupuncture manipulation (lifting-thrusting or twirling), operation amplitude, velocity, and stimulation time (Lyu et al., 2019). Numerous studies have suggested that different stimulation methods of acupuncture can result in different needling sensations and therapeutic effects. For instance, the needling sensation caused by lifting-thrusting is usually stronger than that of twirling (Huang et al., 2012), whereas twirling may further improve the patient's pressure pain threshold (Choi et al., 2013). Meanwhile, even with the same acupuncture manipulation, some studies found that a better analgesic effect could be achieved by greater needling velocity (Yin et al., 2011) or amplitude (Itoh et al., 2011). In addition, the persistence of such sensation and pain-relieving effects is also based on a certain time of stimulation. Comparative studies found that manipulation for a certain period of time has a better effect than simply inserting a needle into acupoints in pain relief (Loyeung and Cobbin, 2013).

Throughout the current research on MA treatment of neuromusculoskeletal disorders, most of them focus on the selection of acupoints before stimulation and the mechanism investigation after stimulation, but the relationship between stimulation parameters during treatment and their therapeutic effects, as well as the influence on mechanism of action, are relatively scattered and lack systematic summary and analysis. In contrast, electroacupuncture (EA) has received increasing attention from acupuncturists due to its four clear, quantified and easily controlled stimulation parameters (waveform, frequency, time, and current intensity) (Omura, 1987; Baba et al., 2002), and there are more RCTs comparing the effects of different stimulation parameters of EA (Liu et al., 2017; Zheng et al., 2018). For example, there are correlations between different frequencies (Humaidan et al., 2006; Yang et al., 2020; Yao S. et al., 2020), current intensities (Tamai et al., 2020), stimulation time (Heo et al., 2022) and different therapeutic effects, so dose-effect relationship studies of EA provide rich evidence and references for its clinical application. This paper reviewed the different stimulation parameters related to the effect of MA intervention, their common options and values, corresponding effects and potential mechanisms of action. The purpose of such efforts is to provide a useful reference for the dose-effect relationship of MA, and the quantification and standardization of its treatment of neuromusculoskeletal disorders to further promote the application of acupuncture in the world.

2. Ma effects on neuromusculoskeletal disorders and potential mechanisms

The therapeutic effects of MA on neuromusculoskeletal disorders are mainly manifested in relieving pain (Shah and Thaker, 2015), reducing local inflammatory response (Xu et al., 2018), improving limited limb mobility (Lu et al., 2010) and so on. When MA stimulates the acupoints, the tissue around the needle body receives mechanical stimulation during the needle's movement, these tissues can further transmit mechanical stimulation to the surrounding cells and activate mechanosensitive ion channels in the cell membrane, including transient receptor potential cation channel subfamily V members (TRPV1, TRPV2, and TRPV4) (Chen et al., 2018; Huang et al., 2018; Zheng et al., 2021), Piezo proteins (Piezo1, Piezo 2) (Guo et al., 2022) and stretch-activated chloride channels (SACs) (Wang and Schwarz, 2012). Then, cellular responses such as mast cell degranulation, fibroblast activation and macrophage polarization are initialized with the ion influx (Yao et al., 2014) and release relevant active substances, including adenosine triphosphate (ATP) (Wang and Schwarz, 2012) and histamine (Huang et al., 2018; Yin et al., 2018). After these substances bind to the corresponding receptors in the nerve endings, the expression of receptors related to pain signal transmission will be downregulated and inhibit the upload of pain signals (Tang et al., 2016). At the same time, stimulation with MA also promotes the release of substance P (SP) from nerve endings, which further promotes the above process to facilitate peripheral analgesia (Gong et al., 2020; Fan et al., 2021). In the central nervous system (CNS), the uploaded acupuncture signal promotes the release of substances such as gamma-aminobutyric acid (GABA), 5-hydroxytryptamine (5-HT), epinephrine (NE), and opioid peptides (Ko et al., 2018; Lin et al., 2020; Qiao et al., 2020) and guides the descending analgesic signal to enhance the analgesic effect. The effects of MA on CNS have also been investigated by some functional neuroimaging studies, the scanning result of functional magnetic resonance imaging (fMRI) showed that the central analgesic effect of MA was based on the increase of default mode network and sensorimotor network connectivity with pain-related brain areas (Cai et al., 2018), and the equilibrium regulation of distributed pain-related central networks (Biella et al., 2001). Meanwhile, the *deqi* sensation of MA may be related to the significant deactivations of brain fMRI blood oxygen level-dependent (BOLD) signals (Asghar et al., 2010).

In addition to relieving the pain symptoms of neuromusculoskeletal disorders, MA can also downregulate the function of the hypothalamic-pituitary-adrenal (HPA) axis (Li et al., 2021), reduce the release of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), promote the secretion of peripheral dopamine and nitric oxide (NO) (Wang M. et al., 2020), and relieve local inflammation (Yu et al., 2009). In the localized lesion (synovial fluid, cartilage, subchondral bone, etc.), MA can effectively inhibit the overexpression of inflammatory cytokines including interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α)and promote the expression of anti-inflammatory cytokine such as IL-10 (Wang M. et al., 2020). With the relief of local inflammation, the movement function of limbs can also be improved. Moreover, the result of a surface electromyographic (sEMG) study of shoulder joint dysfunction suggested that the improvement effect of MA on limb mobility may also lie in the enhancements of muscle excitability and endurance, as well as the delay of muscle fatigue (Wang I. et al., 2020; **Figure 1**).

3. Stimulation parameters of ma for selection

According to the operation methods of MA, the parameters closely related to the stimulation amount mainly include three types, namely, manipulation, kinematic and time parameters (Lyu et al., 2019). Different combinations of the above parameters will have corresponding stimulation amount and therapeutic effects on

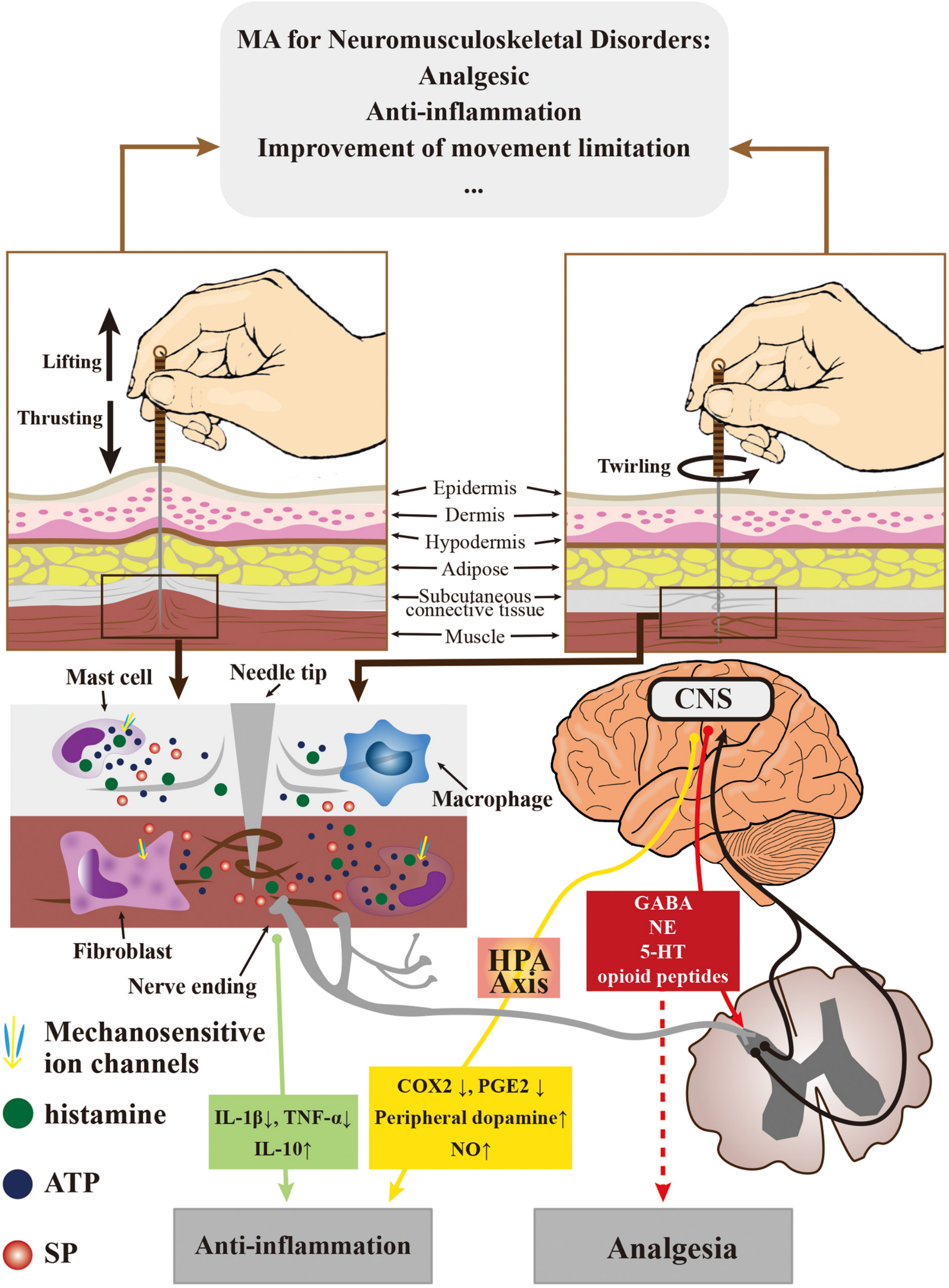

FIGURE 1
The effects of MA on neuromusculoskeletal disorders and the potential mechanism of action.

neuromusculoskeletal disorders (Yoon et al., 2022), which should be considered by acupuncturists.

3.1. Manipulation parameters

The selection of acupuncture manipulations mainly includes two basic needle movements with different operating directions. During treatment, the acupuncturist's thumb and index finger operate the needle handle to move up and down or rotate on a fixed axis (the needle body), respectively (Seo et al., 2014; Xu et al., 2021). These two types of manipulations are named lifting-thrusting and twirling (Lyu et al., 2019). According to the movement mode of acupuncture needles, the mechanical stimulations of the acupoint area are also different. The stimulation of the lifting-thrusting method mainly pulls the epidermis, dermis, connective tissue and muscle through the frictional force along the needle body generated by the interaction between the needle and the surrounding tissue (Lee Y. S. et al., 2018; Yao W. et al., 2020), which significantly changes the morphological structure of the acupoint area, such as the thickening of connective tissues and the muscle layer (Bae et al., 2019). During this manipulation, the amplitude of needle movement can be regarded as the amplitude of the elastic body, and the resistance of the acupoint tissue to the needle can be regarded as the damping of the series of elastic bodies; therefore, such a process is similar to the Maxwell model (Wang, 2011). In terms of twirling, the needle body generates tangential frictional force with the surrounding tissue, which will induce the winding of connective tissues or muscle in the acupoint area and produce a stimulation effect (Yao W. et al., 2020). A clinical study found the sensation produced by lifting-thrusting is stronger than that of twirling (Lu et al., 2021). The result of an energy measurement experiment on animals also reported that the input average energy flux density of lifting-thrusting is greater than that of twirling. Therefore, if the operation time is the same, the stimulation amount of lifting-thrusting may be greater than that of twirling (Wang, 2011). Moreover, the stimulation amount of lifting-thrusting tends to increase with increasing needle diameter, which is a feature that twirling does not have (Lee Y. et al., 2018). However, due to the increased collagen winding or rupture caused by twirling, more cellular responses and release of active substances may be mediated by this process (Zhang et al., 2022).

At present, which manipulation should be selected in the treatment of different neuromusculoskeletal disorders and the applicable symptoms of each manipulation still lack evidence from rigorous RCTs. Therefore, the selection of manipulations in the clinical application of MA is still mainly based on the personal experience and judgment of acupuncturists. Although there are many clinical reports confirming that lifting-thrusting and twirling have positive effects in relieving pain and inflammation in musculoskeletal diseases (Comachio et al., 2020; Wang et al., 2021), according to some comparative studies of the two manipulations, twirling may be more suitable for local analgesia, regulation of blood circulation and anti-inflammation than lifting-thrusting, and the possible explanation for this result is related to its ability to release more neurotransmitters to regulate nerves (Xu et al., 2019). In terms of improving the movement function of joints, MA treatment is often accompanied by active movement of the patient to enhance the therapeutic effect, which is also called motion-style acupuncture. In the process of such treatment, MA often requires greater stimulation to obtain a strong needling sensation, thus, lifting-thrusting may be more suitable. For example, lifting-thrusting at the acupoint "Yanglingquan" (GB34) was selected in some clinical researches, and combined with flexion, extension and rotation of the patient's joints with limited mobility to improve the joint movement functions of cervical spondylosis (Yang et al., 2022) and shoulder pain (Shi et al., 2018).

3.2. Kinematic parameters

The movement control of acupuncture needles by acupuncturists is mainly the adjustment of their kinematic parameters. In MA manipulation, the kinematic parameters of lifting-thrusting include the amplitude along the direction of the needle body and the corresponding velocity. Because these parameters of lifting-thrusting vary greatly among different acupoints, they need to be measured in future work. Take the acupoint "Quchi" (LI11) as an example, it was reported that the needling amplitude was usually around 0.9–1.8 cm, and the needling velocity was around 1.8–4.7 cm/s. The kinematic parameters of the twirling are the rotation angle with the needle body as the axis and the corresponding angular velocity. The common amplitude is between 180 and 360°, and the velocity is approximately 2.5–6 rad/s (Xu et al., 2021). At the same time, the ratio of the respective amplitude and velocity of these two types of manipulations is also the frequency of corresponding manipulations, so the needling frequency can also be adjusted by changing the needling amplitude or velocity (Lyu et al., 2019).

In general, the needling amplitude is most closely related to the stimulation intensity of acupuncture, and many acupuncturists adjust the intensity of stimulation by changing the needling amplitude. Some results of RCTs suggested that a greater needling amplitude may exerted better pain-relieving effects in neuromusculoskeletal disorders than a smaller amplitude (Zhang et al., 2021). For instance, the pressure pain threshold in a 10 cm needling amplitude increased higher than that in a 3 cm needling amplitude (Itoh et al., 2011). Similarly, the sensation of the *de qi* response as well as the pain threshold was also enhanced by a greater twirling angle (Choi et al., 2013). Although an excessively large needling amplitude may create potential risks, such as patient intolerance or neurological or vascular injury (Shen et al., 2021; Zhou et al., 2022), the result of an animal experiment suggested that the analgesic effect of MA may be positively correlated with the needling amplitude (Bae et al., 2019). The occurrence of this phenomenon probably lie in two factors. First, the excitation of afferent nerve fibers. Acupuncture activates baroreceptors, stretch receptors, and free nerve endings, which in turn transmit needling signals to the CNS from the afferent nerve fibers. Some animal studies have reported that small-amplitude MA mainly excites Aα and Aβ afferent fibers, while large-amplitude MA can excite all four types of afferent fibers (Aα, Aβ, Aδ, and C), thereby transmitting more signals and exciting more central nerves (Huo et al., 2020). Especially the twirling amplitude (angles) was reported to have an obvious dose-dependency on the cytoskeletal response in subcutaneous tissue when performing bidirectional rotation, which may also be due to the different winding and squeezing of afferent fibers at different twirling angles (Chang et al., 2019). Second, mechanosensitive ion channels are activated. As a typical mechanical stimulation, MA can activate non-selective mechanosensitive ion channels in the cell membrane during needling and regulate the conduction of needling signals, some key mechanotransducers, such as TRPV1 (Chen et al., 2018), TRPV2 (Huang et al., 2018), Piezo1, and Piezo2 (Guo et al., 2022), are involved in the regulation process. It was also found that the expression of related ion channel proteins exhibits varying degrees of stimulation intensity dependence (Chen et al., 2018; Chen C. et al., 2021). In contrast, this effect can be blocked by non-selective mechanosensitive channel blockers such as gadolinium (Varani et al., 2009). However, because the current real-time measurement technology of MA amplitude cannot meet the requirements of clinical application, and RCTs related to the therapeutic effect and mechanism of different needling amplitudes cannot be carried out. Therefore, it is necessary to focus on the development of MA quantification technology in future work.

Needling velocity is another important stimulation parameter for acupuncturists; moreover, the reinforcing and attenuating methods of acupuncture manipulation are also mainly distinguished according to the needling velocity (Lyu et al., 2019). Needling was able to arouse the deformation of the extracellular matrix and form a mechanical stress field in the interstitium, which hinged on needling velocity (Yao et al., 2018). This stress field causes winding or rupture of collagen fibers and muscles, and its magnitude affects the degree of cellular response around acupoints (Langevin et al., 2001). Although it was suggested that increasing the velocity of twirling (from 2 to 4 rad/s) was beneficial to relieve pain caused by neuromusculoskeletal disorders (Song et al., 2021), more clinical studies have pointed out that too fast or too slow needling velocity may cause a decline in therapeutic effect (Zhang L. et al., 2019). Therefore, the selection of an appropriate needling velocity is an important factor for obtaining a positive effect too. Acupuncture-related neurophysiological studies have proposed a possible explanation for this phenomenon. Since the increase in the needling velocity usually results in an increase in the MA frequency, with the change in synchronization of activated neural circuits, different frequencies of MA may form diverse neuronal connectivities (Yu et al., 2017), thus, the neuronal firing rate and time sequences of interspike intervals could be effectively distinguished at different MA frequencies (Zhou et al., 2014). The different acupuncture frequencies generated by different needle velocities can also regulate the above process, and the characteristics of rate encoding specific to different frequencies of MA have been found in related studies (Yu et al., 2017; Zhang L. et al., 2019). Nonetheless, because of the relative refractory period, the mean neuronal firing rates do not increase evidently when the frequency of MA is over 100 times per minute (Men et al., 2012). Therefore, although increasing the needling velocity can speed up neuronal firing and promote the rapid conduction of needling signals, a velocity that is too fast may not accelerate the above process, improve the therapeutic effect and also bring potential safety risks.

From the above results, it can be seen that the velocity of lifting-thrusting or twirling probably have a relatively effective reference range in the MA treatment of neuromusculoskeletal disorders, and the possible decrease in therapeutic effect or increased safety risk may be generated by too fast or too slow needling velocity outside this range. However, this reference range is likely to be vary according to the different disease locations or individuals. The acquisition of such evidence requires the accumulation of a large amount of clinical or experimental data, as well as the greater innovation and breakthroughs in measurement technology of MA kinematic parameters.

3.3. Time parameters

Complete MA treatment mainly includes three types of time parameters. The first one is needling time, which is the time when the acupuncturist uses his fingers to operate the acupuncture needles and perform manipulation. The second one is retention time. The process of needle retention is when needles stay underneath the skin after penetrating and are usually scheduled after needling is completed to consolidate the stimulation effect. The last one is course of treatment, a period of continuous MA therapy prescribed for specific diseases. According to current clinical studies, the common needling time ranges from 30 s to 5 min, the needle retention time usually ranges from 20 minutes to 1 hour, and the common course of treatment ranges from 2 weeks to 3 months (Lin et al., 2019; Lu et al., 2020).

In the process of MA treatment, the increase of needling time directly leads to an increase of the stimulation amount. An animal experiment comparing the effects of different needling times on neurophysiology have shown that the significant improvements of neurological function and cerebral blood flow were obtained by appropriately extending the needling time (from 5s to 60s). On the contrary, such effects were weakened when the needling time was extended to 180s (Zhang et al., 2015). Based on the above results, the remarkable thing is that there may be no necessary link between the increase in needling time and effect improvement. First, not all patients can tolerate an increased stimulation amount, especially thin female patients, so acupuncturists may need to adjust the other stimulation parameters to improve the therapeutic effect. Second, prolonged acupuncture stimulation probably lead to a weakening of effects, which is considered as a phenomenon called "acupuncture tolerance" (Han, 2011). The possible mechanisms of such a phenomenon may be related to not only the inactivation or downregulation of central opioid peptide receptors caused by excessive stimulation but also the release of anti-opioid peptide substances (such as cholecystokinin) (Han, 1995).

Although the needling stimulation was stopped during needle retention, needle retention can be regarded as an amplification effect on the needling stimulation. It has been found that the therapeutic effect of MA presents stage characteristics as retention time changes. An clinical fMRI study indicated that the related brain nuclei of the limbic system had obvious response patterns that changed over time during the effects of acupuncture, which could be divided into short activation, intermittent activation, bidirectional activation and continuous activation (Bai et al., 2009). Among them, continuous activation is mainly related to the post needling effect, and retention time is one of its main influencing factors. Numerous studies have confirmed that a better therapeutic effect can be obtained by retaining the needles for a certain period of time compared with direct needle withdrawal after needling, while an exceedingly long retention time may cause needle withdrawal resistance and tiresome acupoints (Lin et al., 2019). Moreover, for neuromusculoskeletal disorders, the evidence from an animal experiment showed the analgesic effect of 20 min of retention time for chronic pain is better than that of 10, 30, and 40 min (Cui J.-m Ma et al., 2009), while another clinical study suggested the MA treatment of acute pain can appropriately extend the needle retention time to 45 min (Yao and Liu, 2013).

As far as the course of treatment is concerned, due to the limited stimulation by a single MA treatment, it is necessary to continue such treatment for a period of time to accumulate effect. A study on rheumatoid arthritis showed that longer course of treatment could lead to better therapeutic effects (Wang et al., 2008). Similarly, it was found that better analgesia effect on fibromyalgia was produced by more MA treatments (Harris et al., 2005). However, acupuncture tolerance may also be resulted by an excessively long course of treatment, which has negative effects or even leads to more adverse events (Macpherson et al., 2004).

4. Discussion

Throughout the current research, MA has a relatively positive effect on the treatment of neuromusculoskeletal disorders. The selection of MA stimulation parameters can be summarized as

TABLE 1 Common parameter types, values and corresponding effect of MA in the treatment of neuromusculoskeletal disorders.

Parameter type	Option	Common value	Potential parameter-effect relationship
Manipulation parameter	Lifting-thrusting	–	May be more suitable for improving joint movement
	Twirling	–	May be More suitable for analgesia and anti-inflammation
Kinematic parameter	Needling amplitude	Amplitude of lifting-thrusting: Varies by acupoints Amplitude of Twirling: 180–360°	A certain positive correlation between the needling amplitude and the effect may be existed
	Needling velocity	Velocity of lifting-thrusting: Varies by acupoints Velocity of Twirling: 2.5–6 rad/s	A certain effective reference range is probably existed Too slow: insufficient stimulation Too fast: no effect improvement and potential safety risks
Time parameter	Needling time	30 s–5 min	A certain effective reference range is probably existed Too short: insufficient stimulation Too long: patient intolerableness and acupuncture tolerance
	Retention time	20 min–1 h	A certain effective reference range is probably existed Too short: insufficient post needling stimulation Too long: needle withdrawal resistant and tiresome of acupoints
	Course of treatment	2 weeks–3 months	Accumulation of therapeutic effects of every MA treatment, and a certain effective reference range is probably existed Too short: insufficient accumulated stimulation Too long: patient intolerableness and acupuncture tolerance

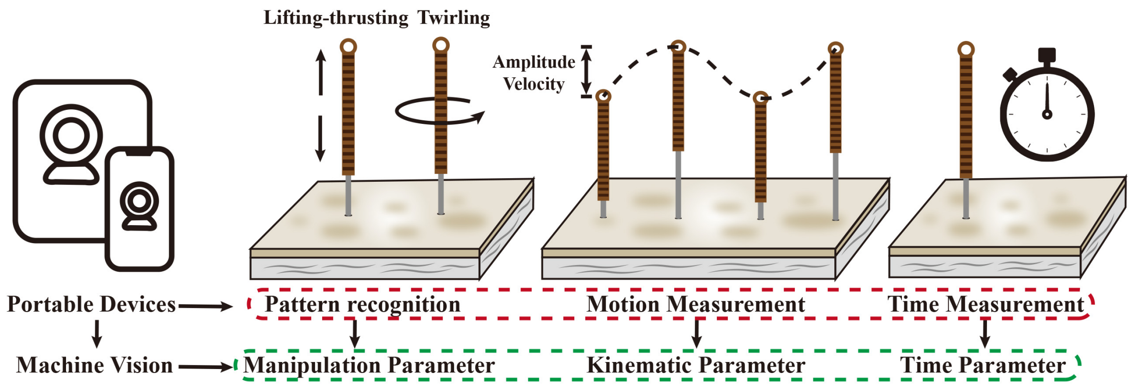

FIGURE 2
Recognition and measurement of stimulation parameters of MA based on machine vision.

follows according to the relevant evidence of its effects (**Table 1**). First, although both lifting-thrusting and twirling have analgesic and anti-inflammatory effects and improve movement limitation, lifting-thrusting may be more suitable for use in motion-style acupuncture to increase the movement amplitudes of joints, while twirling is probably more suitable for relieving pain and inflammation. Second, for the kinematic parameters, appropriately increasing the needling amplitude within a safe range is likely to bring about a certain enhancement in therapeutic effect, but the needling velocity should potentially have a certain effective reference range. Too large or small needling velocity is not conducive to obtaining better prognosis. Finally, the selection of time parameters is similar to that of needling velocity, and the time of needling and retention, as well as the course of treatment need to be adjusted according to different symptoms and individuals. In general, the selection of an excessively short time parameter probably tends to reduce the therapeutic effect because of an insufficient stimulation amount, whereas an excessively long time may not only do not contribute to the improvement of the therapeutic effect but also be prone to other side effects. In summary, it is not difficult to find that the selection of stimulation parameters in the clinical process of MA is still confusing and lacks evidence and a clear reference, which needs a large number of comparative clinical trials in future work.

Regarding the issue above, one of the main breakthroughs for the solution lies in the innovation of the measurement technology of kinematic parameters of MA. Currently, the measurement of MA stimulation parameters mainly includes two technologies. The first is the modification of the acupuncture needle body or needle handle. For example, a small kinematic sensor was attached to the needle handle to obtain the velocity and acceleration of the needle body during the needle movement (Seo et al., 2014; Leow et al., 2016), and the sensor device can also be wrapped around the needle body to obtain the needle movement amplitude and velocity (Davis et al., 2012; Li et al., 2013). Whether it is the modification of the needle handle or the needle body, the shape and weight of the acupuncture needle will be greatly changed. Therefore, this method has a serious influence on the finger sensation of acupuncturists and is not suitable for clinical application (Lyu et al., 2019). The other technology is motion tracking for capturing the movements of the thumb and index finger by placing small tracking markers (reflective balls) on the fingertips and joints of the acupuncturist's fingers (Tang et al., 2018; Xu et al., 2021, 2022). Since the movement of the needle body is mainly generated by the lifting-thrusting or twirling of the thumb and index finger, the kinematic parameters of the needle can be calculated by tracking the movement of fingers. This technology completed real-time in-body parameter acquisition without operational interference and influenced the finger sensation. However, before the implementation of motion tracking technology, it is necessary to build an experimental environment for simultaneous shooting of multiple cameras. The configuration of multiple cameras, tripods and connecting wires still greatly affects the working environment of acupuncturists, which cannot actually be applied in clinical work. Therefore, the technology that is truly suitable for the stimulation parameter acquisition of MA should have the following characteristics: real-time, convenient, stable, and free of operational interference. According to the current development of motion analysis technology, the more suitable solution may be motion analysis technology based on machine vision. After the cameras captured the real-time video of the fingers and acupuncture needle during the operation of the acupuncturist, the image analysis technologies of machine vision such as convolutional neural networks could be used to identify the movement of the fingers or needles, determine the current manipulation mode (lifting-thrusting or twirling) (Su et al., 2022), and calculate the relevant kinematic parameters. Because this technology can be implemented with portable devices such as mobile phones and tablets, it may be a more suitable tool for the measurement of MA stimulation parameters for clinical applications (**Figure 2**).

Another breakthrough lies in the analysis of data. Because MA treatment requires the selection of the above three types of parameters to form a parameter combination for obtaining the therapeutic effect. Thus, compared with the single parameter analysis, different parameter combinations will significantly increase the complexity and difficulty of data analysis. Some studies have also focused on the influence of stimulation parameter interactions on the therapeutic effect. For instance, an investigation on the effects of parameter combinations, including manipulation (present or absent), retention time (1 or 21 min) and selected acupoints ["Hegu" (LI4) or non-acupoint located with the same dermatome of LI4], discovered that the combination of 21-min intervention on LI4 with manipulation showed better needling sensation and analgesic effect (Loyeung and Cobbin, 2013). Another study about the safety of manipulation by an auto manipulation device for acupuncture at different velocities and stimulation times suggested that although the stimulation time was shortened, more collagen rupture was brought about in higher velocity manipulation (Liu et al., 2018). These results indicated that different parameter combinations will result in too many intervention groups and corresponding effects, and traditional RCT experiments may be unable to meet the requirement of such research. On the basis of an innovative measurement solution suitable for clinical application, if this measurement method can be used in the clinical work and fundamental research of MA to obtain a large number of parameter combination data and the correspondence effects, some classification- and regression-related machine learning algorithms, such as decision tree (Ghiasi et al., 2020) and random forest (Wang S. et al., 2020), can be applied to find the different combinations of MA stimulation parameters with ideal therapeutic effects suitable for different neuromusculoskeletal disorders and individuals. We believe that with the continuous iteration of measurement and analysis technologies, the selection of MA stimulation parameters for neuromusculoskeletal disorders will be supported by more evidence and more standardized to achieve better therapeutic effects.

6. Conclusion

This article reviews three types of stimulation parameters that MA can select in the treatment of neuromusculoskeletal disorders and their corresponding effects. The manipulation parameters include lifting-inserting and twirling, both of which can achieve positive therapeutic effects. Lifting-thrusting may be more suitable for improving joint movement, while twirling is probably more preferred for analgesia and anti-inflammation. In terms of the kinematic parameters, appropriately increasing the needling amplitude within a safe range may bring about a certain enhancement in therapeutic effect, but the needling velocity is likely to have a certain effective reference range. A similar situation also exists in the selection of time parameters; too short- or too long-time settings may result in insufficient stimulation and acupuncture tolerance, respectively. At present, there is still a lack of sufficient experimental and clinical evidence to provide clear reference for MA application. It is urgent to pursue innovation in MA stimulation parameter measurement technology and data analysis algorithms, which may be the breakthroughs to solve this issue, and leading to a more standardized MA treatment for neuromusculoskeletal disorders.

Author contributions

JX, GX, and W-CT developed and designed the study. B-GW and L-LX summarized and analyzed the current studies and wrote the manuscript. H-YY and W-CT reviewed and edited the manuscript. All authors read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acupoint catgut embedding for chronic non-specific low back pain: A protocol of randomized controlled trial

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Chronic non-specific low back pain (CNLBP) is one of the leading causes of disability worldwide. Acupoint embedding (ACE) is widely used in China for the treatment of chronic non-specific low back pain, but there are no rigorous randomized controlled trials (RCTs) to confirm the effectiveness and safety of ACE for chronic non-specific low back pain. In this study, we design a single-center, single-blind, prospective RCT, with the aim of evaluating the efficacy and safety of ACE for CNLBP. 82 participants with CNLBP will be randomized in a 1:1 ratio into an ACE group and a sham ACE group. Participants will receive either ACE treatment or sham ACE treatment at once every 2 weeks, for an 8-week period, and followed by 6 months of follow-up. The primary outcome will be the change in visual analog scale (VAS) scores before and after treatment. Secondary outcomes will include the Oswestry Disability Index (ODI), the Roland Morris Disability Questionnaire (RMDQ) and the Short Form 36-Health Survey (SF-36). Adverse events that occur during the course of the trial will be recorded. Data will be analyzed according to a predefined statistical analysis plan. This study was approved by the medical ethics committee of Guangzhou Panyu Hospital of Chinese Medicine (202230). Written informed consent from patients is required. This trial is registered in the Chinese Clinical Trial Registry (ChiCTR2200059245). Trial results will be published in a peer-reviewed academic journal.

Clinical trial registration: https://www.chictr.org.cn, identifier ChiCTR2200059245.

KEYWORDS

chronic non-specific low back pain, acupoint catgut embedding, traditional Chinese medicine, randomized controlled trial, protocol, acupuncture

1. Introduction

Low back pain, a global high incidence and high burden disease, can greatly affect the quality of life of patients, and cause motor dysfunction or even disability (Knezevic et al., 2021). A systematic review of thirteen studies from Northern Europe, North America, and Israel reported that the prevalence of lower back pain ranged from 1.4 to 20.0%, with an annual incidence of 0.024 to 7%, and was highest in the United States (Fatoye et al., 2019). The incidence of chronic low back pain is expected to increase as the population ages, and as technological advances lead to increasingly sedentary lifestyles (Knezevic et al., 2021). A systematic analysis of the global burden of disease showed that low back pain increased the number of years lived with disability by 17.8% between 2007 and 2017 (Disease et al., 2018). A study comprehensively estimated the cost of care for non-severe low back pain episodes in hospitals in three Australian cities over a 5-year period, and showed that the average direct hospital cost for low back pain episodes was AUD$2959 (Coombs et al., 2021). It is estimated that more than $100 billion was spent annually on treating patients with low back pain in the United States (Katz, 2006). Most low back pain is non-specific (commonly cited as 90%) (Knezevic et al., 2021). Currently, for the management of patients with non-specific low back pain, pharmacological (non-steroidal anti-inflammatory drugs, weak opioids, and muscle relaxants) and non-pharmacological (exercise therapy, spinal manipulation, psychotherapy, and physiotherapy) treatments are recommended by guidelines (Vitoula et al., 2018). However, the treatment of patients with chronic non-specific low back pain (CNLBP) remains a great challenge. For example, oral non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to be used with caution and not continuously, considering gastrointestinal and cardiovascular adverse events (Davis and Robson, 2016). Therefore, it is necessary to explore effective and safe non-pharmacological therapies.

Acupuncture, an important part of traditional Chinese medicine (TCM), has been proven to play a critical role in pain management and function recovery, especially for the treatment of CNLBP (Huang et al., 2021). Acupoint catgut embedding (ACE) is an innovative acupuncture method combined with traditional theory and modern materials, which embeds absorbed catgut into the acupoints, where the catgut will undergo softening, liquefaction, and absorption, thereby stimulating the acupoints for a long time (Teng et al., 2022). Compared with traditional acupuncture, ACE not only has the advantages of easy operation, strong stimulation, and long-lasting therapeutic effect, but also extends treatment interval patterns and reduces the discomfort caused by frequent acupuncture treatments, which can make up for the deficiencies in traditional acupuncture and improve patient compliance (Zhang et al., 2012). Previous preclinical studies have elucidated the mechanism of ACE in the treatment of pain. For example, in an *in vivo* experiment, ACE was shown to have a long-lasting analgesic effect on complete Freund's adjuvant-induced inflammatory pain in rats, which was associated with activation of spinal 5-HT1AR, inhibition of GluN1 phosphorylation, and thus inhibition of Ca^{2+}-dependent signaling (Cui et al., 2019). Another study suggested that ACE may exhibit antinociceptive effects by inhibiting Sig-1R regulation of p38 MAPK (Du et al., 2017). In recent years, a growing body of clinical evidence supports the use of ACE for the management of painful conditions. For example, a meta-analysis showed that ACE is beneficial for the relief of neck pain (Jo et al., 2022). However, to our knowledge, no clinical study on ACE for the treatment of CNLBP has been reported. Based on the current conditions, we will conduct a well-designed RCT to discuss the efficacy and safety of ACE, by comparing with a sham control in the treatment of CNLBP.

Abbreviations: CNLBP, chronic non-specific low back pain; ACE, acupoint catgut embedding; NSAIDS, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial; VAS, visual analog scale; ODI, Oswestry Disability Index; RMDQ, Roland Morris Disability Questionnaire; SF-36, Short Form 36-Health Survey; TCM, traditional Chinese medicine; SAE, severe adverse event; CRF, case record form.

2. Methods

2.1. Design and setting

The present study will be a prospective, randomized, patient-assessor-blinded, sham-controlled trial. A total of 82 participants will be recruited for the trial in Guangzhou Panyu Hospital of Chinese Medicine. Participants will be divided randomly at a ratio of 1:1 into the ACE group or the sham ACE group. The trial will contain an enrolment and allocation period of 3 days, an 8-week intervention period, and a 6-month follow-up period. The flow chart of the study procedure is shown in **Figure 1**. This study will be conducted in accordance with the Declaration of Helsinki, the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010) and the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) guidelines (MacPherson et al., 2010) in trial design and reporting. Any modifications to the protocol that may affect the conduct of the study will be expected to draft a formal modification of the protocol. Such update will be determined by the project management group and approved by the ethics committee, before the modification being placed into practice. This trial has been registered at the Chinese Clinical Trial Registry, numbered ChiCTR2200059245.

2.2. Recruitment

The recruitment advertisement for eligible participants will be placed on WeChat, official website of the hospital, and the waiting hall of the outpatient clinic, from April 2022 to December 2024. Eligible individuals who agree to participate in the study will sign written informed consents. By the way, participants will be notified that they are at liberty to withdraw from the study without any negative effects on their future treatments. After recruitment, the characteristic of participants will be preserved by dedicated personnel, which cannot be disclosed or used by unauthorized individuals at any time or for any reason.

2.3. Participants

2.3.1. Diagnostic criteria

The diagnostic criteria for non-specific lower back pain are as follows: (1) pain or discomfort is located in the lumbar region with or without related radiation symptoms to lower extremities; (2) the history of low back pain lasts for more than 12 weeks; (3) the straight leg raising test is negative; and (4) there are no lumbar spine specific diseases diagnosed with imaging examination (e.g., presence of radiculopathy, osteoporosis, cord compression, or cancers). All potential participants will be first screened by a specialist with 20 years of clinical experience based on the diagnosis criteria.

2.3.2. Inclusion criteria

Participants must meet with the following inclusion criteria: (1) 18–60 years old; (2) suffer from ongoing low back pain; (3) the visual analog scale (VAS) of low back pain intensity assessment is greater than 4 cm, but lower than 7 cm; and (4) participate voluntarily in this study, signing written informed consent. The inclusion process

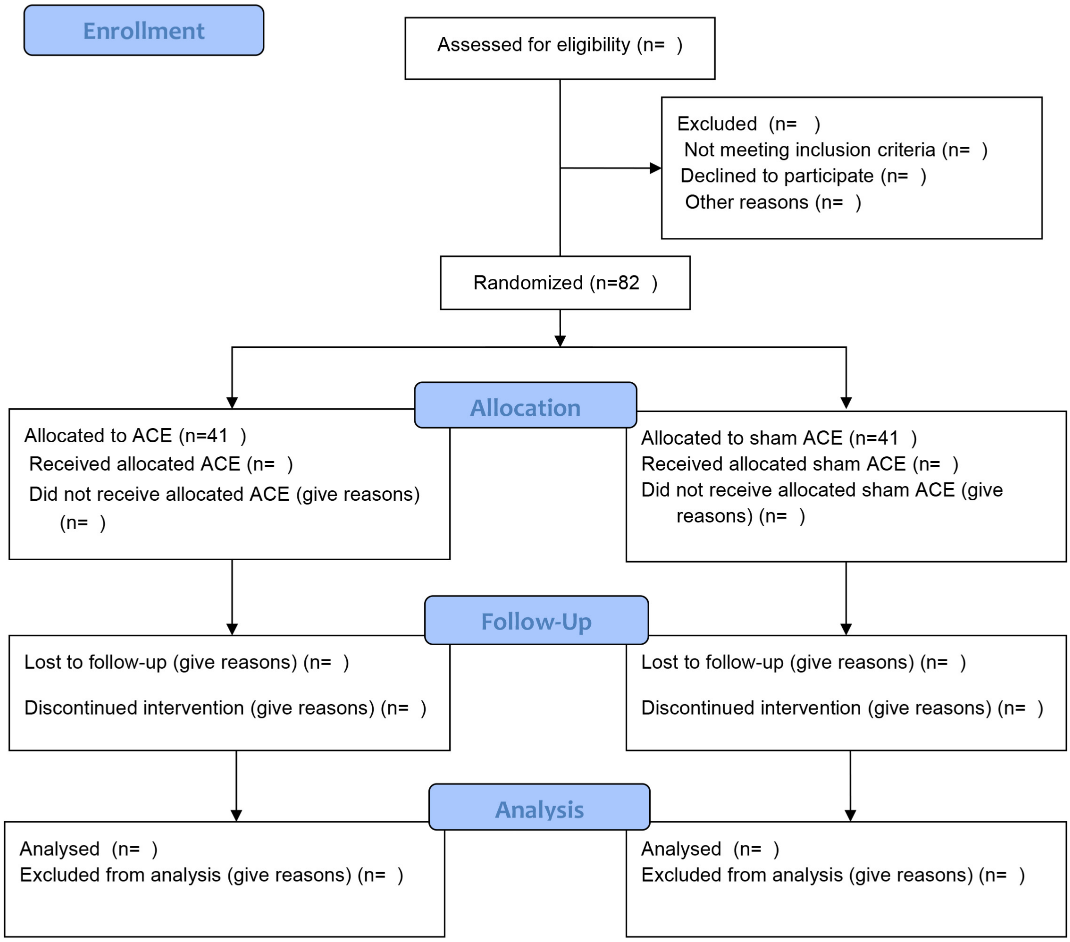

FIGURE 1
Flow chart of the study procedure.

will be conducted by a specific researcher, after being assessed by diagnosis criteria.

2.3.3. Exclusion criteria

Participants who meet any of the following conditions will be excluded: (1) cauda equina syndrome with bladder, bowel, or sexual dysfunction; (2) tumors, fractures, infections in the spine, or skin diseases in the lumbar region, or hemostatic disorder; (3) other serious diseases, such as cardiovascular, kidney, or liver diseases; (4) with diabetes or other diseases characterized by skin and subcutaneous tissue dysfunctions in absorption and renovation; (5) cognitive impairment or serious mental illnesses, such as schizophrenia or severe depression; (6) pregnant or breastfeeding women; (7) fear of acupuncture and have a history of severe acupuncture adverse reactions; (8) participation in other studies related to LBP treatment within the past 3 months; and (9) cannot participate in regular treatment or observation, as required. Exclusion process will be conducted by the same researcher handling the inclusion.

2.3.4. Criteria for withdrawal, dropout, and removal

Participants presenting any of the following situations will be considered as the withdrawal cases: (1) the disease get worse after treatment in this study; (2) complications or severe adverse events (SAEs) occur during the trial; (3) the utilization of related treatments other than the study, which may impact upon the results of this study; (4) poor compliance, or the number of appointments for treatment does not meet the requirements (<80%); (5) unblinding for emergency situations; and (6) participants request to withdraw from the study.

Participants unable to complete the observation procedure of the study, regardless of the reasons, will be classified as dropout cases. The last outcome data of dropout cases will be included in data analysis. During the trial, participants will be removed if (1) they are wrongly enrolled due to misdiagnosis; (2) they do not accept the treatment after being enrolled in the study; (3) they participate in other clinical trials at the same time; and (4) the post-inclusion data is incomplete and there are no evaluable records for the analysis of the results. Data from withdrawal and dropout cases will be included in intention-to-treat analyses.

2.4. Randomization, allocation concealment, and blinding

Eligible participants will be divided randomly into the intervention group (ACE group) or the control group (sham ACE group). The random numbers of allocation sequences will be generated using Statistical Analysis System (version 9.4) by a statistician. Later, the random numbers and groupings will be packaged in opaque and closed envelopes with sequence numbers. The researchers responsible for the participant's enrolment will take the envelopes with the corresponding number according to the inclusion order, and write down the name, gender, and age of the included participant on the surface of the envelope. All the marked envelopes will be kept by another researcher, who is not involved in participant recruitment.

After the baseline assessment of personal conditions and pre-treatment outcome measurements, acupuncturists will be informed about the different treatments of the participants. The outcome assessors will be blinded to the treatments due to the groups of the participants recorded in the case record forms (CRFs) being replaced by "A" and "B" without details. Additionally, the assessors will also be blinded to recruitment and groupings. All in all, participants, outcome assessors, and statistician in the study will be blinded to the different treatments. Under certain conditions, unblinding will be permissible when participants undergo SAEs or other emergency situations. Once unblinded, participants will withdraw from the trial, and the reasons will be documented and reported by the researchers.

2.5. Sample size

The VAS score is the primary outcome indicator for this trial. Based on the results of the pre-test, it is known that the VAS score in the control group was 4.64 ± 1.42 cm and is expected to be reduced by 1.02 cm after treatment with ACE, setting a two-sided test with $\alpha = 0.05$, $\beta = 0.10$. A sample size of 34 cases per group was calculated using PASS 15 software. Considering the 20% lost to follow-up calculation, the final number of cases needed for at least two groups was 41, for a total of at least 82 participants included.

2.6. Interventions

The ACE operation in this study will be carried out in accordance with the Acupuncture Technical Operation Standard of the People's Republic of China for ACE. Participants in both groups will accept treatments once every 2 weeks, for an 8-week period. During treatment, participants will be separated in different treatment rooms to avoid communication. Both treatments will be conducted by trained acupuncturists who are qualified, have acupuncture affiliation, and experience in clinical practice for more than 3 years. During the treatment and observation period of the study, if the participant's pain symptoms worsen, the oral NSAIDs drug celecoxib (Pfizer Pharmaceuticals Ltd.) (Frampton and Keating, 2007; Foster et al., 2018) will be given orally for 2 days at a dose of 200 mg twice daily. If pain remains unrelieved, participants will be withdrawn from the study.

2.6.1. Intervention group

(1) **Acupoints:** According to the theory of TCM and previous clinical practice experience, this study will select the bilateral acupoints of Shenshu (BL23) and Dachangshu (BL25). The position and depth of acupoints for needle insertion are in accordance with the Name and Location of Acupoints (GB/T12346-2006), a standard of The People's Republic of China. Details of selected acupoints are shown in **Table 1** and **Figure 2**.

TABLE 1 Locations of acupoints in the study.

	Acupoints	
	BL23 Bladder meridian	BL25 Bladder meridian
Needle insertion	On the lumbar region, on the same level of the second subspinous of the lumbar vertebra, and 1.5 cun lateral to the posterior midline.	On the lumbar region, on the same level of the fourth subspinous of the lumbar vertebra, and 1.5 cun lateral to the posterior midline.
Major indication and actions	Bone problems, low back pain, difficulty in urination, oedema	Pain in lumbar region and lower extremities.
Manipulation	Insert the needle 1.0 cm perpendicularly	Insert the needle 1.0 cm perpendicularly

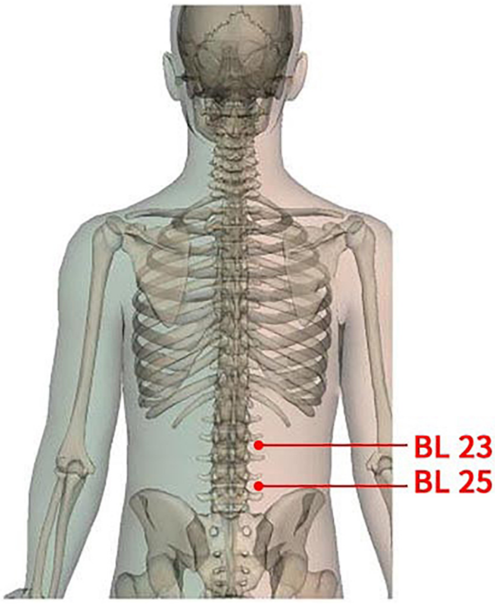

FIGURE 2
Locations of acupoints.

(2) **Preparation of ACE:** The main instruments utilized in the ACE treatment operation include an embedding needle, combinating of needle tubing and liner core, and absorbable surgical chromic catgut (Yangzhou Longhu Medical Instrument Co., Ltd., Yangzhou City, Jiangsu Province, China), all of which are disposable sterile products. The embedding needle is shown in **Figure 3**. Participants will stay in the prone position during the operation process.

(3) **Operation procedures:** Firstly, the skin of the target acupoint region will be exposed and sterilized with iodophor. After disinfecting hands and wearing sterile gloves, the acupuncturists will cut the absorbable surgical chromic catguts into 1 cm long pieces, and place the small catgut into the pinpoint of the embedding needle tubing, where the liner core will be moved up 1 cm. Then, acupuncturist will use the thumb and index fingers to fix the acupoint, while, with the other hand, inserting the needle perpendicularly to the skin surface of the acupoint at a depth of approximately 1 cm. Secondly, acupuncturists will apply lifting, inserting, and twisting techniques to stimulate

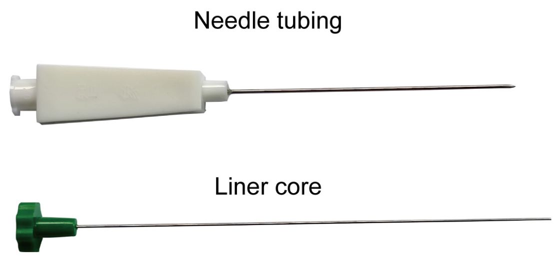

FIGURE 3
Parts of the acupoint catgut embedding device.

special sensations, presenting soreness, such as numbness, swelling, or radiation, but no pain, which are described as *Deqi* in TCM theory. Thirdly, by pressing down the liner core of the embedding needle, the catgut in the needle tubing will be embedded in the muscle layer. Finally, both the liner core and needle tubing will be pulled out of the acupoint, and the post-treatment acupoint will be covered by a cotton ball with tape for 24 h.

For the standard and safe operation of ACE, the acupuncturists should: (1) ensure that the operation of ACE is conducted in a strictly sterile surrounding; (2) avoid catguts being embedded in the adipose tissue, which may cause fat liquefaction; (3) ensure that the chromic catgut is fully embedded in the deep tissue, and will not be exposed to the skin surface; (4) grasp at an appropriate angle and depth of the operation, to avoid damage to internal organs, major blood vessels, and nerves; and (5) inform participants regarding the precautions after treatment, such as keeping the lumbar region away from water for 24 h.

2.6.2. Control group

In the sham ACE group, the embedding needle and acupoints are the same as those of the intervention group, but no catgut will be placed into the needle tubing before being inserted into the acupoints, so that no catgut will be left under the tissue after the needle is pulled out. At the same time, the needle will be withdrawn immediately, because inserting to the acupoints at a depth of 1.0 cm without retaining the needle to activate the *qi*, which is essentially different from traditional acupuncture.

2.7. Outcomes measurement

The efficacy evaluation in this study will include the primary outcome indicator VAS (Bijur et al., 2001). The secondary outcomes are the Roland-Morris Disability questionnaire (RMDQ) (Law et al., 2021), Oswestry Disability Index (ODI) (Mehra et al., 2008), and the Short Form 36-Health Survey (SF-36) (Taft et al., 2004). Safety outcomes will be evaluated by the incidence of adverse event. All evaluation indicators will be assessed at six time points: baseline, mid-treatment (4 weeks of treatment), post-treatment (8 weeks of treatment), and 1 month, 3 months, and 6 months after the treatments. Researchers who do not take responsibility for other processes in the study will be appointed as outcome assessors. Details of the observational items and the time window for data collection are shown in **Table 2**.

2.7.1. Primary outcome

Visual analog scale will be used as the primary outcome to assess the intensity of CNLBP. Participants will be requested to measure their pain intensity on a 10-cm horizontal VAS, with 0 showing no pain and 10 showing the most severe pain.

TABLE 2 Schedule of enrolment, interventions, and assessments.

	Enrolment and allocation		Treatment period				Follow-up period		
Timpepoint	Screening (−3 to 0 d)	Allocation (0 d)	2 w	4 w	6 w	8 w	1 m	3 m	6 m
Enrollment									
Vital signs	X		X	X	X	X			
Previous medical history	X								
Inclusion/exclusion assessment	X								
Informed consent	X								
Allocation		X							
Interventions									
ACE treatment		X	X	X	X	X			
sham ACE treatment		X	X	X	X	X			
Assessments									
VAS		X		X		X	X	X	X
ODI		X		X		X	X	X	X
RMDS		X		X		X	X	X	X
SF-36		X		X		X	X	X	X
Adverse events		X		X		X	X	X	X
Analysis of outcomes									X

d, day; w, week; m, month; ACE, acupoint catgut embedding; VAS, visual analog scale; RMDS, Roland Morris Disability Scale; ODI, Oswestry Disability Index; SF-36, the Short Form 36-Health Survey.

2.7.2. Secondary outcome

2.7.2.1. The Roland-Morris Disability Questionnaire

Dysfunction of daily life caused by CNLBP will be assessed by the RMDQ, which contains 24 questions about the daily physical activities and function in daily life. Participants choose "yes" or "no" as the answer to each question, to describe their situations. The answer "yes" marks one score, with a total score ranging from 0 to 24, and the higher score reflecting more severe dysfunction.

2.7.2.2. The Oswestry Disability Index

Oswestry Disability Index will be used to assess the disability in patients with CNLBP. The ODI consists of 10 items: pain, personal care, lifting, walking, sitting, standing, sleep, sex life, social life, and travel. The score for each question ranges from 0 to 5, according to the different degree from normal to severe. The total score will be worked out with a percentage, where the higher percentage means a more severe disability evaluation.

2.7.2.3. The Short Form 36-Health Survey

Short Form 36-Health Survey is a general health measurement applied in populations with chronic diseases. It covers a systematic evaluation of physical and mental health with 8 domains (pain, physical functioning, role-physical, general health, vitality, role-emotional, mental health, and social functioning) covered by 36 questions. The score for each domain will be converted to a scale of 0–100, with higher scores indicating better quality of life.

2.7.3. Safety assessment

Adverse events that happen during the study will be recorded in the CRFs in detail, including the time of occurrence, symptoms, duration, treatment methods, and outcomes. Adverse events will be assessed by the specialists in the panel, to determine whether the conditions are treatment related and whether further rescues are needed. Adverse events frequently occurring in ACE treatment include fainting, acupoint swelling, and subcutaneous hemorrhage, and will be addressed by symptomatic treatment methods. Once the adverse events are defined as severe, such as acupoints infection, allograft rejection, or major organ damage, the research process will be terminated and the inspectors of the monitoring panel will reveal the participant's allocated intervention at once. Consequently, the participant will withdraw from the study and accept systemic treatments. The cost of treatments for adverse events arising from this study will be paid by the sponsor of this study. The monitoring panel will report the SAEs to the ethics committee, while the researchers will closely follow the participants' condition, and record it in detail in the CRF.

2.8. Data collection and management

After the included participants sign the informed consent forms, researchers will collect individual information, such as general demographic information, clinical history, and baseline data for VAS, RMDQ, ODI, and SF-36. Outcome indicators will be measured at the previously indicated six time points, and documented in the CRFs. When the trial is completed, two researchers who are neither involved in the distribution nor the outcome evaluation will independently extract data from CRFs into an Excel table. The statistician will then conduct statistical analysis on this data after double check confirmation. To protect the privacy of participants, personal names will be replaced by numbers combined with initials. Researchers shall maintain data confidentiality for 5 years after the termination of the trial. In order to reduce the dropout rate of participants, researchers will contact the participants by telephone 2 days before their treatments to enquire on their conditions and encourage them to accept the treatments as scheduled.

2.9. Quality control

To achieve credibility and consistency in the study results, all researchers will receive standardized training in advance, including identification and allocation of eligible participants, treatment procedures, outcome evaluation, management of adverse events, and CRF completion. In addition, a data and safety monitoring panel consisting of three experts in different fields will be established, who are independent from the sponsor and have no conflict of interest with the study. The panel will conduct casual inspection to reduce potential biases in the study process and data analysis. Once any violation of the research requirements or SAEs are identified, the panel will notify the principal investigator, or suspend the study at any time.

2.10. Statistical analysis

Statistical analysis will be computed using Statistical Analysis System (SAS) v9.4 by a statistician. Continuous variables subject to normal distribution are expressed as mean ± standard deviation, otherwise they will be expressed as median (interquartile range). Discontinuous variables will be expressed as composition ratio and rate. The baseline comparison of continuous variables will be performed by *t*-test or non-parametric test, and the baseline comparison of discontinuous variables by the chi-squared test. Repeated measures analysis of variance (RM-ANOVA) will be performed on the measurement data at multiple observation time points, to analyze the trend over time and the interaction between treatment times. The statistical significance level will be 0.05 (bilateral) with 95% confidence interval. The safety analysis will mainly be based on descriptive statistics, including the incidence and the specific description of adverse events.

2.11. Dissemination

Results of the study will be presented at scientific conferences and in peer-reviewed publications. Participants included in the study will also have the opportunity to obtain the study results by telephone or e-mail.

2.12. Trial status

Currently, the protocol is version 1.0, registered on 27 April 2022. At the time of protocol submission, potential participants of the study have been actively enrolled.

3. Discussion

Chronic non-specific low back pain, one of the most common conditions in orthopaedics, rehabilitation, and pain medicine, accounts for 1/3 (Wang et al., 2015) of daily outpatient visits, and is a major cause of increase in years of life lived with disability, in both developed and developing countries (Diseases and Injuries, 2020). Recently, evidence has been published for ACE being beneficial in relieving pain from patients (Jo et al., 2022). However, the evidence for clinical studies targeting ACE in CNLBP treatment is lacking. This trial is a single-center, prospective, randomized, patient-assessor-blinded, sham-controlled trial conducted in China, to evaluate the clinical efficacy and safety of ACE for CNLBP patients, and provide new ideas for the management of CNLBP.

Pain, a major symptom plaguing patients with CNLBP, is a subjective experience that can be influenced by physical, psychological, personal experience, social and cultural factors (Wijma et al., 2016; Reis et al., 2022). An accurate and objective assessment of pain is essential to evaluate the efficacy of ACE. The VAS, a simple scale consisting of a 10-centimeter horizontal line, is widely used as a tool for measuring pain (Grilo et al., 2007). Moreover, one of the advantages of the VAS is that its value changes continuously. On the one hand, it reflects the subtle changes in pain, and, on the other hand, continuous scores can be used for statistic parameter testing, which is recognized internationally and superior to non-parameter testing of the category assessment scale. As a result, VAS will be applied as the primary outcome in this study. The ODI and RMDQ scores will be used to further evaluate the mobility disorders of patients with CNLBP, so as to obtain a more objective evaluation for the ACE treatment. In addition, the SF-36 will be used to assess participants' quality of life. Appropriate acupoints selection is an essential factor for ACE treatment. We will select Shenshu (BL23) and Dachangshu (BL25), which are common acupoints for the treatment of low back pain in clinical practice. Both acupoints are located in the lumbar region, and can be used to treat disorders on or near this certain part of the body, according to the theory of meridian in TCM; further, a previous study indicated that BL23 and BL25 could decrease VAS and RMDQ scores for patients with low back pain (Wang, 2018).

However, there are several limitations in this trial. Firstly, this study is a single-center trial, and the study population is mainly from southern China, meaning that the applicability of ACE in other regions will be not discussed. Secondly, due to the different occupations or living habits of different participants, we do not impose strict requirements on the daily life of participants apart from the clinic, which may affect the results of the study. Finally, the trial lacks a positive control group, to distinguish superiority or inferiority relative to the available treatments. Despite these potential limitations, the results of this trial are expected to provide evidence for the efficacy and safety of ACE in the treatment of CNLBP, which will be useful to doctors, stakeholders, patients, and researchers.

Ethics statement

The studies involving human participants were reviewed and approved by Guangzhou Panyu Hospital of Chinese Medicine (202230). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SW, ZF, and XL designed the study. XL and XY contributed equally to the study, conceptualized the study design, and wrote the manuscript. WL, JZ, and WS modified the manuscript. ZF, SW, HF, and XL participated in the modification of the study protocol. XL and HF designed the method for statistical analyses. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effects of traditional Chinese medicine combined with modern rehabilitation therapies on motor function in children with cerebral palsy: A systematic review and meta-analysis

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Objective: Traditional Chinese Medicine (TCM) has considerable experience in the treatment of cerebral palsy (CP), but little evidence shows the effect of a combination of TCM and modern rehabilitation therapies on CP. This systematic review aims to evaluate the effect of integrated TCM and modern rehabilitation therapies on motor development in children with CP.

Methods: We systematically searched five databases up to June 2022, including PubMed, the Cumulative Index to Nursing and Allied Health, Cochrane Library, Embase, and Web of Science. Gross motor function measure (GMFM) and Peabody Development Motor Scales-II were the primary outcomes to evaluate motor development. Secondary outcomes included the joint range of motion, the Modified Ashworth scale (MAS), the Berg balance scale, and Activities of Daily living (ADL). Weighted mean differences (WMD) and 95% confidence intervals (CIs) were used to determine intergroup differences.

Results: A total of 2,211 participants from 22 trials were enrolled in this study. Among these, one study was at a low risk of bias and seven studies showed a high risk of bias. Significant improvements were found in GMFM-66 (WMD 9.33; 95% CI 0.14–18.52, $P < 0.05$, $I^2 = 92.1\%$), GMFM-88 (WMD 8.24; 95% CI 3.25–13.24, $P < 0.01$, $I^2 = 0.0\%$), Berg balance scale (WMD 4.42; 95% CI 1.21–7.63, $P < 0.01$, $I^2 = 96.7\%$), and ADL (WMD 3.78; 95% CI 2.12–5.43, $P < 0.01$, $I^2 = 58.8\%$). No adverse events were reported during the TCM intervention in the included studies. The quality of evidence was high to low.

Conclusion: Integrated TCM and modern rehabilitation therapies may be an effective and safe intervention protocol to improve gross motor function, muscle tone, and the functional independence of children with CP. However, our results should be interpreted carefully because of the heterogeneity between the included studies.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42022345470.

KEYWORDS

cerebral palsy, traditional Chinese medicine, acupuncture, motor function, systematic review

1. Introduction

Cerebral palsy (CP) is a group of persistent motor and postural development disorders with participation limitations caused by non-progressive brain lesions (Michael-Asalu et al., 2019). CP is mainly divided into seven types: spastic quadriplegia, spastic diplegia, spastic hemiplegia, dyskinesia, ataxia, Worster-Drought syndrome, and mixed types (Chinese Association of Rehabilitation Medicine Pediatric Rehabilitation Committee et al., 2022a). Most children with CP are spastic (85–91%), with symptoms of muscle stiffness (Novak et al., 2017).

Cerebral palsy is a frequent cause of physical disability in children. Functional independence and social participation may be influenced by motor dysfunction, pain, and cognitive impairment in children with CP (Lindsay, 2016). Because of the irreversible brain damage in CP, comprehensive rehabilitation therapies for motor function, cognition, language, and daily living ability are widely used in children with CP (Vargus-Adams and Martin, 2011). Evidence showed that exercise interventions significantly improved gait speed and muscle strength in children with CP (Liang et al., 2021). Invasive therapies, such as selective dorsal rhizotomy, botulinum toxin-A therapy, and intrathecal baclofen therapy, were effective in reducing muscle tone, which can be employed in children with spastic CP (Damiano et al., 2021).

Traditional Chinese medicine (TCM) has been reported as an alternative therapy to CP treatment. CP is described as "congenital deficiencies," "retardation," and "weakness" in the view of TCM. Congenital deficiencies lead to loss of nutrients in the meridians and musculoskeletal system, which prevents the meridians from mobilizing the bones, causing joint stiffness. The spleen and stomach promote the development of the children *via* nutrient absorption, and weakness of the spleen and stomach are associated with a deficiency of kidney essence, which results in developmental delay. The treatment strategy is to stretch and dredge the meridian, and warm and nourish the spleen and kidney to condition the poor state of the congenial deficiencies and the acquired weakness of the spleen and kidney. At the same time, treatment should also focus on mind refreshing and wisdom increasing, because of the lesions of the brain in children with CP. TCM treatments, which include massage, acupuncture, herbs, and Qigong, have been practiced in the treatment of CP for a long time. One study showed that TCM may improve the posture balance and cognition of rats with CP (Niu et al., 2021). Increased secretion of dopamine, brain-derived neurotrophic factor, and nerve growth factor were discovered after stimulations on the meridian in rats, which helped repair neuronal damage (Chuang et al., 2007; Tao et al., 2016). Studies suggested that massage and acupuncture dilate blood vessels and increase blood flow and oxygen supply by stimulating acupoints in children with CP, which may improve the function and metabolism of brain cells and muscles (Wang and Wu, 2005; Wu et al., 2008).

Although modern rehabilitation therapies were widely recommended by the guidelines as the first-line treatment for children with CP (Castelli and Fazzi, 2016; Verschuren et al., 2016; Damiano et al., 2021), there was a paucity of evidence on whether TCM is a beneficial supplement to modern rehabilitation therapy to improve the motor development in children with CP. This systematic review aims to clarify the effectiveness of integrated TCM and modern rehabilitation therapies on motor development compared to modern rehabilitation therapies only in children with CP, and we hypothesize that the combination of TCM and modern rehabilitation therapies may be better in the improvement of motor development than modern rehabilitation therapies only.

Abbreviations: CP, cerebral palsy; TCM, traditional Chinese medicine; GMFM, gross motor function measure; MAS, Modified Ashworth scale; ADL, activities of daily living; RCT, randomized controlled trial; GRADE, grading of recommendation assessment, development, and evaluation; WMD, weighted mean difference; CI, confidence interval.

2. Materials and methods

This systematic review was conducted under the guidance of the Cochrane Handbook for Systematic Reviews of Interventions (Cumpston et al., 2019). To find relevant studies published until June 2022, we systematically searched PubMed, the Cumulative Index to Nursing and Allied Health, Cochrane Library, Embase, and Web of Science. Search terms, such as "traditional Chinese medicine," "TCM," "cerebral palsy," and "motor function," were used, and the full search strategy was listed in the **Supplementary material**. The references of enrolled studies were screened to find additional eligible articles. The protocol of this systematic review has been registered in PROSPERO (No. CRD42022345470).

2.1. Eligibility criteria

The enrolled studies should meet the following conditions: (1) Participants: infants or children under 18 years old with a clear diagnosis of CP and with abnormalities in motor function or postural development. (2) Interventions: TCM treatments combine with conventional modern rehabilitation therapies. (3) Comparisons: conventional modern rehabilitation like physical therapy, occupational therapy, or speech therapy. (4) Outcome measures: primary outcome measures: ① Gross motor function measure (GMFM)-66 and GMFM-88 (Te Velde and Morgan, 2022): measurement of motor function of decubitus position, turn-over, sitting position, creeping, and kneeling, erect position, walking, running, and jumping. ② Fine motor function measure: 2 subscales (grasping and visual-motor integration) of Peabody Development Motor Scales-II (Fay et al., 2019). Secondary outcome measures: ① Muscle tone: Joint range of motion and modified Ashworth scale (MAS) (Bohannon and Smith, 1987). ② Balance function: the Berg balance scale (Downs, 2015). ③ Activities of daily living (ADL): cerebral palsy specified ADL scale to measure functional independence (Deng et al., 2005; Zhang and Hu, 2012). (5) Study design: Randomized Controlled Trial (RCT). (6) Language: English and Chinese.

2.2. Exclusion criteria

(1) Patients with serious heart, lung, or nerve diseases. (2) Concomitant invasive treatments in the intervention group or the control group, including surgery and botulinum toxin injecting. (3) Any TCM treatment that was used in control groups.

2.3. Data extraction

Two reviewers (Z.C. and Z.H.) independently screened the enrolled articles through title and abstract screening and full-text reading. Data were extracted under the guidance of Cochrane Collaboration by Z.C. and Z.H. Extracted data included: publication year, author name, demographics, the severity of CP, data on outcome measures, and adverse events. A third reviewer (Q.D.) would participate in the discussion when disagreements arise.

2.4. Quality assessment

The Cochrane risk of bias tool was used to assess the methodological quality of the included studies. The evidence quality was measured by Grading of Recommendation Assessment, Development, and Evaluation (GRADE). The quality appraisal was done by Z.H.

2.5. Statistical analysis

Stata version 16.0 (StataCorp, College Station, TX, USA) was used for data analysis. The fixed effects model would be chosen for quantitative analysis if there was no significant heterogeneity, otherwise random effects model would be used. The results would be presented as weighted mean difference (WMD) and 95% confidence interval (CI) with a significance value set as 0.05. Data would be synthesized if there were over two TCM intervention groups in one research. Heterogeneity was determined by I^2 statistics with a significant value set as 50%. A sensitivity test was used to identify the outlying studies that may influence the between-study heterogeneity. Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) was used to generate the bias chart of risk of bias evaluation.

3. Results

We obtained 485 relevant papers from the five databases, and 205 articles were removed as duplicates. The remind 280 articles were evaluated based on the relevance and publication type, and 233 articles with obvious irrelevant topics or non-RCTs were ruled out. After the full-text reading, 22 RCTs inclusion met the eligibility criteria. The screening flow diagram is described in **Figure 1**.

3.1. Studies' characteristics

The demographics of the included studies, consisting of author year, number of participants, age, type of CP, outcome measures, significant results, and loss to follow-up, are shown in a customized

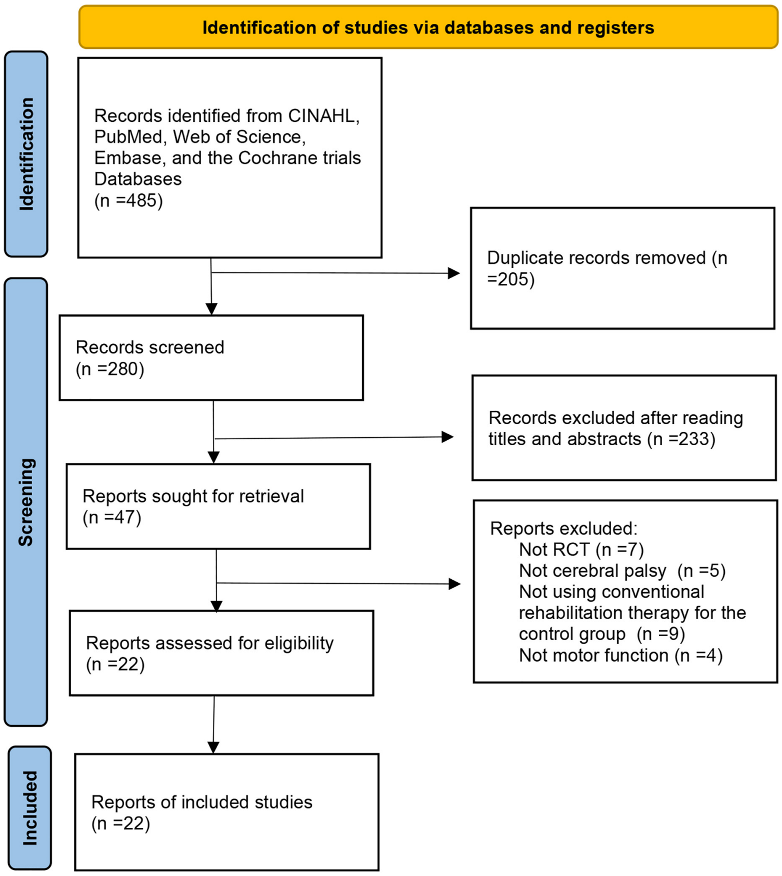

FIGURE 1
Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

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TABLE 1 Baseline demographic and clinical characteristics of study participants.

	References	Study type	No. of participants (% girls)	Age: range/ mean (SD)	Severity and classification of CP	TCM intervention	Outcome measures	Adverse events	Time points	Dropout rate
1	Dabbous et al., 2016#	randomized controlled Trial	T: 40 (42.5) I: 20 C: 20	T: 36 (2) mo.	Hemiplegic spastic CP	Low-level laser on body acupuncture points	1. MAS 2. Wrist and ankle range of motion 3. GMFM-88	Not provided	I: Baseline 3 months C: Baseline 3 months	I: 0% C:0% T:0%
2	Deng et al., 2005#	Randomized controlled trial	T: 90 (33.3) I: 60 (33.3) C: 30 (33.3)	T: 34 between 1–3 y. 56 between 4–7 y.	Severity: T: 47 mild, 22 moderate, 21 severe I: 32 mild, 15 moderate, 13 severe C:15 mild, 7 moderate, 8 severe Classification: T: 44 spastic, 22 dyskinetic, 4 hypotonia, 20 mixed I: 30 spastic, 15 dyskinetic, 2 hypotonia, 13 mixed C: 14 spastic, 7 dyskinetic, 2 hypotonia, 7 mixed	Scalp acupuncture	1. Motor function 2. ADL 3. Social adaptation DQ	Not provided	I: Baseline 2 months C: Baseline 2 months	I: 0% C: 0% T: 0%
3	Duncan et al., 2012	Randomized controlled trial	T: 75 (40) I: 46 (37) C: 29 (55)	I: 28.2 (12.2) months. C: 29.6 (14.9) months.	GMFCS: I: 14 Level I 15 Level II 16 Level III C: 13 Level I 6 Level II 10 Level III Classification: T: spastic CP	Scalp and body acupuncture	1. GMFM-66 2. PEDI-FS	Not provided	I: Baseline 12 weeks 4 weeks gap 12 weeks follow-up C: Baseline 12 weeks 4 weeks 12 weeks acupuncture	I: 8% C: 29.3% T: 17.6%
4	Ji et al., 2019#	Randomized controlled trial	T: 220 (38.2) I: 110 (37.3) C: 110 (39.1)	I: 3.6 (0.9) year. C: 3.7 (0.8) year.	GMFCS: I: 75 Level I&II 35 Level III C: 72 Level I&II 38 Level III Classification: Spastic CP I: 77 quadriplegia, 33 diplegia C: 72 quadriplegia, 38 diplegia	Body acupuncture	1. GMFM-88 2. FMFM 3. Comprehensive functional score 4. Brain Doppler ultrasound	Not provided	I: Baseline 3 months C: Baseline 3 months	I: 0% C: 0% T: 0%
5	Ji et al., 2008	Randomized controlled trial	T: 80 (50) I: 40 (47.5) C: 40 (52.5)	I: 5.15 (2.78) year. C: 6.04 (2.37) year.	Spastic CP	Scalp acupuncture	1. GMFM 2. Functional Independence Measure	Not provided	I: Baseline 3 months C: Baseline 3 months	I: 0% C: 0% T: 0%
6	Li J. et al., 2021#	Randomized controlled trial	T: 28 (32.1) I: 14 (35.7) C: 14 (28.6)	I: 64.42 (21.10) months. C: 69.28 (18.15) months.	GMFCS: I: 8 Level I 3 Level II 3 Level III C: 5 Level I 6 Level II 3 Level III Classification: Spastic CP I: 5 hemiplegia, 9 diplegia C: 6 hemiplegia, 8 diplegia	Wrist-ankle acupuncture	1. GMFM-66 2. Modified Tardieu Scale 3. Motor Evoked Potentials	Not provided	I: Baseline 4 weeks C: Baseline 4 weeks	I: 14.3% C: 7.1% T: 10.7%

(Continued)

TABLE 1 (Continued)

	References	Study type	No. of participants (% girls)	Age: range/ mean (SD)	Severity and classification of CP	TCM intervention	Outcome measures	Adverse events	Time points	Dropout rate
7	Li et al., 2017#	Randomized controlled trial	T: 300 (32.3) I: 150 (35.3) C: 150 (29.3)	I: 3.5 (1.44) year. C: 3.58 (0.88) year.	Classification: I: 116 spastic, 2 ataxic, 9 mixed, 23 dyskinetic C: 115 spastic, 15 mixed, 20 dyskinetic	Scalp acupuncture	1. GMFM-88 2. Gesell scale 3. Head MRI/CT	Not provided	I: about 6 months C: about 6 months	T: 0
8	Liu et al., 2013#	Randomized controlled trial	T: 200 (24) I: 100 (31) C: 100 (17)	I: 66 between 1–3 years. 34 between 3–7 years. C: 72 between 1–3 years. 28 between 3–7 years.	Classification: I: 78 spastic, 4 ataxic, 10 dyskinetic, 23 hypotonia C: 71 spastic, 14 dyskinetic, 13 hypotonia, 2 ataxic	Body acupuncture	1. GMFM-66 2. DQ of gross motor, fine motor, social adaptation 3. Head MRI/CT	None	I: Baseline 90 days 1 year follow up C: Baseline 90 day 1 year follow up	I: 0% C: 8% T: 4%
9	Luo et al., 2020#	Randomized controlled trial	T: 60 (43.3) I: 30 (46.7) C: 30 (40)	I: 2.7 (0.6) year. C: 2.5 (0.7) year.	Spastic CP	Scalp acupuncture	1. GMFM-88 D and E 2. Berg balance scale	Not provided	I: Baseline 6 months C: Baseline 6 months	T: 0
10	Mo et al., 2016	Randomized controlled trial	T: 70 (44.3) I: 35 C: 35	T: 30 (10) months.	Spastic CP	TCM herb fumigation	1. FMFM scale	Not provided	I: Baseline 3 months C: Baseline 3 months	T: 0
11	Qi and Wang, 2018#	Randomized controlled trial	T: 120 (36.7) I: 80 (37.8) C: 40 (32.5)	I: 29.5 (15.0) months. C: 27 (8) months.	GMFCS: I: 52 Level III 28 Level IV C:21 Level III 19 Level IV Classification: I: 53 spastic, 3 ataxic, 13 dyskinetic, 3 hypotonia, 8 mixed C: 28 spastic, 5 dyskinetic, 3 hypotonia, 4 mixed	Body acupuncture	1. Surface electromyography 2. GMFM-88 3. Berg balance scale	Not provided	I: Baseline 12 weeks C: Baseline 12 weeks	I: 7.5% C: 7.5% T: 7.5%
12	Shen et al., 2017#	Randomized controlled trial	T: 60 (46.7) I: 30 (40) C: 30 (53.3)	I: 202.3 (6.4) days C: 196.4 (5.6) days	Spastic CP	Body Acupuncture +TCM tuina	1. GMFM -88 dimension ABCD 2. Muscle tone of gastrocnemius muscle	Not provided	I: Baseline 6 months C: Baseline 6 months	T: 0
13	Wang et al., 2011#	Randomized controlled trial	T: 120 (36.7) I: 60 (38.3) C: 60 (35)	I: 3.26 (2.05) year. C: 3.51 (1.83) year.	Spastic CP Severity: I: 7 mild, 39 moderate, 14 severe C: 8 mild, 39 moderate, 13 severe	Body acupuncture	1. MAS 2. GMFM-88 3. Comprehensive Function Assessment	None	I: Baseline 3 months C: Baseline 3 months	T:0
14	Wang et al., 2008#	Randomized controlled trial	T: 60 (40) I: 30 (43.3) C: 30 (36.7)	I: 6–36 months. C: 6–36 months.	Spastic CP I: 25 diplegia, 4 hemiplegia, 1 triplegia. C: 24 diplegia, 4 hemiplegia, 2 triplegia.	TCM tuina	1. MAS 2. GMFM-66	Not provided	I: Baseline 3 months C: Baseline 3 months	T:0
15	Zhang and Du, 2013#	Randomized controlled trial	T: 120 (47.5) I: 60 (48.3) C: 60 (46.7)	I: 13.6 (4.2) months. C: 13.9 (4.9) months.	Classification: I: 32 spastic, 2 ataxic, 9 dyskinetic, 16 hypotonia, 1 mixed C: 34 spastic, 2 ataxic, 10 dyskinetic, 14 hypotonia	Electric acupuncture	GMFM -88 dimension B	Not provided	I: Baseline 4 weeks C: Baseline 4 weeks	T:0

(Continued)

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TABLE 1 (Continued)

	References	Study type	No. of participants (% girls)	Age: range/ mean (SD)	Severity and classification of CP	TCM intervention	Outcome measures	Adverse events	Time points	Dropout rate
16	Zhang and Liu, 2018#	Randomized controlled trial	T: 90 I: 60 C: 30	I: 3.76 (0.88) months. C: 3.72 (0.89) months.	Spastic CP	Body acupuncture	1. Clinical spasm index 2. MAS 3. Surface electromyogram	Not provided	I: Baseline 20 days C: Baseline 20 days	T: 0
17	Zhang et al., 2020#	Randomized controlled trial	T: 118 (39.8) I: 79 (39.2) C: 39 (41.0)	I: 38 (2) months. C: 37 (2) months.	Spastic CP	Scalp acupuncture	1. MAS 2. Wrist active range of motion 3. Grasping and Visual-motor integration of Peabody Developmental motor scale-II	Not provided	I: Baseline 6 months C: Baseline 6 months	I: 1.67% C: 2.5% T: 1.25%
18	Zhang N. et al., 2014	Randomized controlled trial	T: 80 (41.3) I: 40 (37.5) C: 40 (45)	I: 4 (1) year. C: 4 (1) year.	Spastic CP	Scalp acupuncture	1. GMFM-88 dimensions D and E 2. MAS	Not provided	I: Baseline About 75 days C: Baseline About 75 days	T:0
19	Zhang et al., 2007	Randomized controlled trial	T: 40 I: 21 C: 19	I: 21.75 (10–60) months. C: 23.63 (4–60) months.	I: 3 spastic hemiplegia, 14 spastic diplegia, 2 ataxic, 1 hypotonic, 1 quadriplegia C: 2 spastic hemiplegia, 9 spastic diplegia, 3 ataxic, 1 quadriplegia, 3 hypotonic, 1 mixed	Body acupuncture	1. GMFM-88 2. Comprehensive function	Not provided	I: Baseline 6 months 12 months C: Baseline 6 months 12 months	T:0
20	Zhang N. X. et al., 2014	Randomized Controlled trial	T: 60 (35) I: 30 (50) C: 30 (20)	I: 28.7 (13.8) months. C: 34.9 (15.0) months.	Not provided	Body acupuncture	1. GMFM-66	Not provided	I: Baseline 6 months 12 months C: Baseline 6 months 12 months	T:0
21	Zhang and Hu, 2012#	Randomized controlled Trial	T: 60 (41.7) I: 30 (46.7) C: 30 (36.7)	I: 4.3 (2–12) years. C: 4.1 (2–13) years.	31 spastic, 2 dyskinetic, 8 ataxic, 12 hypotonia, 7 mixed	Scalp acupuncture	1. Berg balance scale 2. ADL	Not provided	I: Baseline Intervention for 28 days or until hospital discharge C: Baseline Intervention for 28 days or until hospital discharge	T:0
22	Zhao et al., 2017#	Randomized controlled trial	T: 120 (38.3) I: 60 (36.7) C: 60 (40)	I: 2.9 (1.0) year. C: 2.8 (1.0) year.	Spastic CP	Body acupuncture	1. GMFM-88 2. ADL 3. Grasping and Visual-motor integration of Peabody Developmental motor scale-II	Not provided	I: Baseline 120 days C: Baseline 120 days	T:0

T, total participants; I, intervention group; C, control group; GMFM, gross motor function measure; CP, cerebral palsy; GMFCS, the Gross motor function classification system; ADL, activities of daily life living; DQ, developmental quotient; MAS, Modified Ashworth scale; FMFM, fine motor function measure; PEDI-FS, pediatric evaluation of disability inventory-functional skills; #Included in meta-analysis.

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TABLE 2 Traditional Chinese medicine combined with rehabilitation and control interventions in the included trials.

	References	Traditional Chinese medicine combined with rehabilitation in the intervention group	Control group intervention	Duration
1	Dabbous et al., 2016#	Laser acupuncture: Yanglingquan (GB 340), Hegu (LI 4), Zhouliao (LI 12), Taichong (Liv 3) Low-level laser 650 nm, 50 mW power, each point 30 s, energy density: 1.8 J/cm^2; 2 days/week. + Conventional physiotherapy Same as the control group.	Physiotherapy	3 months
2	Deng et al., 2005#	Protocol 1: Scalp acupuncture: Foot motor sensory area, Motor Area, The Second Speech Area, and the Third Speech Area, Intellectual area. Needles retained for 1 h, performed 3 times, 300 times/min, 1 time/day, 6 days/week. Protocol 2: Scalp acupuncture+ modern rehabilitation Same as the control group.	Rehabilitation training therapy: Head control training, upper and lower limb exercise training, correct posture training, turning over, from supine to sitting position, and standing training. OT: Functional OT, training in ADL, and controlling eating, dressing and undressing, and urination.	10 weeks
3	Duncan et al., 2012	Acupuncture: Scalp+ body; Manual+ electrostimulation. 5 times/week. +Massage 5 times/week. + Conventional therapies (PT/OT/HT) Same as the control group.	Conventional therapies: PT: gross motor tasks: rolling, sitting, transitions, independent sitting, walking, and stair climbing/ OT: fine motor tasks: eye-hand coordination and ADL/ HT: relaxation in warm water.	12 weeks
4	Ji et al., 2019#	Acupuncture: Zusanli (ST36), Xuanzhong (GB39), Sanyinjiao (SP6), Pishu (BL20), Shenshu (BL23), Qihai (CV6), Quchi (LI11), Neiguan (PC6), Hegu (LI4), Tianshu (ST25) + Rehabilitation training Same as the control group. + Transcranial magnetic stimulation Same as the control group.	Rehabilitation training: Bobath, Assistive device training, reflex inhibition patterns, key points of control, hand function training 30 min/time, 1 time/day, 5 days/week. Transcranial magnetic stimulation: 1 Hz, 20 min/time, 1 time/day, 5 days/week.	3 months
5	Ji et al., 2008	Scalp acupuncture: Both sides of the motor area, balance area, sensory area, tremor control area, foot motor sensory area, the second speech area and the third Speech area, Baihui (GV 20) and Sishencong (EX-HN 1)○ Retained for 30 s, performed every 15 min, 100 times/min, 45 min/time, 1 times/day, 5 days/week. + Exercise therapy Same as the control group.	Exercise therapy: Bobath, recumbent position, rolling over, sitting position, crawling, kneeling and standing position, walking. 45 min/time, 2 times/day, 5 days/week.	3 months
6	Li J. et al., 2021#	Wrist-ankle acupuncture: Upper 4, upper 5, lower 1, and lower 4 on the affected side. 30 min/time, 1 time/day, 5 days/week. +Routine rehabilitation+ 5-Hz rTMS Same as the control group.	Routine rehabilitation: Stretch and strength training. + Hz rTMS 15 min, 40 stimulation+1,000 pulses/time, 5 days/week.	4 weeks
7	Li et al., 2017#	Governor Vessel-unblocking and brain-refreshing Scalp acupuncture: Shenting (GV 24), Qianding (GV 21), Houding (GV 19), Toulinqi (GB 15), Touwei (ST 8), Sishencong (EX-HN 1), Motor Area, Foot Motor-sensory Area, and Three Brain Needles on both sides. Adjunct points: The Second Speech Area and the Third Speech Area. Retain 1–3 h, lift and twist 3 times, 1–3 min/time, more than 200 r/min. +Electricstimulation Shenting (GV 24), Houding (GV 19) and Motor Area WQ1002k Han's treatment apparatus, 2 Hz to 15–100 Hz, 2.5 s/time, 15 min/time, 3 times/week. + Rehabilitation therapies Same as the control group.	Rehabilitation therapies: PT (Bobath method, Ueda method, and Vojta method), structured teaching, ST, and music therapy. 1–2 h/time, 1 time/day.	About 6 months
8	Liu et al., 2013#	Acupuncture therapy: Clearing the Governor Vessel needling: Yaoshu (GV 2), Yaoyangguan (GV 3), Mingmen (GV 4), Xuanshu (GV 5), Jizhong (GV 6), Zhongshu (GV 7), Jinsuo (GV 8), Zhiyang (GV 9), Lingtai (GV 10), Shendao (GV 11), Shenzhu (GV 12), Taodao (GV 13) and Dazhui (GV 14), Shenshu (BL 23), Taixi (KI 3), Yanglingquan (GB 34), Zusanli (ST 36), and Sanyinjiao (SP 6). Refreshing the mind needling: Shenting (GV 24) to Qianding (GV 21), Qianding (GV 21) to Baihui (GV 20), Baihui (GV 20) to Naohu (GV 17), and Sishencong (Ex-HN 1). Scalp motor area, scalp foot motor sensory area and balance area, Speech areas 1, 2, and 3. Retain 4 h/time and twirling 3 times for 1–3 min, 200 times/minute, every 2 days/time, 10 days/month. + Rehabilitation training Same as the control group.	Rehabilitation training: PT (Bobath therapy) / OT / ST 1–2 h/day, 7 days/week.	3 months

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TABLE 2 (Continued)

	References	Traditional Chinese medicine combined with rehabilitation in the intervention group	Control group intervention	Duration
9	Luo et al., 2020#	Scalp acupuncture: The motor area, foot motor sensory area, balance area, and parietal temporal anterior oblique line. Twist 200 times/minute for 2 min. Retain 1 h/time, manipulate every 30 min, 1 time/day, 5 days/week. + Rehabilitation training Same as the control group.	Rehabilitation training: Practice training, balance training, spasmotherapy apparatus, electromyography biofeedback apparatus, and orthotics. 5 days/week, Orthotics: at least 4 h/day.	6 months
10	Mo et al., 2016	Chinese herbal fumigation: 19 grams of *Eucommia ulmoides* (Chuanduzhong), 19 grams of *Chaenomeles speciosa* (Sweet) Nakai (Mugua), 12 grams of *Angelica sinensis* (Danggui), 16 grams of *Heracleum hemsleyanum* Diels (Duhuo), 6 grams of Cinnamon (Guipi), 18 grams of Chuanduan, 10 grams of Fangfeng, 14 grams of *Ramulus mori* (Sangzhi), 12 grams of *Ramulus cinnamomi* (Guizhi), 12 grams of *Lycopodium japonicum* Thunb (Shenjincao), 10 grams of *Acanthopanax senticosus* (Wujiapi), 10 grams of Mori folium (Sangye), 12 grams of Radix Paeoniae Rubra (Chishao), 16 grams of *Taxillus sutchuenensis* (Lecomte) Danser (Sangjisheng), 10 grams of *Astragalus* (Huangqi). Temperature: 38°C∼40°C, 20 min/time 1 time/day, 5 days/week. + OT Same as the control group.	Routine OT: Passive activity, Bobath, hand support training, weight-bearing training on the affected side, separate movement of arm and shoulder girdle, correct abnormal shoulder posture, grasping ability under visual guidance, restriction-induced training for children with hemiplegia, both hands coordination training, ADL training.	3 months
11	Qi and Wang, 2018#	Protocol 1: Intradermal needling: Lumbar Yange Gate (DU3), Mingmen (DU4), L2∼L5 Jiaji (EX-B2) Retain 24 h, compress 1 min/time, 80–120 times/minute, moderate force, pause more than 4 h between two compressions, 3 times/day, 5 days/week. + Rehabilitation training Same as the control group. Protocol 2: Acupuncture Lumbar Yange Gate (DU3), Mingmen (DU4), L2∼L5 Jiaji (EX-B2) 30 min/time, 1 times/day, 5 days/week. + Rehabilitation training Same as the control group.	Rehabilitation training: Head-up training, rollover training, sitting training, crawling training, kneeling training, standing walking training, passive movement, active movement, static balance training, dynamic balance training, postural control training, support training, and Bobath. 30 min/time, 1 times/day, 5 days/week.	3 months
12	Shen et al., 2017#	Acupuncture: Acupoints on the head: Baihui (GV 20), Sishencong (EX-HN 1), Zhisanzhen [Shenting (GV 24), bilateral, Benshen (GB 13)], Niesanzhen. Other acupoints: Shenshu (BL 23), Mingmen (GV 4), Ganshu (BL 18), Pishu (BL 20), Huantiao (GB 30), Weizhong (BL 40), Chengshan (BL 57), Kunlun (BL 60), Futu (ST 32), Zusanli (ST 36), Jiexi (ST 41) and Sanyinjiao (SP 6). every other day. + Tuina: First step: An-pressing, Na-grasping, plucking method, and dot-pressing method to relax spasm; Second step: Digital An-pressing, Kou-knocking, and Gun-rolling method; Apply digital An-pressing, Kou-knocking, and Gun-rolling manipulations to the muscles of the disadvantaged side of the spasm; Third step: Bashen-pulling and Yao shaking to the hip joint, knee joint, and ankle joint; Fourth step: Nie-pinching spine manipulation, An-pressed and Rou-kneaded Ganshu (BL 18), Pishu (BL 20), and Shenshu (BL 23). every other day. + Rehabilitation treatment Same as the control group.	Rehabilitation treatment: Bobath. 2 times/day, 30 min/time.	6 months
13	Wang et al., 2011#	Acupuncture: Bladder meridian Yuzhen (BL 9) and Tianzhu point (BL 10) connection. Twist: 1 min, retain: 30 min, 1 time/day, 7 days/week. + Rehabilitation training Same as the control group.	Rehabilitation training: Exercise therapy: Bobath and Vojta 45 min/time. OT 30 min/time. ST 30 min/time. 1 time/day, 7 days/week.	3 months
14	Wang et al., 2008#	Tuina with manipulation of SMKT: Massaging of spine Governor Vessel (DU), Bladder Meridian of Foot-Taiyang (BL), and symptomatic massage for head and limbs. 5 days/week. + Rehabilitation training Same as the control group.	Rehabilitation training: Bobath 1–2 time/day, 30 min/time.	3 months

(Continued)

TABLE 2 (Continued)

	References	Traditional Chinese medicine combined with rehabilitation in the intervention group	Control group intervention	Duration
15	Zhang and Du, 2013#	EA: Apply to Mingmen (GV4), Jizheng (GV6), Shenshu (BL23), and Pishu (BL20) 4 Hz, tolerable strength; 1 time/day, 30 min/time, 5 days/week. + Sitting training Same as the control group. + Conventional exercise therapy + Hyperbaric Oxygen Therapy	Sitting training: Assist-sitting, legs-crossing-sitting, sitting with one-leg extending, long-term sitting, balancing-sitting, chair-climbing, and prone hand-supporting. 2 time/day, 15–20 min/time, 5 days/week. + Conventional exercise therapy + Hyperbaric Oxygen Therapy	4 weeks
16	Zhang and Liu, 2018#	Protocol 1: yin-meridian group: Xuehai (SP 10), Yinlingquan (SP 9), Sanyinjiao (SP 6), Taixi (KI 3), and Taichong (LR 3) along yin meridians. Retain 15 min (no retain for frail children), once each other day, 9 a.m.-12 p.m. + Routine rehabilitation treatment Same as the control group. Protocol 2: yang-meridian group: Futu (ST 32), Zusanli (ST 36), Yanglingquan (GB 34), Guangming (GB 37) and Xuanzhong (GB 39) along yang meridians Retain: 15 min (no retain for frail children), once each other day, 9 a.m.-12 p.m. + Routine rehabilitation treatment Same as the control group.	Routine rehabilitation treatment: Exercise therapy (Bobath and Vojta), OT, ST, music psychotherapy, and cognitive rehabilitation. each other day, 40 min/time.	20 days
17	Zhang et al., 2020#	Protocol 1: Jin's three-needle therapy Nie sanzhhen, Zhisanzhen, Naosanzhen, Sishenzhen, Dingshenzhen, Shousanzhen, and Shouzhizhen Scalp acupuncture: 1 h/time; Body acupuncture: 30 min/time 1 time/day, 5 days/week. + Conventional OT Same as the control group. Protocol 2: Conventional OT +MyoTrac biostimulation Therapy Same as the control group. + Jin's three-needle therapy	Conventional OT: Bobath, affected limb muscle strength training, restriction-induced exercise therapy, bimanual coordination training, and ADL. 1 time/day, 30 min/time, 5 days/week. +MyoTrac biostimulation therapy: Placed electrodes at the origin and insertion point of the extensor carpi radialis muscle of the affected limb. EMG-Stim mode, Part 1 (upper limb), "Auto Threshold Adjustment Mode," "Low Arm Strength," and perform active wrist dorsiflexion and relaxation according to the "work-rest" prompt. 1 time/day, 15 min/time, 5 days/week.	6 months
18	Zhang N. et al., 2014	Jin three-needle therapy: Sishenzhen, Naosan needle, Zhisanzhen, Temporal (Nie) three-needle, Zusanzhen, Xisanzhen, Chengjin (BL56), Chengshan (BL57). Retain:30 min (If the patient does not cooperate, use rapid twisting, each point 1 min), 1 time/day. + MOTOmed Same as the control group. + Conventional rehabilitation training Same as the control group.	MOTOmed: Connect with the competitive players in "Fitness e-Road Ride" to play bicycle competitive games; 1. Resistance: 0∼10 N.m, 2∼3 min passive training, speed: 5∼30 r/min. 2. Video simulation competition: 6–7 min, active training. 3. Passive relaxation training: 2–3 min. 4. Active training: 6–7 min. 1 time/day, 20 min/time. + Conventional rehabilitation training: 1. Flex the hip, flex the knee, dorsiflexion, and bridge-like exercise; 2. Hip abduction, extend the knee and ankle dorsiflexion, bridge exercise with both knees extended; 3. Abduction and external rotation of both hip joints, alternately extending and flexing both lower limbs are performed repeatedly; 4. The therapist supports the children's knee and foot and induces dorsiflexion of the ankle. Repeat each movement 5 times; 1 time/day, 30 min/time.	20 Times as a course of treatment, 3–5 days rest between courses, 3 courses of treatment
19	Zhang et al., 2007	Acupuncture: Body Acupuncture: Bai hui (GV 20), Zusanli (ST 36), Quchi (LI 11), Huantiao (GB 30), Yinlingquan (GB 34), Yanglingquan (GB 34), Sanyinjiao (SP 6), Qiangjian (GV18), Yamen (GV15), Fengchi (GB20), Hegu (LI4) Xuanzhong (GB 39). No retain. Scalp acupuncture: Zhisanzhen, Naosanzhen, Balance Zone, Motor Zone. Retain for 1 h, no twisting, every other day. + Rehabilitation training Same as the control group.	Rehabilitation training: PT: (Bobath and Vojta): turn over, abdominal crawling, four-point hold, kneeling position, standing balance training, position conversion between lying and sitting positions, weight loss walking training, calf triceps stretch, single-leg weight-bearing on the right lower extremity, etc. 45 min/time, 5 days/week. OT: (upper extremity fine motor and ADL): cognitive improvement, upper extremity fine motor training, midline hand-eye coordination, two-hand coordination movement training, and two-hand synergy training. 30 min/time, 5 days/week. ST: (promoting language development level and dysarthria training): gesture-symbol stage training, language imitation training. 30 min/time, 5 days/week.	6 months

(Continued)

TABLE 2 (Continued)

	References	Traditional Chinese medicine combined with rehabilitation in the intervention group	Control group intervention	Duration
20	Zhang N. X. et al., 2014	Acupuncture treatment: Body acupuncture: Jiaji (EX-B2), Jianyu (LI 15), Qiichi (LI 11), Hegii (LI 4), Yanglingquan (GB 34), Yinlingquan (SP 9), Xuanzhong (GB 39), Zusanli (ST 36), Sanylnjiao (SP 6), Chengshan (BL 57), TaichOng (LR 3), Taixi (KI 3), Shenmen (HT 4), and heat-reinforcing manipulation. Twist at Jiaji (EX-B2) and pull it out immediately. 7 days/week. Scalp acupuncture: Baihui GV 20), Sishencong (EX-HN 1), Zhisanzhen, Naosanzhen, Niesanzhen and motor area. Retained 1 h without manipulation, every other day. + Rehabilitation training Same as the control group.	Rehabilitation training: Bobath and PDMS-2 exercise training. 5 days/week, 40 min/time.	6 months
21	Zhang and Hu, 2012#	Scalp acupuncture: Parietal region: Between Baihui (GV 20) and Qiandfng (GV 21), and four parallel lines. Sub-occipital region: Two lines between Naohu (GV 17) to Fengfii (GV 16), Yuzhen (BL 9) to Tianzhu (BL 10). Twist 200 times/min, retain 8 h/time, twist every 30 min for two times, then twist every 2 h; once a day. + Rehabilitation training Same as the control group.	General rehabilitation therapy: Bobath and Vojta. Training raise head, turning over, creeping, sitting, kneeling, standing with a ladder chair, moving with an assistant, standing and walking by oneself. Playing games and recreation. 7 days/week, 40 min/time. + Balance training: General balance training: (Bobath therapy), Provide an unbalanced location, letting children return to the neutral or balanced place by themself. Visual feedback: posture mirror. Decrease or increase muscle tonus. Correcting abnormally developed muscles and bones. 7 days/week, 40 min/time.	3 months
22	Zhao et al., 2017#	Acupuncture: Baihui (DU20), Fengfu (GV16), Shenzhu (GV12), Zhiyang (GV9), Jinsuo (GV8), Yaoyangguan (GV3), Mingmen (GV4), Pishu (BL20), Shenshu (BL23), Zusanli (ST 36), Sanyinjiao (SP 6). Retain 10 min/time, once every other day. + Physiotherapeutic and hand function training Same as the control group.	Physiotherapeutic and hand function training: Bobath: 40 min/time. hand function training: 20 min/time. 7 days/week.	Acupuncture: 10 times of treatment as a course of treatment Control Group: 20 days of treatment as a course of treatment. The interval between courses of treatment is 20 days, a total of 3 courses of treatment.

#Included in meta-analysis. OT, occupational therapy; ADL, activities of daily living; PT, physical therapy; HT, hydrotherapy; GMFM, gross motor function measure; ST, speech therapy; TMS, transcranial magnetic stimulation; SMKT, supplementing marrow and kneading tendon; EA, electroacupuncture; PDMS-2, peabody developmental motor scales 2nd edition.

Table 1. The intervention method, treatment frequency, and treatment duration of the intervention group and the control group are shown in Table 2.

This review includes 22 articles published from 2005 to 2021, and data from 15 studies were included in the meta-analysis. This systematic review included 2,211 children aged 4 months to 13 years old. The participants in both the intervention group and control group were diagnosed with spasticity, dyskinesia, ataxia, or mixed types of CP depending on the types of motor abnormalities. Hemiplegia, diplegia, or quadriplegia is further diagnosed according to the affected body parts in children with spasticity CP (Sellier et al., 2016; Novak et al., 2017). All included studies were RCTs in English and Chinese language.

The duration of intervention for children with CP ranged from 20 days to 6 months, and the frequency of treatment ranged from 2 to 7 days per week. The duration of TCM treatments was 10–240 min with a median of 45 min. The duration of modern rehabilitation therapies ranged from 30 min to 240 min, and the median duration was 55 min. All participants received conventional modern rehabilitation therapy, and the intervention group was additionally treated with TCM. Modern rehabilitation therapy includes physiotherapy (Zhang et al., 2007; Duncan et al., 2012; Liu et al., 2013; Li et al., 2017), occupational therapy (Zhang et al., 2007; Wang et al., 2011; Duncan et al., 2012; Liu et al., 2013; Zhang and Liu, 2018), speech therapy (Zhang et al., 2007; Wang et al., 2011; Liu et al., 2013; Li et al., 2017; Zhang and Liu, 2018), and hydrotherapy (Dabbous et al., 2016). Fifteen studies explicitly used Bobath therapy (Zhang et al., 2007, 2020; Ji et al., 2008, 2019; Wang et al., 2008, 2011; Zhang and Hu, 2012; Liu et al., 2013; Zhang N. X. et al., 2014; Mo et al., 2016; Li et al., 2017; Shen et al., 2017; Zhao et al., 2017; Qi and Wang, 2018; Zhang and Liu, 2018), and 5 conducted ADL training (Deng et al., 2005; Zhang et al., 2007, 2020; Duncan et al., 2012; Mo et al., 2016). Zhang et al. (2020) used biofeedback therapy, and Zhang N. et al. (2014) added virtual reality games

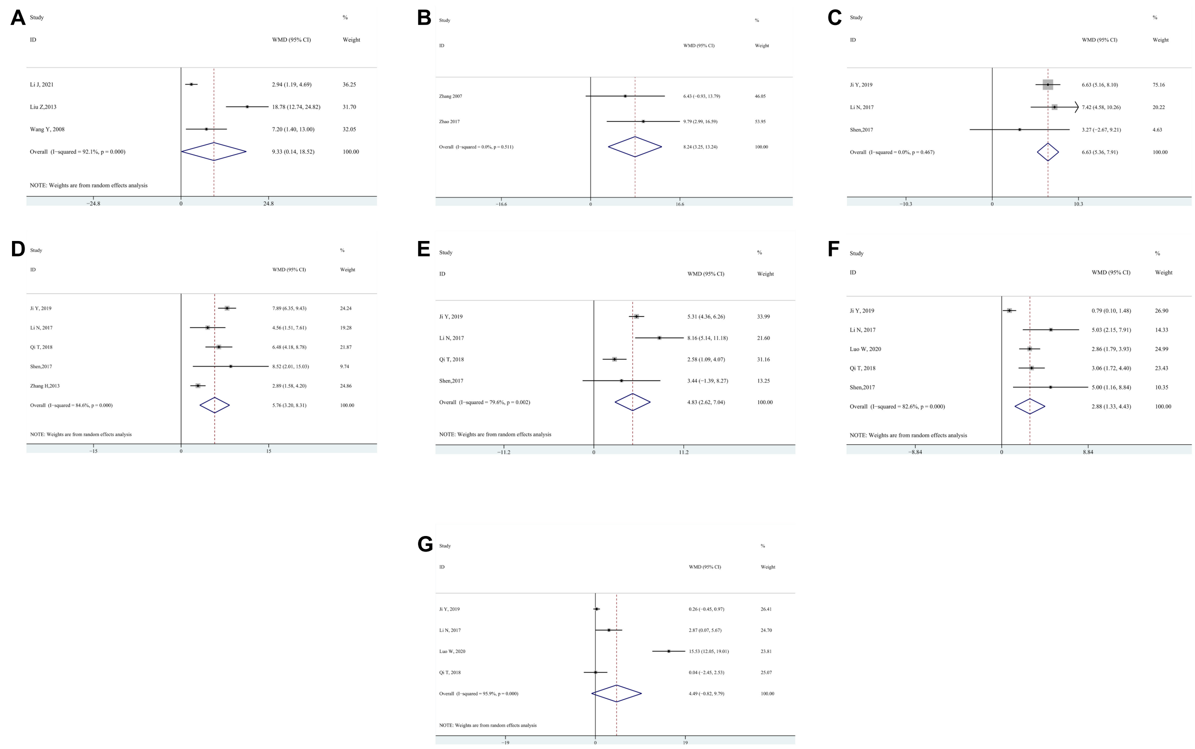

FIGURE 2
Forest plot of pooled results for gross motor function measure (GMFM) **(A)** GMFM−66. **(B)** GMFM−88. **(C)** GMFM−88−Dimension A. **(D)** GMFM−88−Dimension B. **(E)** GMFM−88−Dimension C. **(F)** GMFM−88−Dimension D. **(G)** GMFM−88−Dimension E.

for treatment. In the TCM treatment of the intervention group, 21 studies applied acupuncture treatment, 2 studies used massage therapy (Wang et al., 2008; Shen et al., 2017), and 1 study applied TCM fumigation (Mo et al., 2016). Particularly, 10 studies applied scalp acupuncture (Deng et al., 2005; Zhang et al., 2007, 2020; Ji et al., 2008; Duncan et al., 2012; Zhang and Hu, 2012; Liu et al., 2013; Zhang N. X. et al., 2014; Li et al., 2017; Luo et al., 2020).

3.2. Primary outcomes

3.2.1. Gross motor function measure

Four studies evaluated gross motor function according to GMFM-66 (Wang et al., 2008; Duncan et al., 2012; Liu et al., 2013; Li J. et al., 2021). One study provided average GMFM-66 scores without standard deviation, which was excluded from the meta-analysis (Duncan et al., 2012). The pooled analysis reported a significantly better improvement in GMFM-66 in intervention groups than in control groups (WMD 9.33; 95% CI 0.14–18.52, P = 0.047, I^2 = 92.1%) (**Figure 2A**). When Liu et al. (2013) was excluded from the pooled results according to the sensitivity analysis, there were still significant differences between the two groups without significant heterogeneity (WMD 3.30; 95% CI 1.62–4.97, $P < 0.001$, I^2 = 47.4%).

GMFM-88 consists of 88 items in five dimensions: dimension A (lying and rolling), dimension B (sitting), dimension C (crawling and kneeling), dimension D (standing), and dimension E (walking, running, and jumping). Twelve studies applied GMFM-88 or part of GMFM-88 to measure gross motor function. We analyzed each of the five dimensions and the total score of GMFM-88.

The sum of five dimension scores of GMFM-88: Pooled data from 2 studies (Zhang et al., 2007; Zhao et al., 2017) showed a significant result (WMD 8.24; 95% CI 3.25–13.24, P = 0.001, I^2 = 0.0%) (**Figure 2B**).

Dimension A: Pooled data from 3 studies (Li et al., 2017; Shen et al., 2017; Ji et al., 2019) showed a significant result (WMD 6.63; 95% CI 5.36–7.91, $P < 0.001$, I^2 = 0.0%) (**Figure 2C**).

Dimension B: Pooled data from 5 studies (Zhang and Du, 2013; Li et al., 2017; Shen et al., 2017; Qi and Wang, 2018; Ji et al., 2019) showed a significant result (WMD 5.76; 95% CI 3.20–8.31, $P < 0.001$, I^2 = 84.6%) (**Figure 2D**). After removing Zhang and Du (2013) based on sensitivity analysis, the pooled results still showed significant differences between the intervention group and the control group while there was no significant heterogeneity (WMD 7.07; 95% CI 5.90–8.23, $P < 0.001$, I^2 = 27.4%).

Dimension C: Pooled data from 4 studies (Li et al., 2017; Shen et al., 2017; Qi and Wang, 2018; Ji et al., 2019) showed a significant result (WMD 4.83; 95% CI 2.62–7.04, $P < 0.001$, I^2 = 79.6%) (**Figure 2E**). After removing Qi and Wang (2018), there were still significant differences between the intervention group and the control group without significant heterogeneity (WMD 5.49; 95% CI 4.60–6.38, $P < 0.001$, I^2 = 47.7%).

Dimension D: Pooled data from 5 studies (Li et al., 2017; Shen et al., 2017; Qi and Wang, 2018; Ji et al., 2019; Luo et al., 2020) showed a significant result (WMD 2.88; 95% CI 1.33–4.43, $P < 0.001$, I^2 = 82.6%) (**Figure 2F**). After removing Ji et al. (2019) from the pooled data based on sensitivity analysis, there was no significant statistical heterogeneity, but the intervention group still showed a significantly better effect than the control group (WMD 3.18; 95% CI 2.39–3.97, $P < 0.001$, I^2 = 0.0%).

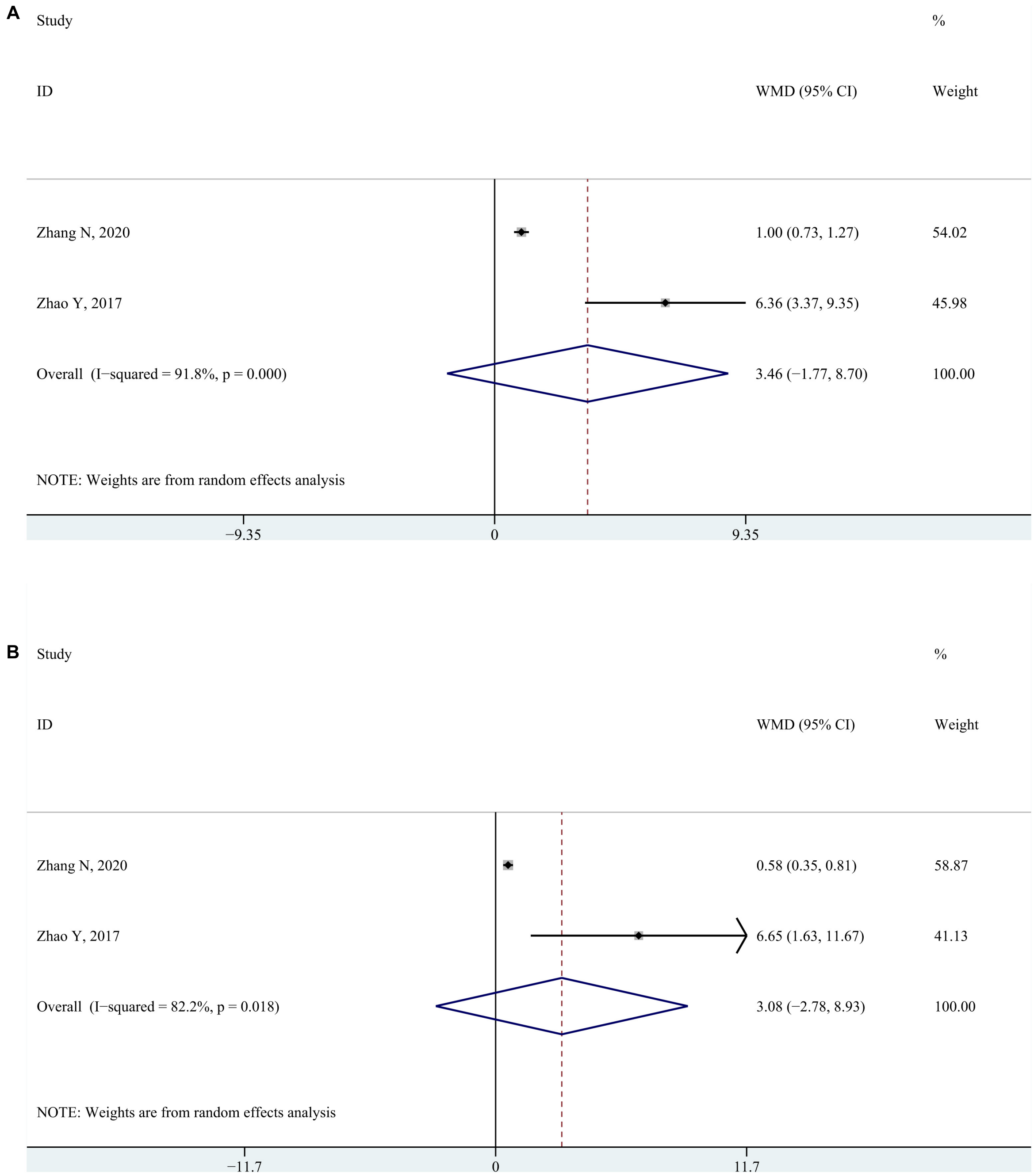

FIGURE 3
Forest plot of pooled results for Peabody Development Motor Scales-II **(A)** Peabody Developmental Motor Scales−Grasping. **(B)** Peabody Developmental Motor Scales−Visual motor integration.

Dimension E: Pooled data from 4 studies (Li et al., 2017; Qi and Wang, 2018; Ji et al., 2019; Luo et al., 2020) showed no significant result (WMD 4.49; 95% CI −0.82 to 9.79, P = 0.097, I^2 = 95.9%) (**Figure 2G**). After removing Luo et al. (2020) from the pooled results based on the sensitivity analysis, no significant results were found (WMD 0.39; 95% CI −0.27 to 1.05, P = 0.248, I^2 = 37.7%).

3.2.2. Fine motor function measure

Two studies, respectively measured fine motor development using the grasping and visual-motor subscales of the Peabody Development Motor Scales-II (Zhao et al., 2017; Zhang et al., 2020). No significant changes were found in neither grasping part (WMD 3.46; 95% CI −1.77 to 8.70, P = 0.195, I^2 = 91.8%) nor visual-motor integration part (WMD 3.08; 95% CI −2.78 to 8.93, P = 0.303, I^2 = 82.2%) (**Figures 3A, B**).

3.3. Secondary outcomes

3.3.1. Joint range of motion

Two studies that recruited children with hemiplegia spastic CP used the joint range of motion to measure the changes in spasticity. Dabbous et al. (2016) described flexion, and extension of the wrist and

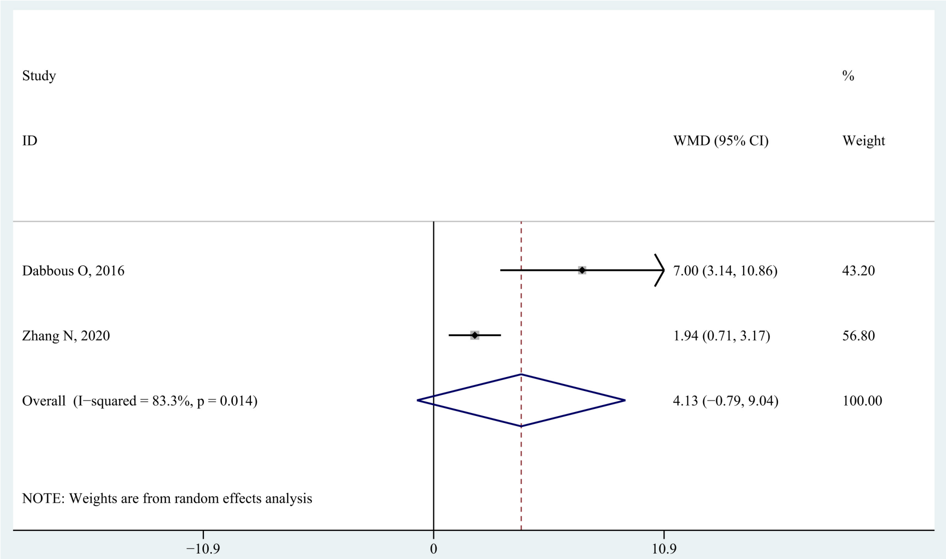

FIGURE 4
Forest plot of pooled results for joint range of motion.

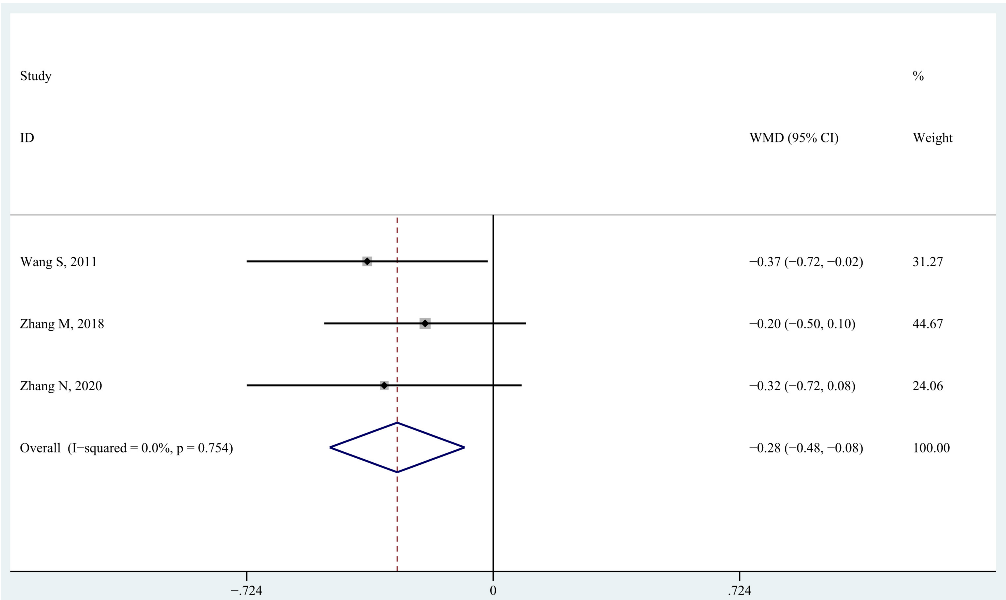

FIGURE 5
Forest plot of pooled results for modified Ashworth scale.

ankle while Zhang et al. (2020) measured the wrist active extension. It showed no significant differences in wrist extension range of motion when data were pooled (WMD 4.13; 95% CI −0.79 to 9.04, P = 0.100, I^2 = 83.3%) (**Figure 4**).

3.3.2. Modified Ashworth scale

Modified Ashworth scale includes six levels to describe muscular tone (0, 1, 1+, 2, 3, 4, from normal to high). We replaced these six levels with scores ranging from 0 to 5 from low to high in data analysis. Three studies recruited children with spastic CP and used MAS to measure the changes in spasticity (Wang et al., 2011; Zhang and Liu, 2018; Zhang et al., 2020). The results showed that the MAS level decreased more in intervention groups than in control groups when data from the three studies were pooled together (WMD −0.28; 95% CI −0.48 to −0.08, P = 0.005, I^2 = 0%) (**Figure 5**).

3.3.3. Berg balance scale

Berg balance scale is used in three studies to evaluate static and dynamic balance (Zhang and Hu, 2012; Qi and Wang, 2018; Luo et al., 2020). As shown in **Figure 6**, children in intervention groups achieved significantly better improvement in balance ability than those in control groups (WMD 4.42; 95% CI 1.21–7.63, P = 0.007, I^2 = 96.7%). There was still significant heterogeneity between studies (all I^2 > 80%) when the three studies were eliminated from the pooled data gradually through the sensitivity analysis.

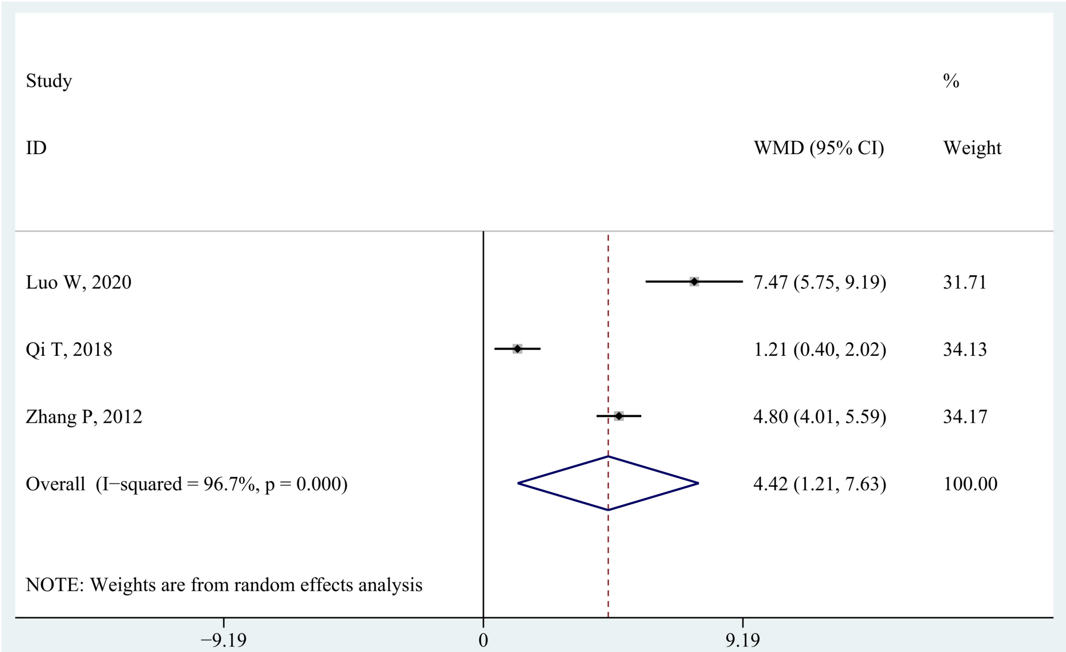

FIGURE 6
Forest plot of pooled results for Berg balance scale.

3.3.4. Activities of daily living

Two studies reported ADL scores (**Figure 7**; Deng et al., 2005; Zhang and Hu, 2012). The pooled analysis reported a significantly better improvement in ADL scores in intervention groups than that in control groups (WMD 3.78; 95% CI 2.12–5.43, $P < 0.001$, $I^2 = 58.8\%$).

3.4. Quality appraisal

According to the Cochrane risk of bias tool, seven studies had a high risk of bias, while 14 studies showed an unclear risk of bias, with only one study having a low risk of bias (**Table 3** and **Figure 8**). The quality of evidence of the included outcome measures is shown in **Table 4**, with only one outcome measure (GMFM-88–Dimension A) showing high quality, while five of the thirteen outcome measures, including GMFM-88 Dimension B, C, D, and E, and MAS, have moderate quality.

4. Discussion

Our study found that integrated TCM and modern rehabilitation therapies significantly improved motor development in children with CP (ΔGMFM-66 score: 9.33, ΔGMFM-88 score: 8.24, ΔBerg balance scale score: 4.42), reduced muscle tone (ΔMAS score: −0.28), and increased the functional independence (ΔADL score: 3.78). These results suggested that TCM treatments combined with modern rehabilitation therapies may be an effective package of intervention for children with CP, compared to modern rehabilitation therapies only.

Developmental delay, especially motor development, is a symptom of widespread concern for children with CP. The brain remodeling theory is the basis of modern rehabilitation to improve motor development in children with CP (Aisen et al., 2011). Brain remodeling refers to the plasticity and modifiability of the brain. The neurons in the brain may reconnect by external stimuli, thus compensating for the dysfunction caused by brain damage (Gulyaeva, 2017). Modern rehabilitation therapy may help children with CP *via* neuroplasticity that reshapes the brain and compensates for the development delay (Dancause and Nudo, 2011). For example, the contralateral movement evoked field and ipsilateral motor field of the cortex were activated and reorganization in children with CP after constraint-induced movement therapy (Sutcliffe et al., 2007). Different from the brain remodeling theory of modern rehabilitation therapy, the mechanism of TCM improving motor development may be the blood flow regulation for the brain, which might promote the development of neurons and synaptic interconnection (Shepherd et al., 2018; Niu et al., 2019). Especially in scalp acupuncture, some special acupoints, such as DU-20 and X-HN1, may expand the blood vessels of the corresponding brain areas or promote collateral circulation (Chinese Association of Rehabilitation Medicine Pediatric Rehabilitation Committee et al., 2022b). Expression of endothelin receptor type A, which was associated with vasoconstriction, decreased in mice after being treated with acupuncture (Li J. et al., 2021). Some studies demonstrated that another mechanism of TCM in improving motor development might be the mediation of neurotransmitters, such as gamma-aminobutyric acid, an inhibitory neurotransmitter for motoneurons to improve motor development (Shorter and Segesser, 2013).

Our systematic review showed that the spasticity was improved by the integrated TCM and modern rehabilitation therapies, compared to modern rehabilitation therapy only. In the theory of TCM, children with spastic CP may have a constitution with Yin-deficiency (Zhang et al., 2016). The kidney stores the essence of life and is responsible for body development. The liver is the organ

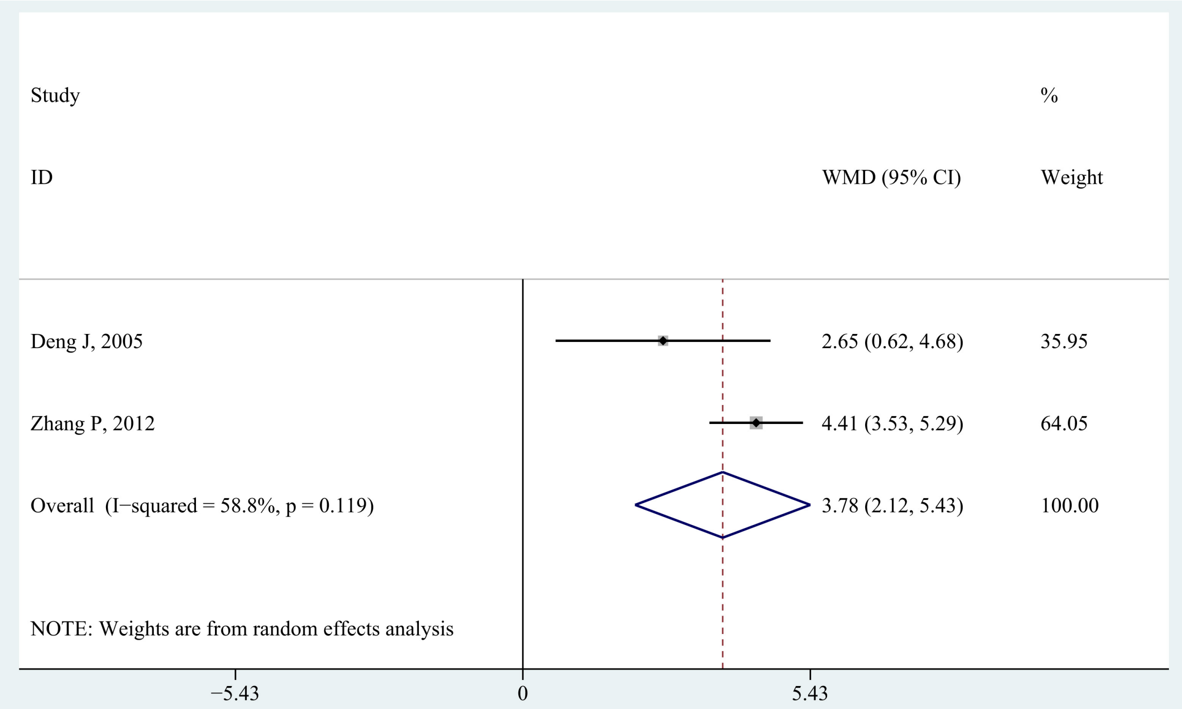

FIGURE 7
Forest plot of pooled results for activities of daily living.

TABLE 3 The Cochrane collaboration's tool of assessing risk of bias for methodological assessment.

References	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias	Overall bias
Dabbous et al., 2016	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Deng et al., 2005	Low	Low	Unclear	Unclear	Low	Low	High	High
Duncan et al., 2012	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Ji et al., 2008	Unclear	High	Unclear	Unclear	Low	Low	Low	High
Ji et al., 2019	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Li J. et al., 2021	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Li et al., 2017	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Liu et al., 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High	High
Luo et al., 2020	Low	Low	Low	Unclear	Low	Unclear	Low	Unclear
Mo et al., 2016	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Qi and Wang, 2018	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Shen et al., 2017	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Wang et al., 2011	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Wang et al., 2008	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Zhang and Du, 2013	Low	Low	Low	Low	Low	Low	Low	Low
Zhang and Liu, 2018	High	High	Low	Unclear	Low	Low	Low	High
Zhang N. et al., 2014	Low	Low	Low	Unclear	Low	Low	Low	Unclear
Zhang et al., 2020	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Zhang et al., 2007	Low	Low	Low	High	Low	Low	Low	High
Zhang N. X. et al., 2014	High	High	Low	High	Low	Low	Low	High
Zhang and Hu, 2012	Unclear	Unclear	High	Unclear	Low	Low	Low	High
Zhao et al., 2017	Low	Low	Low	Unclear	Low	Low	Low	Unclear

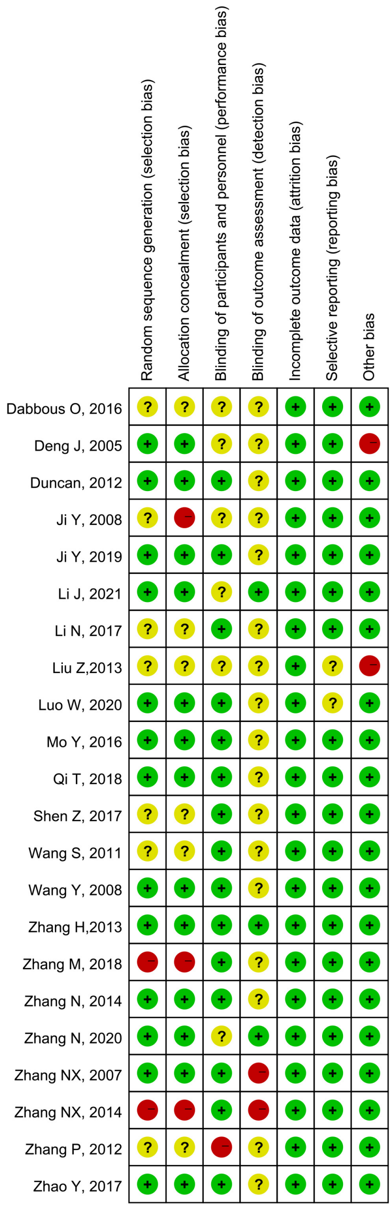

FIGURE 8
The bias chart of the included studies assessed by the Cochrane risk of bias tool.

that stores blood. The spleen-stomach is responsible for digestion and nutrient absorption, which is then converted into Qi-blood-body fluid for brain and body development. Therefore, the treatment for spastic CP should aim at brain recovery and start with the Yin deficiency. Acupuncture, massage, or herbal fumigation should consider tonifying Yin deficiency *via* the acupoints on Yin meridians (such as spleen, liver, and kidney meridians) based on the dialectical diagnosis. With regard to the mechanism related to the effect of the TCM treatments on spasticity, one study suggested that scalp acupuncture may increase and disentangle the white matter fiber bundles in rats with CP (Wang et al., 2021), which may be the anatomical evidence for improving spasticity. A neuroimaging study showed that acupuncture on LR3 may relieve the spasticity of children with CP by reducing the activation of the frontal lobe cortex, an important brain region that controls muscle tone and active movement (Wu et al., 2008).

However, no significant improvement was found in fine motor development in the integrated TCM and modern rehabilitation therapies group, compared to the control group. The possible explanation might be that fine motor improvement requires targeted training. Evidence supported that task-oriented motor training based on the requirements of daily routines may be effective in the improvement of fine motor development (Baker et al., 2022). With regard to unilateral hand function, constraint-induced movement therapy may be effective in children who were diagnosed with unilateral CP (Tinderholt Myrhaug et al., 2014). However, few included studies in our systematic review employed targeted training for fine motor in the conservative rehabilitation protocol. Massage and acupuncture were also recommended for fine motor development delay in children with CP, but individualized treatment should be considered because children with CP vary in the syndrome classifications based on the TCM theory (Chinese Association of Rehabilitation Medicine Pediatric Rehabilitation Committee et al., 2022b). Our results suggest that targeted and individualized therapy should be added to promote fine motor development in children with CP.

Seventeen studies declared that none of the participants withdrew from the studies and no severe adverse event was reported in any of the enrolled studies, indicating that TCM treatments are safe in the clinical setting for children with CP. The duration of intervention for children with CP ranged from 20 days to 6 months with a median intervention time of 3 months. Future studies should focus on the long-term effects of TCM treatments on CP.

4.1. Limitations

There were some limitations of our systematic review, which should be interpreted with caution. First, methodological heterogeneity in the included should not be ignored. Due to the differences in the age and CP severity of the participants, TCM treatments varied among the included studies, such as acupuncture, massage, and herbal fumigation. Subgroup analysis of different intervention protocols could not be conducted because of the insufficient number of included studies. Future studies should consider standardized TCM diagnosis and treatment for children with CP. Second, the pooled results of our systematic review may suffer from methodological quality. Seven of the included studies showed a high risk of bias, while only two studies specified the blinding of the assessors. Third, 21 of the 22 included studies are from China, which indicates that the integrated TCM and modern rehabilitation therapies for CP are not widely used in the world. In the future, the promotion of TCM needs to be strengthened, such as the training of international TCM practitioners. Fourth, it is difficult to quantitatively divide the proportion of TCM treatments and modern rehabilitation therapies because of the differences in basic theory between TCM and modern rehabilitation.

4.2. Implications for clinical practice and research

This systematic review with meta-analysis suggests that TCM may be integrated into the traditional rehabilitation

TABLE 4 Quality of evidence measured by grading of recommendation assessment, development, and evaluation.

Patient or population: Children with cerebral palsy Settings: Intervention: Integrated Traditional Chinese medicine and modern rehabilitation therapies						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Integrated traditional Chinese medicine and conventional rehabilitation therapies				
Gross motor function measure–66 questionnaire		The mean gross motor function measure–66 in the intervention groups was **9.33 higher** (0.14–18.52 higher)		285 (three studies)	⊕⊕⊝⊝ **Low**[1,2]	
Gross motor function measure–88 questionnaire		The mean gross motor function measure–88 in the intervention groups was **8.24 higher** (3.25–13.24 higher)		160 (two studies)	⊕⊕⊝⊝ **Low**[1,2]	
Gross motor function measure–88–Dimension A questionnaire		The mean gross motor function measure–88–Dimension A in the intervention groups was **6.63 higher** (5.36–7.91 higher)		580 (three studies)	⊕⊕⊕⊕ **High**	
Gross motor function measure–88–Dimension B questionnaire		The mean gross motor function measure–88–Dimension B in the intervention groups was **5.76 higher** (3.20–8.13 higher)		811 (five studies)	⊕⊕⊕⊝ **Moderate**[1]	
Gross motor function measure–88–Dimension C questionnaire		The mean gross motor function measure–88–Dimension C in the intervention groups was **4.83 higher** (2.62–7.04 higher)		691 (four studies)	⊕⊕⊕⊝ **Moderate**[1]	
Gross motor function measure–88–Dimension D questionnaire		The mean gross motor function measure–88–Dimension D in the intervention groups was **2.88 higher** (1.33–4.43 higher)		751 (five studies)	⊕⊕⊕⊝ **Moderate**[1]	
Gross motor function measure–88–Dimension E questionnaire		The mean gross motor function measure–88–Dimension E in the intervention groups was **4.49 higher** (0.82 lower to 9.79 higher)		691 (four studies)	⊕⊕⊕⊝ **Moderate**[1]	
Peabody Developmental Motor Scales–Grasping questionnaire		The mean Peabody Developmental Motor Scales–Grasping in the intervention groups was **3.46 higher** (1.77 lower to 8.70 higher)		238 (two studies)	⊕⊕⊝⊝ **Low**[1,2]	
Peabody Developmental Motor Scales–Visual motor integration questionnaire		The mean Peabody Developmental Motor Scales–Visual motor integration in the intervention groups was **3.08 higher** (2.78 lower to 8.93 higher)		238 (two studies)	⊕⊕⊝⊝ **Low**[1,2]	

(Continued)

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TABLE 4 (Continued)

Patient or population: Children with cerebral palsySettings:Intervention: Integrated Traditional Chinese medicine and modern rehabilitation therapies						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Integrated traditional Chinese medicine and conventional rehabilitation therapies				
Joint range of motion–Wrist extension protractor		The mean Joint range of motion– Wrist extension in the intervention groups was **4.13 higher** (0.79 lower to 9.04 higher)		158 (two studies)	⊕⊕⊝⊝ **Low**[1,2]	
Modified Ashworth scale (MAS) questionnaire		The mean Modified Ashworth scale (MAS) in the intervention groups was **0.28 lower** (0.48 to 0.08 lower)		325 (three studies)	⊕⊕⊕⊝ **Moderate**[2]	
Berg balance scale (BBS) questionnaire		The mean Berg balance scale (BBS) in the intervention groups was **4.42 higher** (1.21 to 7.63 higher)		231 (three studies)	⊕⊕⊝⊝ **Low**[1,2]	
Activities of daily living (ADL) questionnaire		The mean activities of daily living (ADL) in the intervention groups was **3.78 higher** (2.12–5.43 higher)		150 (two studies)	⊕⊕⊝⊝ **Low**[1,2]	

The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. [1]$I^2 > 50\%$ [2]There were less than 400 participants in total.

treatment of children with cerebral palsy to improve gross motor development and regulate muscle tone. With regard to fine motor improvement, further studies on the targeted and individualized treatment protocol for children with CP should be noticed. For example, meridians and acupoints should be selected based on syndrome differentiation.

Children with CP also showed a significant increase in functional independence after the treatment of integrated TCM and modern rehabilitation therapies compared to modern rehabilitation therapies only. More studies will be needed in the future to explore the long-term effect of integrated therapies on activities of daily living, given that long-term application of the integrated therapies to children with CP may help them to return to school in adolescence and return to society in adulthood.

Traditional Chinese medicine therapies included in this systematic review consist of body and scalp acupuncture, massage, and fumigation. The methodological heterogeneity needs attention in this systematic review, which may be due to the diversity of TCM treatments. Future studies should focus on the standardization of TCM diagnosis and treatment for children with CP. To promote the application of TCM worldwide, an international training program of TCM should be established to increase the accreditation of TCM practitioners.

5. Conclusion

This systematic review indicated that integrated TCM and modern rehabilitation therapies may be recognized as an effective and safe therapy to improve gross motor function, reduce muscle tone, and improve the functional independence of children with CP, compared to modern rehabilitation therapy only. Due to the methodological heterogeneity and the potential risk of bias in the included studies, our results should be interpreted with caution. Future studies should focus on the standardization of TCM treatments, and training of international TCM practitioners may be considered for TCM promotions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ZC and ZH contributed to the studies retrieval and data extraction. QD and XZ designed and developed the framework for the manuscript. All authors contributed to the article's writing, read the manuscript, and agreed to submit this version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1097477/full#supplementary-material

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The efficacy and safety of acupuncture therapy for sciatica: A systematic review and meta-analysis of randomized controlled trails

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Background and objective: Sciatica is a common type of neuropathic pain disease which poses a huge financial burden to the patient. For patients with sciatica, acupuncture has been recommended as an effective method for pain relief, while there is currently a lack of sufficient evidence to support its efficacy and safety. In this review, we aimed to critically assess the published clinical evidence on the efficacy and safety of acupuncture therapy for treating sciatica.

Methods: An extensive literature search strategy was established in seven databases from their inception to 31 March 2022. Two independent reviewers performed the literature search, identification, and screening. Data extraction was performed on studies that meet the inclusion criteria, and a further quality assessment was performed according to the Cochrane Handbook and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations. Summary Risk ratio (RR) and standardized mean differences (SMDs) with 95% confidence interval (CI) were calculated using the fixed-effects or the random-effects model. Heterogeneity in effect size across studies was explored using the subgroup analysis and the sensitivity analysis. The quality of evidence was estimated following the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results: A total of 30 randomized controlled trials (RCTs) involving 2,662 participants were included in the meta-analysis. The results of the integration of clinical outcomes showed that the clinical efficacy of acupuncture was superior to that of medicine treatment (MT) in improving the total effective rate (relative risk (RR) = 1.25, 95% confidence interval (CI) [1.21, 1.30]; moderate certainty of evidence), reducing the Visual Analog Scale (VAS) pain score (standardized mean difference (SMD) = −1.72, 95% CI [-2.61, −0.84]; very low certainty of evidence), increasing pain threshold (SMD = 2.07, 95% CI [1.38, 2.75]; very low certainty of evidence), and decreasing recurrence rate (RR = 0.27, 95% CI [0.13, 0.56]; low certainty of evidence). In addition, a few adverse events (RR = 0.38, 95% CI [0.19, 0.72]; moderate certainty of evidence) were reported during the intervention, which indicated that acupuncture was a safe treatment option.

Conclusions: Acupuncture therapy is an effective and safe treatment for patients with sciatica, and it can be considered a suitable replacement for medicine treatment (MT). However, given the high heterogeneity and a low methodological quality of previous studies, future RCTs should be well-designed according to the rigorous methodology.

Systematic review registration: International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (https://inplasy.com/register/), identifier [INPLASY202240060].

KEYWORDS

acupuncture, sciatica, nerve pain, meta-analysis, systematic review

Introduction

Sciatica, a common type of neuropathic pain, is characterized by radicular pain radiating from the lower back region and down to the leg, sometimes with or without numbness, paresthesia, and muscle weakness (Valat et al., 2010). These symptoms are mostly related to the compression of the spinal nerve root by disc herniation, accounting for 85% of the total cases (Ropper and Zafonte, 2015). The prevalence of sciatica varies widely from 1.2 to 43% with an annual incidence of 1–5% and a peak incidence in the fourth decade of life (Konstantinou et al., 2015; Davis et al., 2022). Sciatica is normally self-limiting with the relieving of pain over time in some cases (Oosterhuis et al., 2019). However, it remains more prevalent among certain populations, especially physical laborers (Fairag et al., 2022). Owing to the lack of an effective treatment, a significant proportion of patients with sciatica experience pain that persists for 1 year or longer. Persistent or unresolved pain could eventually lead to neurological deficits and functional disability, which have a serious impact on the quality of life (QoL) and pose a significant burden on the patient's healthcare resources (Maslak et al., 2020).

Seeking an appropriate method of treatment for sciatica is essential. Currently, the treatment options for sciatica can be classified into two categories: surgery and non-surgery, mainly depending on the severity of the condition. Patients with acute radicular pain may be considered for surgery, owing to the advantages of fast pain relief (Schoenfeld and Kang, 2020). However, the long-term efficacy of surgery remains to be determined. A systematic review reported that there were no differences in any clinical outcome (e.g., pain intensity, recurrence rate, and so on) between surgery and conservative care at 1- and 2-year follow-ups (Jacobs et al., 2011). Thus, the preferred treatment for the management of patients with sciatica is conservative, which includes exercise and manual therapy, medication, and spinal injections (Valat et al., 2010; Jensen et al., 2019). Based on the primary purpose of pain relief, analgesic drugs such as for example, non-steroidal anti-inflammatory drugs (NSAIDs) (Friedman et al., 2019) are often prescribed for patients with sciatica. However, several issues could arise from the use of NSAIDs, among which safety and adverse events are the most critical issues (Enthoven et al., 2016). As a result, it is imperative to search for effective and safe alternative pharmaceutical approaches.

Acupuncture therapy, as a non-pharmacological treatment derived from traditional Chinese medicine (TCM), is an established analgesic modality for treating pain. Modern medical research indicates that acupuncture exerts analgesic effects by regualting the activation of microglia, inhibiting inflammatory response and modulating certain receptors along the pain pathways in the central or peripheral nervous systems (Coutaux, 2017; Wang et al., 2020). The results of clinical studies on acupuncture therapy for sciatica showed that acupuncture is effective in relieving its symptoms (Liu et al., 2019; Yu et al., 2022). The effects of acupuncture treatment are also determined by selecting the appropriate acupuncture method, including manual acupuncture (MA) with twirling, lifting, and thrusting manipulation, electroacupuncture (EA) with an electric microcurrent device, and warm acupuncture (WA) with a combination of acupuncture and moxibustion treatment (Cao et al., 2021). According to the efficacy and safety of acupuncture for pain relief, patients with sciatica often give consent to undergo acupuncture treatment in China.

Two systematic reviews were performed to investigate the effectiveness of acupuncture for sciatica in 2015 (Ji et al., 2015; Qin et al., 2015); however, recent guidelines did not recommend acupuncture as a suitable treatment for sciatica, which mainly resulted from a limited sample size and a high interstudy heterogeneity (Jensen et al., 2019). In recent years, more randomized controlled trials (RCTs) have been published, and we plan to renew the included literature and conduct a comprehensive meta-analysis to evaluate the efficacy and safety of acupuncture therapy for sciatica.

Methods

The protocol of this study was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (https://inplasy.com/register/), and the registration number was INPLASY202240060. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) (Supplementary Table 1).

Literature search strategy

The databases, including three Chinese databases [China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals (VIP), and Wanfang Database] and four English databases (PubMed, Cochrane Library, Embase, and Web of Science), were searched for literature from their inception date until 31 March 2022. The key search terms were composed of the following group terms: (1) sciatica (sciatic neuralgia, sciatic pain, and sciatic neuropathy), (2) acupuncture (electroacupuncture, needle, needling, acupuncture and moxibustion, and warm acupuncture), and (3) sciatica plus acupuncture. The detailed search strategies for each database are presented in Supplementary Table 2.

Inclusion criteria

The studies which were included must meet the following eligibility criteria.

Types of studies

In the design of studies, we included all RCTs which were used to evaluate the effectiveness and safety of acupuncture treatment for sciatica with no limitations set in language, blinding, or publication type.

Types of participants

Patients diagnosed with sciatica were included in this meta-analysis. The diagnostic criteria were based on symptoms, physical examination, medical imaging, and relevant published guidelines. There was no restriction in either age, gender, race, or ethnicity.

Types of interventions

The intervention of the experimental group was acupuncture therapy, including MA, EA, WA, and acupuncture plus moxibustion, regardless of acupoints, needle types, and materials. While in the control group (CG), the intervention was medicine treatment (MT), including conventional Western medicine or Chinese patent medicine. In addition, considering the potential placebo effects of acupuncture, sham acupuncture (SA) was included as another control intervention.

Types of outcome measures

The primary outcomes included total effective rate and pain intensity. The total effective rate was calculated by dividing the number of cured, markedly improved, and improved patients by the number of total patients. The pain intensity was measured by the Visual Analog Scale (VAS) with a 10-cm scale (0 cm represented no pain and 10 cm represented extreme pain). The secondary outcomes included the pain threshold, recurrence rate, and adverse events.

Exclusion criteria

Studies were excluded if they did not meet the aforementioned criteria. In addition, the following studies were excluded if: (1) the types of studies included observational studies, animal studies, theoretical studies, data mining studies, thesis or dissertation, review, and meta-analyses; (2) the types of acupuncture included acupoint injections, laser acupuncture, cupping, and percutaneous stimulation; (3) interventions included a combination of acupuncture and medication; (4) the articles were duplicates; and (5) missing source literature or original data cannot be retrieved from the literature.

Studies' selection and data extraction

The retrieved records were imported into NoteExpress, and the duplicates were removed. First, two reviewers (PY Huang and Z Huang) independently reviewed the titles and abstracts to eliminate irrelevant records and then read the full text to identify eligible studies. Finally, all relevant studies were retrieved for further assessment according to the inclusion and exclusion criteria. Disagreements were resolved through a team discussion and entrusted to a third reviewer (XC Zhang).

Two reviewers (ZH Zhang and TT Hu) independently extracted data from each included study by using a predesigned form. The general data of these studies were extracted, including the first author, publication year, sample size, diagnostic criteria, treatment details of treatment groups and control groups, outcome measures, follow-up period, and adverse events. After data extraction, each other's data were checked to ensure accuracy. When the results of the concerned study were ambiguous or incorrect, we contacted the authors for clarification and details. Meanwhile, we checked the source data to recalculate, and any disagreements were resolved *via* discussion with the third reviewer (XL Zhang).

Quality assessment of risk of bias

Two reviewers (YW Xia and MN Yang) independently assessed the risk of bias for each included study. According to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), the domains of bias included random sequence generation, allocation concealment, blinding method, incomplete outcome data, selective reporting, and other biases (Higgins and Green, 2011). For the risk of bias, "high risk of bias," "low risk of bias," or "unclear risk of bias" was assigned as the three levels to each domain. Any difference was resolved by discussion with a third reviewer (GX Ni) to reach a consensus.

Quality assessment of acupuncture protocol

The detailed acupuncture treatment protocol of the included studies was assessed according to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist (MacPherson et al., 2010). The STRICTA checklist includes six items with 17 subitems, including the acupuncture rationale, details of needling, treatment regimen, other components of treatment, practitioner's background, and control or comparator interventions. We assessed the overall quality score (OQS) with 17 items from the STRICTA checklist (Zhuang et al., 2014). The score of each item was 0 or 1. If the item was completely reported, the score was "1," but if the item was unreported or if the reported item was unclear, the score was "0." In addition, the total score of each study was calculated to be in the range of 0 to 17, which indicated the rating of the overall reporting quality of an acupuncture protocol.

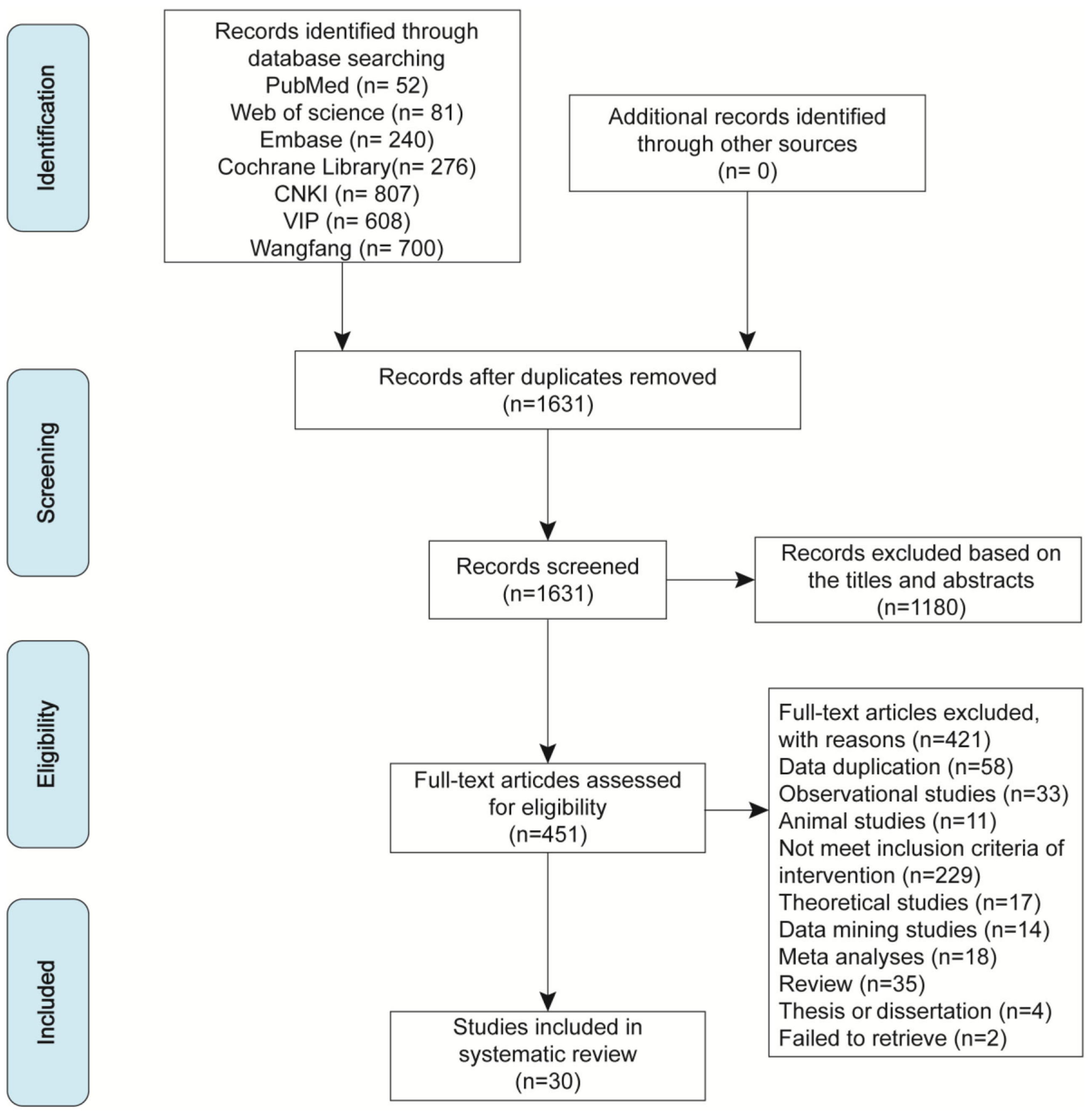

FIGURE 1
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature search and screening.

Statistical analysis

Data analyses were conducted using RevMan (version 5.3) and R software (version 4.2.0). Continuous variables (i.e., pain threshold and pain intensity) were measured using the standardized mean difference (SMD) with a 95% confidence interval (CI), and dichotomous variables (i.e., total effective rate and recurrence rate) were measured using the risk ratio (RR) with a 95% CI. According to the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0), a value of $P < 0.05$ indicates a statistically significant difference (Higgins and Green, 2011). Cochrane's Q statistic and I^2 statistic were used to inspect heterogeneity between studies. Heterogeneity was classified into two levels, when I^2 is <50%, pooled effects of heterogeneous trials were calculated using the fixed-effects model, and when I^2 is >50%, pooled effects of heterogeneous trials were calculated using the random-effects models.

Subgroup analysis

We performed the subgroup analysis based on the following aspects: (1) types of acupuncture interventions (i.e., MA, WA, and EA) and (2) sessions of acupuncture treatment (i.e., <15 or ≥15).

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Sensitivity analysis

Sensitivity analysis was performed to verify the robustness of the results of the heterogeneity tests by eliminating studies case-by-case. In addition, the Baujat plot was used to further characterize the contribution to the overall heterogeneity in each study and identify high heterogeneity studies from the meta-analytic data (Baujat et al., 2002).

Publication bias

Publication bias was visually shown by funnel plots. In addition, we further formally tested the potential publication bias by using Egger's test or Peters' test, which are two significant testing methods based on the asymmetry of funnel plots. Egger's test was applied for continuous variables (i.e., pain intensity) and Peters' test was applied for dichotomous variables (i.e., total effective rate). If there was a value of $P < 0.05$, publication bias existed (Sterne et al., 2011).

Evidence quality assessment on GRADE

Based on the GRADE recommendations, we graded the quality of evidence through GRADEpro online software (https://www.gradepro.org/) (Atkins et al., 2004). The quality of included studies was graded high, moderate, low, or very low. The following aspects were used for assessment, including the risk of bias, inconsistent results, indirect evidence, imprecision, and publication bias.

Results

Search results

The flow diagram of the screening process is shown in Figure 1. The search retrieved 2,764 records. After duplicates were removed, 1,631 records were screened for potential relevance by reviewing titles and abstracts. Among these, 1,180 records were excluded, and the remaining 451 records required a full-text assessment. Through screening, we finally included 30 studies (Chen et al., 2005; Li and Meng, 2011; Jiang, 2012, 2018; Liu, 2012, 2015, 2017; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015, 2019; Nie, 2015; Ye et al., 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Zou, 2017; Li, 2018; Zheng, 2019; Gu, 2020; Huo, 2020; Li et al., 2021). A total of 421 studies were excluded after screening the full text. The main reason for exclusion was that the intervention of studies did not meet the inclusion criteria. Additionally, we excluded animal studies, reviews, meta-analyses, theoretical studies, data mining studies, and theses or dissertations, among others because they were not randomized controlled trials (RCTs).

Study characteristics

This review included 30 studies with 2,662 participants in total. Almost all studies were conducted in China, whereas two articles (Huang et al., 2019; Li et al., 2021) were English publications. The sample sizes ranged from 30 to 310 participants per study. The gender information on participants showed that the male-to-female ratio of the acupuncture group (AG) was 1.36 (575/423) and the male-to-female ratio of the control group was 1.43 (573/402), which were identified from 22 studies (Chen et al., 2005; Zhai, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015, 2019; Liu, 2015, 2017; Ye et al., 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Zou, 2017; Jiang, 2018; Li, 2018; Li et al., 2019, 2021; Zheng, 2019; Huo, 2020). All participants in the included trials must be diagnosed with sciatica. As regards diagnostic criteria, 10 studies used the published clinical guidelines as diagnostic criteria (Chen et al., 2005; Li and Meng, 2011; Liu, 2012; Zeng and Liao, 2012; Ai, 2015; Huang et al., 2015, 2019; Ye et al., 2015; Li et al., 2019, 2021), six studies reported the cause of sciatica induced by lumbar disc herniation (LDH) (Shang et al., 2014; Liu, 2015; Jiang, 2018; Zheng, 2019; Gu, 2020; Huo, 2020), seven studies were based on medical imaging as well as diagnostic criteria (Zhang, 2012; Liu, 2015; Wang, 2017; Yu, 2017; Li, 2018; Li et al., 2019; Gu, 2020), two studies used physical tests (i.e., straight-leg-raising test) (Li and Kang, 2016; Li et al., 2019), and nine studies did not report the diagnostic criteria (Jiang, 2012; Zhai, 2012; Nie, 2015; Wang, 2016, 2020; Wei, 2016; Hu, 2017; Liu, 2017; Zou, 2017). Acupuncture, MT, or SA was involved in intervention comparisons in studies. Twenty-eight studies compared acupuncture with MT (Chen et al., 2005; Li and Meng, 2011; Jiang, 2012, 2018; Liu, 2012, 2015, 2017; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015; Nie, 2015; Ye et al., 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Zou, 2017; Li, 2018; Li et al., 2019; Zheng, 2019; Gu, 2020; Huo, 2020) and two studies compared acupuncture with SA (Huang et al., 2019; Li et al., 2021). Further details of these studies are summarized in Table 1.

Acupuncture therapy protocols of included trials

A total of 27 studies used MA (Chen et al., 2005; Jiang, 2012, 2018; Liu, 2012, 2015, 2017; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Nie, 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Zou, 2017; Li, 2018; Huang et al., 2019; Li et al., 2019, 2021; Zheng, 2019; Gu, 2020; Huo, 2020) and the rest of the three studies used EA (Li and Meng, 2011; Huang et al., 2015; Ye et al., 2015). As for the intervention types of MA, 12 studies used only needles (Shang et al., 2014; Liu, 2015, 2017; Yu, 2017; Zou, 2017; Jiang, 2018; Huang et al., 2019; Li et al., 2019, 2021; Zheng, 2019; Gu, 2020; Huo, 2020), 10 studies used acupuncture and moxibustion (Jiang, 2012; Liu, 2012; Zeng and Liao, 2012; Zhang, 2012; Nie, 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Li, 2018), and five studies used WA (Chen et al., 2005; Zhai, 2012; Ai, 2015; Wei, 2016; Hu, 2017). All included studies reported the choice of acupoints. As shown in Figure 3A, the most frequent acupoints were GB30, BL25, BL4, BL60, BL23, BL54, and GB34. A total of 26 studies reported the retention time of needles (Chen et al., 2005; Li and Meng, 2011; Jiang, 2012, 2018; Liu, 2012, 2017; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015, 2019; Nie, 2015; Ye et al., 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Li, 2018; Li et al., 2019, 2021; Huo, 2020). It was reported that the retention time ranged mostly from 15 to 30 min. Only two studies showed that the retention time was only 5 min (Liu, 2012; Nie, 2015). The frequency

TABLE 1 Characteristics of included studies.

Included trails	Sample size (M/F)		Interventions		Diagnosis	Outcomes	Adverse events	Follow-up
	AG	CG	AG	CG (medicine/dosage/frequency)				
Huo (2020)	60 (34/26)	60 (36/24)	Acupuncture	MT: Diclofanac Sodium Sustained Release Tablets/75 mg/qd	Sciatica caused by LDH	① ②	/	/
Gu (2020)	35	35	Acupuncture	MT: Brufen, Prednisone/NA/ NA	Sciatica caused by LDH/ medical imaging (MRI)	① ②	/	/
Zheng (2019)	155 (88/67)	155 (87/68)	Acupuncture	MT: Brufen/0.6 g/bid. Prednisone/10 mg/bid	Sciatica caused by LDH	①	/	/
Li et al. (2019)	46 (29/17)	46 (26/20)	Acupuncture	MT: Compound Mannitol Injection/125–250 ml/ NA. Dexamethasone/5–10 mg/ NA Aceclofenac Dispersible Tablets (1st week po./0.1 g/bid 2st week po./0.1 g/qd)	Physical tests/medical imaging (MRI/CT)/≪The clinical diagnostic and curative criteria of disease≫	① ②	/	/
Jiang (2018)	60 (38/22)	60 (37/23)	Acupuncture	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	Sciatica caused by LDH	①	Y	/
Zou (2017)	30 (17/13)	30 (16/14)	Acupuncture	MT: Nimesulide/0.1 g/ bid	NA	① ③	/	/
Yu (2017)	28	22	Acupuncture	MT: Indomethacin/30mg/bid Vitamin B12/500μg/qd	Medical imaging (CT/X-rays)	①	/	/
Liu (2015)	48 (29/19)	48 (30/18)	Acupuncture	MT: Brufen/0.6 g/d/tid Prednisone/10 mg/d/tid	Medical imaging (CT/MRI)/ sciatica caused by LDH	①	/	/
Shang et al. (2014)	60 (36/24)	60 (38/22)	Acupuncture	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	Sciatica caused by LDH	①	/	/
Liu (2017)	42 (28/14)	41 (27/14)	Acupuncture	MT: Nimesulide/0.1 g/bid	NA	① ②	/	/
Zeng and Liao (2012)	65	65	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	Criteria of therapeutic effect and diagnosis of diseases and syndromes in TCM	①	/	/
Zhang (2012)	70	75	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	Medical imaging (CT/X-rays)	①	/	/
Wang (2020)	40 (23/17)	40 (20/20)	Acupuncture and moxibustion	MT: Nimesulide/0.1 g/bid	NA	①	Y	/
Li (2018)	33 (24/9)	33 (25/8)	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	medical imaging (CT/X-rays)	①	/	/
Wang (2016)	90 (51/39)	90 (48/32)	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	NA	①	/	/
Wang (2017)	25 (14/11)	25 (15/10)	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	medical imaging (CT/X-rays)	①	/	/

(Continued)

TABLE 1 (Continued)

Included trails	Sample size (M/F)		Interventions		Diagnosis	Outcomes	Adverse events	Follow-up
	AG	CG	AG	CG (medicine/dosage/frequency)				
Nie (2015)	39	37	Acupuncture and moxibustion	MT: Nimesulide/0.1 g/bid	NA	①	/	/
Jiang (2012)	41	41	Acupuncture and moxibustion	MT: Brufen/0.6 g/tid Prednisone/10 mg/tid	NA	①	/	/
Liu (2012)	30	20	Acupuncture and moxibustion	MT: Nimesulide/0.1 g/bid	≪The clinical diagnostic and curative criteria of disease≫	③	/	/
Li and Kang (2016)	30 (19/11)	30 (22/8)	Acupuncture and moxibustion	MT	Physical tests	①	/	/
Hu (2017)	40 (20/20)	40 (21/19)	Warm acupuncture	MT: Nimesulide/0.1 g/bid	NA	① ④	Y	Y
Wei (2016)	15 (12/3)	15 (9/6)	Warm acupuncture	MT: Nimesulide/0.2 g/bid	NA	① ④	/	Y
Ai (2015)	30 (20/10)	30 (21/9)	Warm acupuncture	MT: Nimesulide/0.3 g/bid	The clinical diagnostic and curative criteria of disease/Criteria of therapeutic effect and diagnosis of diseases and syndromes in TCM	①	/	/
Zhai (2012)	28 (17/11)	28 (16/12)	Warm Acupuncture	MT: Nimesulide/0.4 g/bid	NA	①	/	/
Chen et al. (2005)	30 (22/8)	30 (21/9)	Warm Acupuncture	MT: Nimesulide/0.5 g/bid	The clinical diagnostic and curative criteria of disease (1999)	① ③	/	/
Huang et al. (2015)	35 (24/11)	35 (27/8)	Electroacupuncture	MT: Brufen/0.3 g/bid Mecobalamin/0.5 mg/tid	Criteria of therapeutic effect and diagnosis of diseases and syndromes in TCM	① ②	/	/
Li and Meng (2011)	49	37	Electroacupuncture	MT: Brufen/0.3 g/bid VitaminB1/20 mg/tid	3,200 standard diagnoses of diseases in internal medicine	① ② ④	/	Y
Ye et al. (2015)	31 (12/19)	30 (11/19)	Electroacupuncture	MT: Dichofenac Diethylammon (drug external)/NA/ qid	Criteria of therapeutic effect and diagnosis of diseases and syndromes in TCM/Guiding principle of clinical research on new drugs of TCM (trial)	②	/	/
Huang et al. (2019)	23 (7/16)	23 (8/15)	Acupuncture	SA	The North American Spine Society clinical guidelines	②	Y	Y
Li et al. (2021)	37 (11/26)	36 (12/24)	Acupuncture	SA	Inclusion criteria-Patients with unilateral sciatica who meet the diagnostic criteria(P6)	②	Y	Y

①total effective rate; ②pain intensity; ③pain threshold; ④recurrence rate.
AG, acupuncture group; CG, control group; NA, Not applicable; MT, medicine treatment; SA, sham acupuncture; LDH, lumbar disc herniation.

TABLE 2 Details of characteristics of acupuncture intervention.

Included trails	Acupuncture Style	Acupoints formula	Details of acupuncture therapy		Treatment regimen			Other acupuncture treatment
			Needle stimulation	Needle type	Retention time	Session	Frequency	
Huo (2020)	TCM	BL57, BL25, GB30, BL40, BL54, GB34, GB30, GB39, ABL60, BL25, GB30, GB34	Manual	(1) GB30, BL54: 0.30 × 75 mm; (2) other acupoints: 0.25 × 40 mm	30 min	15	once a day	/
Gu (2020)	TCM	Pain syndromes or near the site of pain	Manual	According to site of acupoints	NA	NA	/	/
Zheng (2019)	TCM	GB30, BL40, BL57, BL25, GB34, GB30, GB39	Manual	/	NA	NA	/	/
Li et al. (2019)	TCM	GB30, BL54, GB39, GB34, GB30, BL57, BL40, BL25, GB30, BL60, GB34, BL25	Manual	(1) GB30, BL54: 0.30 × 75 mm; (2) other acupoints: 0.25 × 40 mm	30 min	14	once a day	/
Jiang (2018)	TCM	GB30, GB39, GB34, BL25, GB30, BL57, BL40, GB30, BL25, GB34, BL60	Manual	/	30 min	14	once a day	/
Zou (2017)	TCM	BL23, GB30, BL25, BL60, BL40	Manual	/	NA	23	once a day	/
Yu (2017)	TCM	BL57, GB30, BL25, BL40, GB30, ST40, GB34, GB39, BL25, BL54, GB34, GB30, BL60	Manual	0.45 × 150 mm	30 min	14	once a day	/
Liu (2015)	TCM	GB30, BL25, BL40, BL57, GB30, GB34, GB39, BL25, GB30, GB34, BL60.	Manual	According to the site of acupoints	NA	NA	/	/
Shang et al. (2014)	TCM	GB30, BL25, BL40, BL57, GB30, GB34, GB39.	Manual	0.45 × 150 mm; 0.45 × 40–75 mm	30 min	14	once a day	/
Liu (2017)	TCM	BL23, GB30, BL40, BL57, BL25, BL60, GB34, BL54, BL23, GB30, GB34, BL25, GB40, GB39, SP9, LR2, LI11, SP10, BL26, ST36, SP10, BL18, BL17	Manual	/	30 min	23	once a day	/
Zeng and Liao (2012)	TCM	BL25, GB30, BL54, GB34, BL60	Manual	/	30 min	14	once a day	Indirect Moxibustion
Zhang (2012)	TCM	BL25, GB30, BL40, BL57, GB30, GB34, ST40, GB39, BL25, GB30, BL54, GB34, BL60	Manual	/	30 min	14	once a day	Indirect Moxibustion
Wang (2020)	TCM	BL25, BL23, GB30, BL40, BL60	Manual	0.3 × 60–75 mm	25 min	10	once a day	Direct Moxibustion
Li (2018)	TCM	GB34, BL40, BL54, GB30, EX-B2, BL25, GV3, BL23, ST32, GB31, BL36, BL26, BL60, GB39, GB34, BL57, BL32	Manual	/	30 min	23	once a day	Indirect Moxibustion
Wang (2016)	TCM	GB30, BL25, BL54, BL60, BL23, BL40, GB34	Manual	0.3 × 70 mm	20–30 min	21	once a day	Indirect Moxibustion

(Continued)

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TABLE 2 (Continued)

Included trails	Acupuncture Style	Acupoints formula	Details of acupuncture therapy		Treatment regimen			Other acupuncture treatment
			Needle stimulation	Needle type	Retention time	Session	Frequency	
Wang (2017)	TCM	BL40, GB30, BL57, BL25, GB39, ST40, GB30, GB34, BL60, GB30, BL54, BL25, GB34, BL20, SP9, BL23, GV3, BL40,BL32, BL17, ST36, SP6	Manual	0.45 × 150 mm	30 min	29	once a day	Indirect Moxibustion
Nie (2015)	TCM	BL23, GB30, BL25, BL60, BL40	Manual	0.3 × 60–75 mm	5 min	23	once a day	Direct Moxibustion
Jiang (2012)	TCM	GB30, BL25, BL54, BL60, GB34	Manual	/	30 min	28	once a day	Indirect Moxibustion
Liu (2012)	TCM	BL23, BL25, GB30, BL40, BL60	Manual	0.3 × 60–75 mm	5 min	23	once a day	Direct Moxibustion
Li and Kang (2016)	TCM	BL32, GB30, BL54, BL40	Manual	/	30 min	15	once a day	Heat-Sensitive Moxibustion
Hu (2017)	TCM	BL23, BL25, GB30, BL54, ST33, BL40, BL60	Manual	(1) BL23, BL25, BL40: 0.30 × 40 mm; (2) GB30, BL54, ST33:0.30 × 60 mm; (3) BL60: 0.25 × 30 mm	30 min	10	once a day	Warm Acupuncture
Wei (2016)	TCM	BL23, BL60, BL40, GB30, BL25	Manual	0.3 × 60-75 mm	25min	23	once a day	Warm Acupuncture
Ai (2015)	TCM	BL23, BL25, GB30, BL40, BL60	Manual	0.3 × 65 mm	15–30 min	21	once a day	Warm Acupuncture
Zhai (2012)	TCM	BL23, BL25, GB30, BL40, BL60	Manual	0.3 × 60–75 mm	15–30 min	23	once a day	Warm Acupuncture
Chen et al. (2005)	TCM	BL23, BL25, GB30, BL40, BL60	Manual	0.3 × 60–75 mm	15–30 min	23	once a day	Warm Acupuncture
Huang et al. (2015)	TCM	BL25, BL26, GB30, BL40, BL54, BL36, ST32, GB31, GB39, BL60; BL57, BL32, GB30	Electrical	/	30 min	22	once a day	/
Li and Meng (2011)	TCM	GB30, GB34, BL57, BL60, BL54, BL40, GB31, GB39, GB41	Electrical	0.3 × 40 mm	30 min	27	once a day	/
Ye et al. (2015)	TCM	EX-B2 (L4-5, L5-S1), BL54, GB30	Electrical	/	30 min	21	once a day	/
Huang et al. (2019)	TCM	BL25, BL23, BL40, BL57	Manual	0.35 × 75 mm; 0.35 × 40 mm	30 min	28	once every other day	/
Li et al. (2021)	TCM	BL25	Manual	/	30 min	112	/	/

TCM, Traditional Chinese medicine; NA, not applicable.

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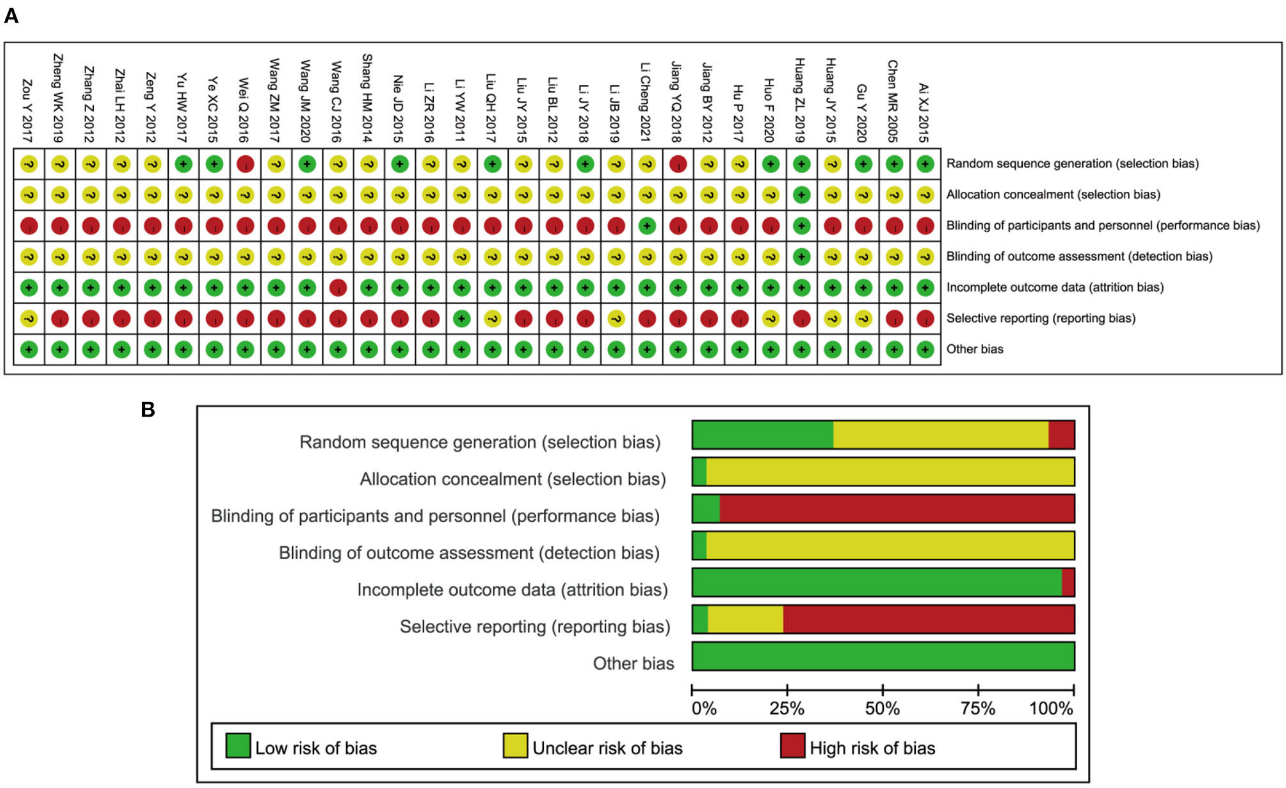

FIGURE 2
Risk of bias from included studies. **(A)** Risk of bias summary. **(B)** Risk of bias graph.

of treatment was one time a day (Jiang, 2012, 2018; Liu, 2012, 2017; Zeng and Liao, 2012; Zhang, 2012; Shang et al., 2014; Nie, 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Zou, 2017; Li, 2018; Li et al., 2019; Huo, 2020) and one time every other day (Huang et al., 2019). Details of the acupuncture intervention are summarized in Table 2.

Risk of bias assessment

The results of the "risk of bias" assessment by domain for each study are displayed in Figure 2A, and the percentage results of risk evaluation in each domain are provided in Figure 2B. The specific reasons for the judgments are shown in Supplementary Table 3. In all studies, one to three domains were judged to be at high risk of bias. The main issue in most of the studies (28 studies, more than 90%) was the high risk of performance bias due to nonblinding of participants and personnel, which was related to the characteristic of acupuncture. During the process of acupuncture treatment, it is hard to implement blind procedures for acupuncturists and patients. Only two studies (Huang et al., 2019; Li et al., 2021) were judged to have a low risk of performance bias because they used acupuncture with sham intervention, which ensured that the participants were blinded. One study had a low risk of detection bias (Huang et al., 2019), while the rest of the studies had an unclear detection bias risk, as there was no indication of whether the assessors were blinded or not. A total of 11 studies mentioned random methods, including the random number table, randomized controlled parallel design, and computer-based random number generator (Chen et al., 2005; Ai, 2015; Nie, 2015; Ye et al., 2015; Liu, 2017; Yu, 2017; Li, 2018; Huang et al., 2019; Gu, 2020; Huo, 2020; Wang, 2020). However, two studies were judged to have a high selection bias because the sequence was generated by the time of admission (Wei, 2016; Jiang, 2018). The remaining studies were rated as "unclear risk" due to insufficient information to permit judgment of the sequence generation process (Li and Meng, 2011; Jiang, 2012; Liu, 2012, 2015; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Huang et al., 2015; Li and Kang, 2016; Wang, 2016, 2017; Hu, 2017; Zou, 2017; Li et al., 2019, 2021; Zheng, 2019). For the assessment of incomplete outcome data, almost all studies were graded to be at low risk of attrition bias. Among these, the data from three studies were found to contain mistakes which were later modified (Jiang, 2012; Zhang, 2012; Shang et al., 2014). Only one study was rated to be at high attrition bias risk because the data on pain threshold were not reported (Wang, 2016).

STRICTA checklist for the included studies

The summary of the assessment report on acupuncture details is provided in Supplementary Table 4 using the STRICTA checklist. As shown in Figure 3B, almost all studies reported the style of acupuncture (1a), treatment reasoning (1b), acupoints (2b), needle stimulation (2e), and a precise description of the control group (6b); more than half of the studies mentioned the retention time (2f), the number of treatment sessions (3a), the frequency of treatment

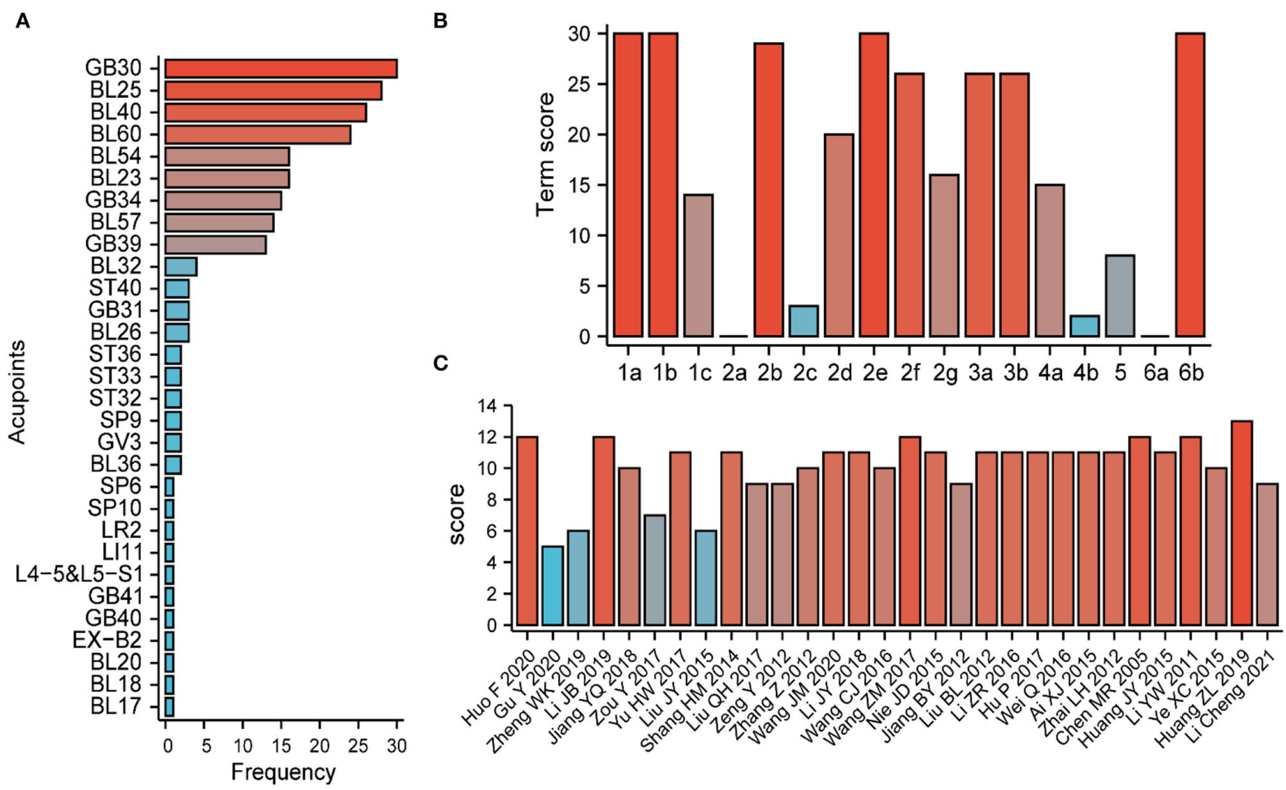

FIGURE 3
Acupuncture details and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist summary. **(A)** The frequency of acupoints in the included studies. **(B)** The total score for each STRICTA term. **(C)** The total STRICTA checklist score for each included study.

sessions (3b), the frequency of responses sought (2d), the needle type (2g), and the details of other interventions (4a); less than half of the studies reported the depth of insertion (2c), places and facilities of treatment (4b), and description of participating acupuncturists (5). The OQS from the STRICTA checklist of each study is presented in Figure 3C. The scores of 22 studies were ≥10 (Chen et al., 2005; Li and Meng, 2011; Liu, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015, 2019; Nie, 2015; Ye et al., 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Jiang, 2018; Li, 2018; Li et al., 2019; Huo, 2020), while the rest of the studies scored <10 (Jiang, 2012; Zeng and Liao, 2012; Liu, 2015, 2017; Zou, 2017; Zheng, 2019; Gu, 2020; Li et al., 2021). The overall reporting quality of interventions in controlled trials of acupuncture was relatively good.

Effects of interventions

Primary outcomes

Total effective rate

The total effective rate was reported in 26 studies (Chen et al., 2005; Li and Meng, 2011; Jiang, 2012, 2018; Zeng and Liao, 2012; Zhai, 2012; Zhang, 2012; Shang et al., 2014; Ai, 2015; Huang et al., 2015; Liu, 2015, 2017; Nie, 2015; Li and Kang, 2016; Wang, 2016, 2017, 2020; Wei, 2016; Hu, 2017; Yu, 2017; Zou, 2017; Li, 2018; Li et al., 2019; Zheng, 2019; Gu, 2020; Huo, 2020) in which the efficacy of acupuncture therapy was compared with that of MT on sciatica. The results of the meta-analysis revealed that the total effectiveness of acupuncture therapy was statistically significantly better than that of MT (RR = 1.25, 95%CI [1.21, 1.30], $P < 0.00001$) (Figure 4).

The results of subgroup analyses are summarized in Table 3. With regard to the types of acupuncture interventions, the results of subgroup analyses presented that MA (RR=1.25, 95%CI [1.21, 1.30]), WA (RR = 1.27, 95%CI [1.13, 1.43]), and EA (RR = 1.26, 95%CI [1.07, 1.49]) were superior to MT in improving the total effective rate. As for treatment sessions, we found that acupuncture treatments of <15 sessions (RR = 1.28, 95%CI [1.20, 1.37]) and ≥15 sessions (RR = 1.24, 95%CI [1.19, 1.29]) exhibited a statistically significant effect in improving the total effective rate compared with MT.

Pain intensity

Nine studies, including 701 participants, used the VAS score (0–10cm scale) to calculate the pain intensity of acupuncture for sciatica. Among these, seven studies (Li and Meng, 2011; Huang et al., 2015; Ye et al., 2015; Liu, 2017; Li et al., 2019; Gu, 2020; Huo, 2020) compared acupuncture with MT, and two studies (Huang et al., 2019; Li et al., 2021) compared real acupuncture with SA. The results of the VAS score in the acupuncture group showed a statistically significantly lower value than that in the MT group (MD = −1.77, 95%CI [−1.89, −1.66], $P < 0.00001$) (Figure 5). In addition, two studies (Huang et al., 2019; Li et al., 2021) reported that real acupuncture was statistically superior to SA in improving the VAS score for sciatic pain (MD = −1.13, 95%CI [-1.66, −0.60], $P < 0.0001$) (Figure 5), and there was no evidence of heterogeneity ($P = 1.00$, $I^2 = 0\%$).

Study or Subgroup	Acupuncture Events	Acupuncture Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ai XJ 2015	28	30	22	30	2.4%	1.27 [1.01, 1.61]
Chen MR 2005	27	30	22	30	2.4%	1.23 [0.96, 1.57]
Gu Y 2020	31	35	26	35	2.9%	1.19 [0.95, 1.50]
Hu P 2017	35	40	27	40	3.0%	1.30 [1.01, 1.66]
Huang JY 2015	32	35	25	35	2.8%	1.28 [1.01, 1.62]
Huo F 2020	57	60	49	60	5.4%	1.16 [1.02, 1.33]
Jiang BY 2012	38	41	34	41	3.8%	1.12 [0.95, 1.32]
Jiang YQ 2018	57	60	42	60	4.6%	1.36 [1.14, 1.62]
Li JB 2019	45	46	39	46	4.3%	1.15 [1.01, 1.31]
Li JY 2018	29	33	23	33	2.5%	1.26 [0.97, 1.63]
Li YW 2011	43	49	26	37	3.3%	1.25 [0.99, 1.58]
Li ZR 2016	28	30	12	30	1.3%	2.33 [1.49, 3.65]
Liu JY 2015	43	48	29	48	3.2%	1.48 [1.16, 1.90]
Liu QH 2017	40	42	31	41	3.5%	1.26 [1.05, 1.52]
Nie JD 2015	37	39	27	37	3.1%	1.30 [1.05, 1.60]
Shang HM 2014	53	60	39	60	4.3%	1.36 [1.10, 1.67]
Wang CJ 2016	88	90	75	90	8.3%	1.17 [1.06, 1.29]
Wang JM 2020	39	40	32	40	3.5%	1.22 [1.04, 1.43]
Wang ZM 2017	23	25	18	25	2.0%	1.28 [0.98, 1.67]
Wei Q 2016	14	15	10	15	1.1%	1.40 [0.95, 2.05]
Yu HW 2017	26	28	16	22	2.0%	1.28 [0.97, 1.68]
Zeng Y 2012	60	65	49	65	5.4%	1.22 [1.05, 1.43]
Zhai LH 2012	26	28	21	28	2.3%	1.24 [0.98, 1.57]
Zhang Z 2012	66	75	46	70	5.3%	1.34 [1.11, 1.62]
Zheng WK 2019	153	155	136	155	15.0%	1.13 [1.06, 1.20]
Zou Y 2017	29	30	21	30	2.3%	1.38 [1.08, 1.76]
Total (95% CI)		**1229**		**1203**	**100.0%**	**1.25 [1.21, 1.30]**
Total events	1147		897			

Heterogeneity: Chi² = 30.77, df = 25 (P = 0.20); I² = 19%

Test for overall effect: Z = 12.29 (P < 0.00001)

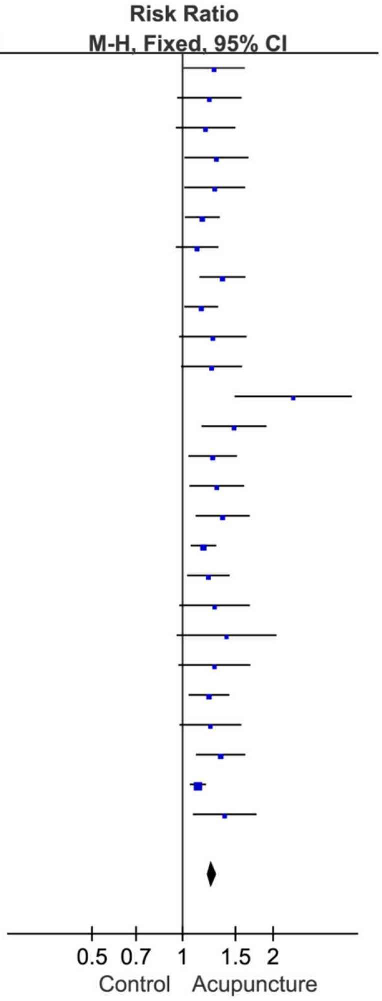

FIGURE 4
A Forest plot for total effective rate.

The subgroup analysis indicated that both MA (SMD = −3.16, 95%CI [−4.48, −1.83]) and EA (SMD=-0.50, 95%CI [−0.89, −0.12]) reduced the VAS score more than MT. However, there was high heterogeneity ($I^2 = 94\%$) in the comparison of MA vs. MT. For the sessions of acupuncture therapy, we found that acupuncture therapy with ≥15 sessions (SMD = −1.86, 95%CI [−3.50, −0.22]) had a better effect of reducing the VAS score than MT, while it had a little effect within 15 sessions (SMD = −1.98, 95%CI [−4.06, 0.10]) (Table 3).

Secondary outcomes

Pain threshold

Three studies with 170 participants examined the effects of acupuncture therapy on the pain threshold induced by sciatica vs. MT (Chen et al., 2005; Liu, 2012; Zou, 2017). The pooled results indicated that acupuncture had a statistically significantly better effect than medicine in improving pain threshold (SMD = 2.07, 95%CI [1.38, 2.75], $P < 0.00001$) (Supplementary Figure 1). The subgroup analysis showed that both MA (SMD = 1.82, 95%CI [1.06, 2.59]) and WA (SMD=2.57, 95%CI [1.88, 3.27]) were statistically significantly better than MT where the pain threshold increased (Table 3).

Recurrence rate

The data of recurrence rate during follow-up were obtained in three studies (Li and Meng, 2011; Wei, 2016; Hu, 2017). The pooled results showed that acupuncture had a superior long-term effect in reducing the occurrence of relapse for sciatic pain than MT (RR=0.27, 95%CI [0.13, 0.56]) (Supplementary Figure 2). There was no significant heterogeneity between the three studies ($P = 0.49$, $I^2 = 0\%$). The subgroup analysis indicated that WA (RR=0.38, 95%CI [0.16, 0.88]) and EA (RR=0.14, 95%CI [0.03, 0.58]) had a superior long-term effect in reducing the recurrence rate than MT (Table 3).

Adverse events

Several adverse events took place during the treatment and were reported in five studies (Hu, 2017; Jiang, 2018; Huang et al., 2019; Wang, 2020; Li et al., 2021). We evaluated the incidence of adverse events by the subgroup analysis, including acupuncture vs. MT and real acupuncture vs. SA. The pooled results indicated a higher incidence rate of adverse effects in drug reactions compared with acupuncture (RR=0.19, 95%CI [0.08, 0.45]) (Figure 6). The adverse events of MT included dizziness, edema, gastrointestinal bleeding, acne, heart failure, and heartburn. Although subcutaneous hematoma and pinhole hemorrhage appeared occasionally in the

TABLE 3 The subgroup analysis for the outcomes of included studies.

Subgroup	Eligible studies	Intervention group (n)	Control group (n)	RR/SMD (95% CI)	*P* value	Heterogeneity test	Effect model
Total effective rate							
Acupuncture categories							
MA vs. MT	19	1,002	988	1.25 [1.20, 1.30]	<0.001	$P = 0.04, I^2 = 39\%$	Fixed
WA vs. MT	5	143	143	1.27 [1.13, 1.43]	<0.001	$P = 0.98, I^2 = 0\%$	Fixed
EA vs. MT	2	84	72	1.26 [1.07, 1.49]	<0.001	$P = 0.88, I^2 = 0\%$	Fixed
Total sessions of treatment							
<15	8	381	290	1.28 [1.20, 1.37]	<0.001	$P = 0.77, I^2 = 0\%$	Fixed
Greater than or equal to 15	17	723	581	1.24 [1.19, 1.29]	<0.001	$P = 0.08, I^2 = 35\%$	Fixed
Pain intensity							
Acupuncture categories							
MA vs. MT	4	183	182	−3.16 [−4.48, −1.83]	<0.001	$P < 0.01, I^2 = 94\%$	Random
EA vs. MT	3	115	102	−0.50 [−0.89, −0.12]	<0.001	$P = 0.14, I^2 = 48\%$	Fixed
RA vs. SA	2	60	59	−0.34 [−0.89, 0.20]	0.22	$P = 0.14, I^2 = 53\%$	Random
Total sessions of treatment							
<15	3	100	99	−1.98 [−4.06, 0.10]	0.060	$P < 0.01, I^2 = 97\%$	Random
Greater than or equal to 15	4	186	173	−2.08 [−3.96, −0.19]	0.030	$P < 0.01, I^2 = 98\%$	Random
Pain threshold							
Acupuncture categories							
MA vs. MT	2	60	50	1.82 [1.06, 2.59]	<0.001	$P = 0.10, I^2 = 64\%$	Random
WA vs. MT	1	30	30	2.57 [1.88, 3.27]	<0.001	NA	Random
Recurrence rate							
Acupuncture categories							
WA vs. MT	2	55	55	0.38 [0.16, 0.88]	0.020	$P = 0.90, I^2 = 0\%$	Fixed
EA vs. MT	1	49	37	0.14 [0.03, 0.58]	0.007	NA	Random

RR, risk ratio; SMD, standardized mean difference; 95% CI, 95% confidence interval; MT, medicine treatment; MA, manual acupuncture; EA, electroacupuncture; WA, warm acupuncture; RA, real acupuncture; SA, sham acupuncture; NA, not applicable.

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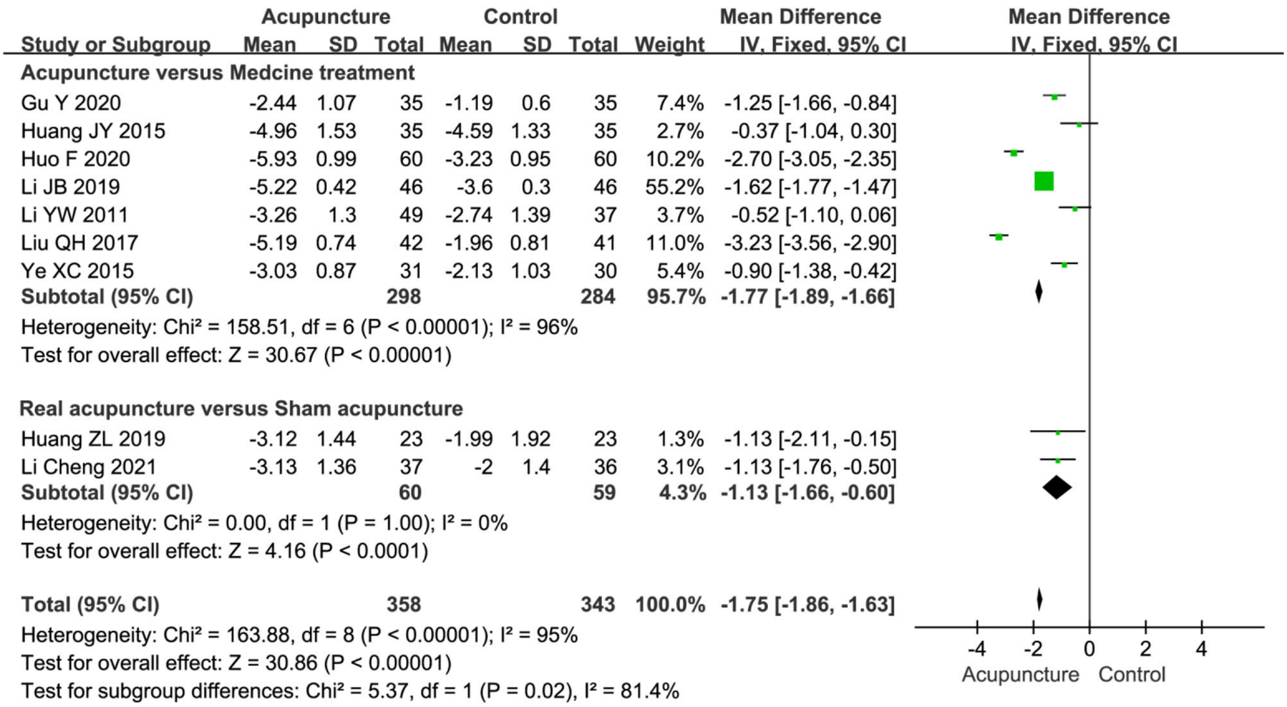

FIGURE 5
A Forest plot for pain intensity.

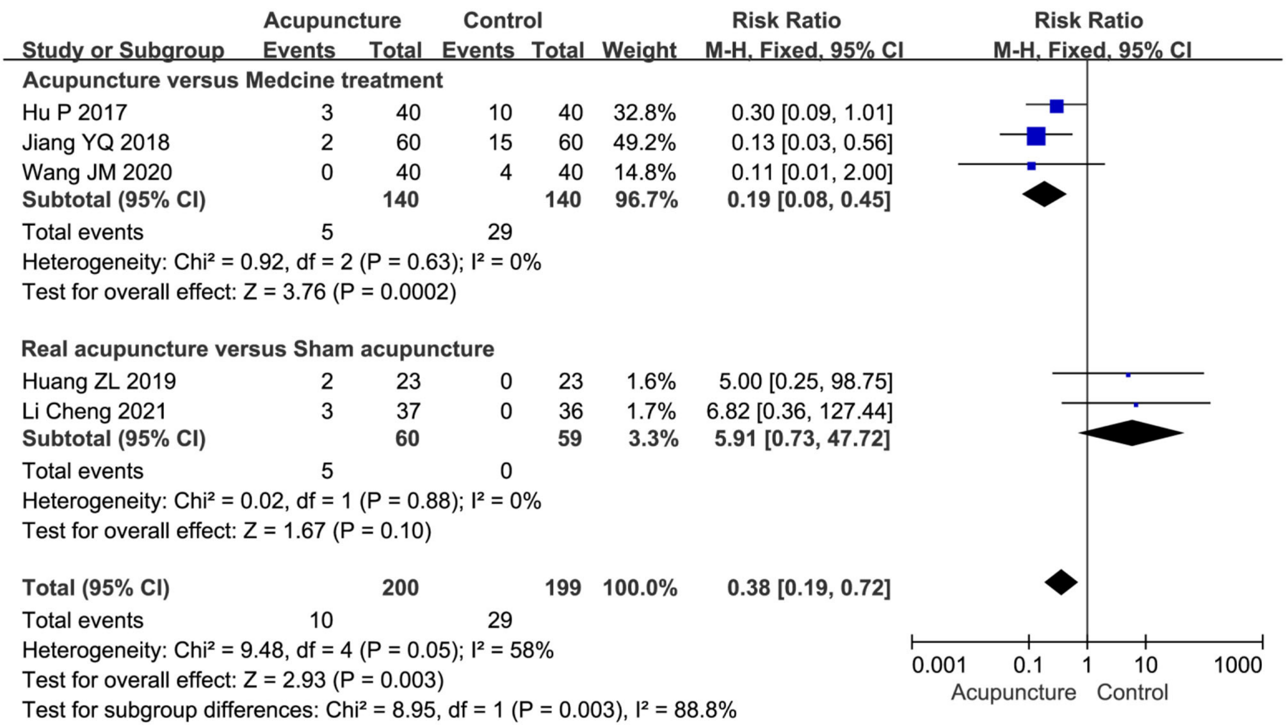

FIGURE 6
A Forest plot for adverse events.

process of acupuncture therapy, there was no statistically significant difference between real acupuncture and SA based on the two studies (Huang et al., 2019; Li et al., 2021) (RR = 5.91, 95%CI [0.73, 47.72]) (Figure 6).

Sensitivity analysis

As regards the high heterogeneity found in the comparison of acupuncture vs. MT on VAS pain score ($I^2 = 96\%$) and pain threshold ($I^2 = 69\%$), we performed the sensitivity analysis. By excluding studies individually, there was no significant change in the pooled effect size of the VAS score, but an extremely weak decrease in heterogeneity was observed when one study was excluded (Li et al., 2019) (Supplementary Table 5). Moreover, from the results of the Baujat plot, we found that two studies (Liu, 2017; Li et al., 2019) unduly influenced heterogeneity as well as the pooled effect of the VAS score (Figure 7). In the sensitivity analysis of pain threshold, the results showed that the I^2 value significantly decreased from 69 to 0% after the exclusion of one study (Zou, 2017) (Supplementary Table 5), and there were two studies (Chen et al., 2005; Zou, 2017) that contributed overly to the heterogeneity from the results of the Baujat plot (Figure 7).

Publication bias

We drew the funnel plot (Figure 8A) and used Peters' test ($t = 1.500$, $P = 0.146$) to calculate the outcome of the total effective rate, which indicated no publication bias. However, publication bias in the outcome of pain intensity may exist due to the asymmetrical funnel distribution and Egger's test ($t = -3.562$, $P = 0.009$) (Figure 8B).

Certainty of evidence

The results of the GRADE score are summarized in Supplementary Table 6. The quality of evidence for these two outcomes (total effective rate and adverse events) was both rated as "moderate quality," while the evidence of recurrence rate was rated as "low quality" and the rest of the outcomes (pain threshold and pain Intensity) were rated as "very low quality".

Discussion

This systematic review and meta-analysis demonstrated that acupuncture was more effective than MT or SA, with respect to reducing the VAS score, the recurrence rate and improving the total effective rate and pain threshold. In addition, a few adverse events were observed in the follow-up duration. Consistently, pooled effects of primary outcomes remained stable in the subgroup analysis apart from high heterogeneity in some results. Owing to concerns on the methodological quality and poor reporting quality, the aforementioned conclusions should be interpreted with great caution.

Our results showed that the quality of evidence on the outcomes ranged from very low to moderate. Moderate-certainty evidence showed that acupuncture was superior to MT in terms of the total effective rate and adverse events. However, we found that there was very low-certainty evidence showing that acupuncture offered greater pain relief than MT by reducing the VAS score and increasing the pain threshold, which was mainly related to the weakness of the study design and methodology in the included studies. Moreover, there was low-certainty evidence showing that a lower recurrence rate was observed in the patients with acupuncture treatment compared with MT at a long-term follow-up period.

Subgroup analysis of the pooled data was conducted to explore further the potential sources of significant heterogeneity observed in the 30 included studies. The results of the subgroup analysis showed that all types of acupuncture interventions obtained better results than MT, while the MA contributes to high heterogeneity in the outcome of pain intensity. Conversely, the EA subgroup significantly reduced the heterogeneity. As a type of acupuncture method, EA is being gradually used in clinical practice with unique advantages of combining traditional acupuncture therapy and absorbing the modern electronic theory. Compared with MA, EA was advocated to be more precise in the amount of needle stimulation. Furthermore, the SA group setting was an ideal method for controlling the placebo effects. Among the included studies, the SA group setting was used in two studies (Huang et al., 2019; Li et al., 2021). Huang and colleagues (Huang et al., 2019) found that acupuncture had a better effect than SA in relieving the symptoms of sciatic pain, and the same conclusion has been drawn in another study (Li et al., 2021). Unfortunately, no significant pooled effect was observed in the subgroup analysis of pain intensity, partly due to the limited number of included studies. So, it was necessary to investigate further the potential placebo effect in the future. Additionally, we observed that more sessions of acupuncture might show a certain degree of heterogeneity, which was most likely due to more reporting bias and difficulty in compliance in a long course of treatment.

Sensitivity analysis and Baujat plot were applied to evaluate the heterogeneity among studies in this review. Greater heterogeneity was observed in two studies on the total effective rate (Li and Kang, 2016; Zheng, 2019), while two other studies focused on pain intensity (Liu, 2017; Li et al., 2019). All the aforementioned studies belonged to the MA subgroup, and a few details on acupuncture were reported in two studies (Li et al., 2019; Zheng, 2019), which resulted in high heterogeneity in clinical methodologies. In addition, we focused on publication bias in primary outcomes. Significant publication bias was detected in pain intensity instead of the total effective rate. All the included studies in this meta-analysis were conducted in China, which was a source of potential publication bias.

In the theory of traditional Chinese medicine (TCM), sciatica belongs to the category of "bi" disease and "waist and leg pain" syndrome, which is mainly caused by the poor operation of "qi and blood" that flows through the bladder meridian and the gallbladder meridian. Acupuncture was suggested as a widely used non-pharmacological intervention for pain control, with the advantages of various treatment modalities (i.e., MA, EA, and WA) and minor side effects (Qiao et al., 2020). Inflammatory and neuropathic pain can be relieved effectively by acupuncture. It is the main mechanism involved in the alternation of blood rheology, immune defense, and neuromediators. Considering the particularity of acupuncture treatment, it is significant to assess the quality of the report on acupuncture intervention using the STRICTA checklist. The

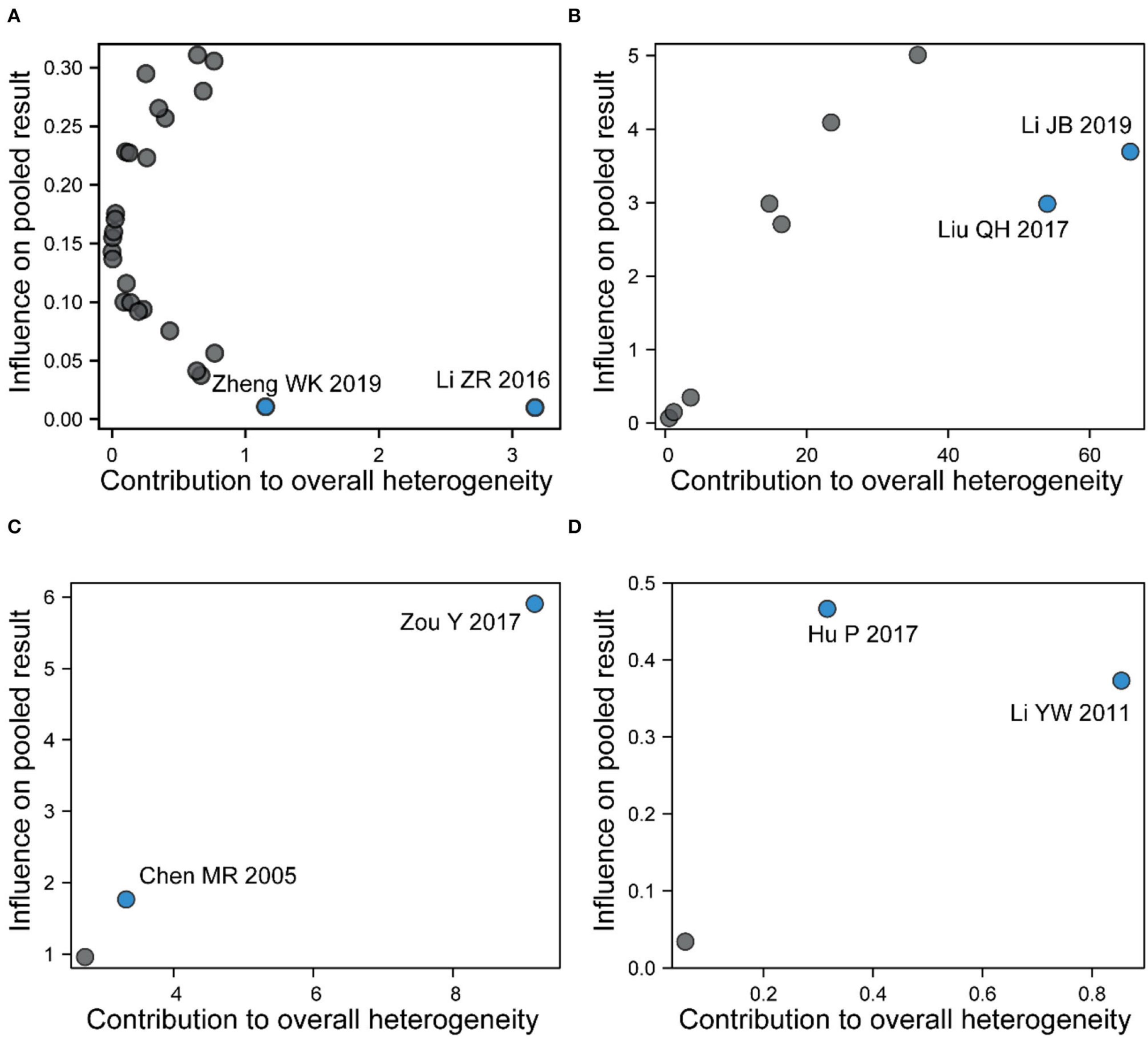

FIGURE 7
A Baujat plot for **(A)** total effective rate, **(B)** pain intensity, **(C)** pain threshold, and **(D)** recurrence rate. Each circle indicates an individual study, while the circle in blue indicates the study contributing more to heterogeneity and pooled effect.

overall quality of interventions reported in the controlled trials of acupuncture was relatively good, though it still needs to be improved in details pertaining to needle insertion and treatment context. Additionally, we found that GB30, BL25, BL4, BL60, BL23, BL54, and GB34 were the most frequently used acupoints during acupuncture therapy. According to the TCM-based acupuncture meridian system, these selected primary acupoints are sciatic nerve-related acupoints consistent with clinically recommended commonly used primary acupoints (Zhang et al., 2020). With the more detailed elucidation of the stimulation mechanism of each acupoint, it is expected that more effective treatment strategies could be established based on the main symptoms of patients with sciatica.

Previous reviews investigated the effectiveness of acupuncture therapy for sciatica in 2015, while the lack of evaluation of acupuncture intervention details and evidence of quality, insufficient sample size, and a relatively inadequate assessment for heterogeneity limited the strength of conclusions (Ji et al., 2015; Qin et al., 2015). Compared to previous studies, our study had four novel advancements. First, more studies with a larger sample size were included to further enhance the reliability and stability of the meta-analysis. Second, the STRICTA checklist was added to raise the quality of reporting of the clinical trials of acupuncture. Next, acupuncture-associated subgroups not mentioned before (i.e., types of acupuncture interventions and sessions of treatment) were introduced for further analysis. In addition, the recurrence rate as a long-term outcome measure was considered as the secondary outcome mainly due to the characteristic of chronic and easy-to-relapse nature during the course of the disease. Finally, we assessed the quality level of the evidence and took into account the level of certainty of evidence for each outcome.

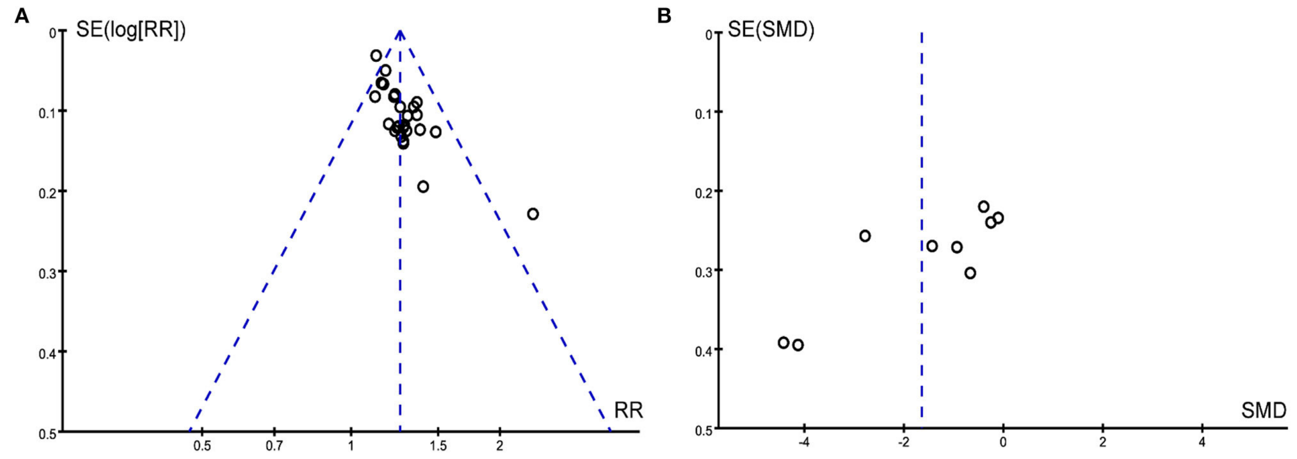

FIGURE 8
Funnel plots for **(A)** the total effective rate and **(B)** pain intensity.

However, of course, there are still the following limitations in this review: (1) there were insufficient studies that compared acupuncture with SA supporting to avoid placebo effects, while fewer studies have been included currently; (2) the diversity of acupuncture methods, especially MA, contributed to the heterogeneity of the clinical outcome, and the results based on the STRICTA checklist found that the reporting of acupuncture details in existing studies is still incomplete, which limits our possibility to improve the quality of clinical evidence; and (3) the included studies still used efficiency as the primary assessment of acupuncture effectiveness. Nevertheless, pain intensity and pain threshold, indicators of patient pain evaluation, are still rarely used as the primary assessment in the literature. Therefore, changes in pain on patients with sciatica require further attention in the future.

In the future research on RCTs, well-designed and methodologically rigorous studies are needed to evaluate the true effects of acupuncture objectively on sciatica with a view to ultimately providing high-quality evidence for clinical practice. Fewer studies are currently undergoing pre-registration, and we strongly urge registry centers to prospectively register study protocols so that others follow these studies. In addition, it is quite difficult to achieve the blinding of acupuncturists but may be necessary and feasible for patients and outcome assessors. The assessment of outcome indicators also needs to be conducted on a uniform scale. In addition, high heterogeneity was reflected in a set of acupuncture-related factors, including acupoints, retention time of needles, acupuncturists' qualifications, and so on, and exploring heterogeneity in depth depends on the detailed description of the aforementioned factors. Therefore, we also expect that, with the help of the STRICTA checklist, more standardized acupuncture RCTs can be expected in the recent future.

Conclusion

In summary, acupuncture therapy on sciatica was superior to MT or SA intervention, both in terms of clinical efficacy and safety, which suggested that acupuncture could be recommended as a feasible alternative therapy for patients with sciatica. However, given the high heterogeneity and low methodological quality of previous studies, future RCTs should be well-designed according to the rigorous methodology.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Author contributions

GN, XinZ, and XiaZ designed the study. XinZ and XiaZ designed the search strategy. PH and ZH searched, screened studies, and assessed the risk of bias. ZZ and TH extracted the data. MY and ZH finished the reports on acupuncture interventions based on the STRICTA checklist. ZZ, TH, and PH analyzed the data. ZZ, XinZ, and YX wrote and drafted the manuscript. GN and XinZ provided administrative, technical, or administrative support. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1097830/full#supplementary-material

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Global trends of traditional Chinese exercises for musculoskeletal disorders treatment research from 2000 to 2022: A bibliometric analysis

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Background: Traditional Chinese exercise has been shown to be effective in relieving long-term chronic pain, physical dysfunction, decreased ability to participate in society and decreased quality of life in musculoskeletal diseases. In recent years, there has been a steady increase in publications on the treatment of musculoskeletal disorders by traditional Chinese exercises. The purpose of this study is to review the characteristics and trends of Chinese traditional exercise studies on musculoskeletal diseases published since 2000 through bibliometric analysis, and identify current research hotspots, so as to guide the direction of future research.

Methods: Publications regarding traditional Chinese exercises for musculoskeletal disorders from 2000 to 2022 were downloaded from the Web of Science Core Collection. VOSviewer 1.6.18 and CiteSpace V software were used for bibliometric analyses. Bibliometric visualization and comparative analysis were conducted for authors, cited authors, journals, co-cited journals, institutions, countries, references, and keywords.

Results: A total of 432 articles were obtained, with an upward trend over time. The most productive countries and institutions in this field are the USA (183) and Harvard University (70). Evidence-based Complementary and Alternative Medicine (20) was the most prolific journal, Cochrane Database System Review (758) was the most commonly cited journal. Wang Chenchen published the largest number of articles (18). According to high frequency keywords, the hot spot musculoskeletal disorder and the type of traditional Chinese exercise are knee osteoarthritis and Tai Chi.

Conclusion: This study provides a scientific perspective for the research of traditional Chinese exercises for musculoskeletal disorders and provides valuable information for researchers to discover the current research status, hot spots and new trends of future research.

KEYWORDS

traditional Chinese exercises, musculoskeletal disorders, bibliometric, VOSviewer, CiteSpace

Background

Musculoskeletal disorders are a group of diseases of the body's motor structures, particularly the bones, joints, muscles, fascia, and other supporting structures such as ligaments and cartilages (Safiri et al., 2021). Musculoskeletal disorders include neck pain, low back pain, osteoarthritis, rheumatoid arthritis and other diseases (Jin et al., 2020). Many musculoskeletal disorders are recurrent or lifelong, with the main consequences are long-term chronic pain, physical dysfunction, self-care ability, social participation and reduced quality of life (Tung et al., 2021). Patients with musculoskeletal disorders are more likely to suffer from depression, anxiety, and further exacerbation of musculoskeletal disorders (Singh, 2022). Long-term musculoskeletal disorders may even increase the incidence of accidental disability and death, especially in the elderly. According to the WHO, falls are the leading cause of injury and death among older adults which also the second leading cause of unintentional injury deaths worldwide. Musculoskeletal disorders such as muscle weakness, knee osteoarthritis, and fractures are risk factors for falls (Dunlop et al., 2014; Wang et al., 2022b). Epidemiological studies in many developed countries show that musculoskeletal disorders are characterized by high rates of disability and absenteeism (Shanahan, 2019). It has a serious negative impact on the social life and emotions of patients, especially elderly patients. It causes great trouble to human health and great economic burden to individuals, families and even the society (Wu et al., 2021). Studies have shown that obesity, poor nutrition, smoking habits, excessive exercise and occupational injuries are all risk factors for musculoskeletal disorders.

Adjusting diet, moderate exercise, quitting smoking and drinking, are considered to be effective ways to reduce the incidence of muscle diseases and treat musculoskeletal diseases (Gwinnutt et al., 2022a,b). Traditional Chinese exercises is a kind of physical and mental exercise and complementary medical exercise therapy with Chinese cultural characteristics (Guo et al., 2016). Common traditional Chinese exercises include Tai Chi, Yi Jin Jing, Baduanjin, Wuqinxi and so on (Feng et al., 2020). Traditional Chinese exercises are low-intensity aerobic exercise suitable for people of all ages due to its slow and gentle movements. For example, Tai Chi is a traditional Chinese exercise which is widely regarded as a physical and mental exercise (Zou et al., 2018). Tai Chi is widely practiced for its health benefits (Lan et al., 2013). Tai Chi is a low intensity, non-competitive and non-impact exercise. It puts emphasis on the coordination of breathing, thinking and physical activity. The traditional Chinese exercises are gradually formed on the basis of the holistic concept of Traditional Chinese medicine, with the theory of five elements, Yin and Yang, meridians and zangfu. Many studies have shown that Tai Chi is beneficial for the medical management of musculoskeletal disorders such as neck pain, low back pain, knee osteoarthritis, Fibromyalgia and so on (Zhang et al., 2017; Slomski, 2018; Xie et al., 2021; Wang et al., 2022a.

Bibliometrics is widely used to discover research hotspots and analyze research results and research trends, which can help researchers identify current research hotspots and guide future research directions. In recent years, bibliometrics has been applied to Traditional Chinese exercises research fields, such as Tai Chi and traditional Chinese exercises for pain so on (Zhang et al., 2020a; You et al., 2021). But no article has ever been written to analyze the treatment of musculoskeletal disorders by traditional Chinese exercises from a bibliometric perspective.

Therefore, from the perspective of bibliometrics, this article sorts out and summarize the development, research hotspots and development trends of traditional Chinese exercises for musculoskeletal research. The aim of this study is to provide an overview of the published characteristics and trends of traditional Chinese exercises for musculoskeletal disorders since 2000 through bibliometric analysis.

Materials and methods

Data sources and search strategy

We selected Web of Science Core Collection (WoSCC) as the data source to identify and extract relevant publications. To cover as many target documents as possible, we chose terms that most scientific publications might use to build the search strategy. Terms related to traditional Chinese exercises and musculoskeletal disorders were extracted from the Medical Subject Headings (MeSH) in PubMed (**Supplementary material** for retrieval information). In order to avoid possible problems such as duplication, missing or inconsistency with the theme, it is necessary to screen and standardize the data before analysis to avoid the quality of the data itself affecting the results. The detailed search strategy is in **Supplementary material**.

The inclusion criteria are as follows:(1) The literature retrieval period is from 1 January 2000 to 14 August 2022; (2) the literature type is "article" and "review;" and (3) the language type is English.

The exclusion criteria are as follows: (1) The literature whose research topic was not related to the traditional Chinese exercise exercises for musculoskeletal diseases; (2) Letters, reports, short papers or briefs.

The errata type of documents resulted in 432 papers. The data collection flow chart is shown in **Figure 1**.

The steps of data review and screening in this study were as follows: (1) Two team members independently reviewed the articles and screened out the articles which were inconsistent with the research topic. These controversial articles were voted out by our team. (2) We corrected and harmonized of the selected articles, institutions and countries in order to avoid the influence of author, institution, country name on the results. (3) Keywords were standardized, because the non-standardized keywords would lead to meaningless repetition in the keyword co-occurrence graph due to the inconsistency of pos and plural and singular versions, so keywords were standardized.

For example, the three keywords of "metaanalysis," "meta analysis," and "Meta analysis" are unified as "meta-analysis" in this study.

Statistical analysis

VOSviewer 1.6.18 and CiteSpace 6.1.R1 software were used to conduct bibliometrics analysis on key characteristics of literatures such as the number of publications, countries/regions, institutions, authors, journals, literatures, keywords and so on. VOSviewer and CiteSpace are widely used bibliometric tools. VOSviewer is a freely available program which has the added advantage of graphical representation in bibliometric mapping by displaying large bibliometric maps in an easy-to-interpret manner. CiteSpace

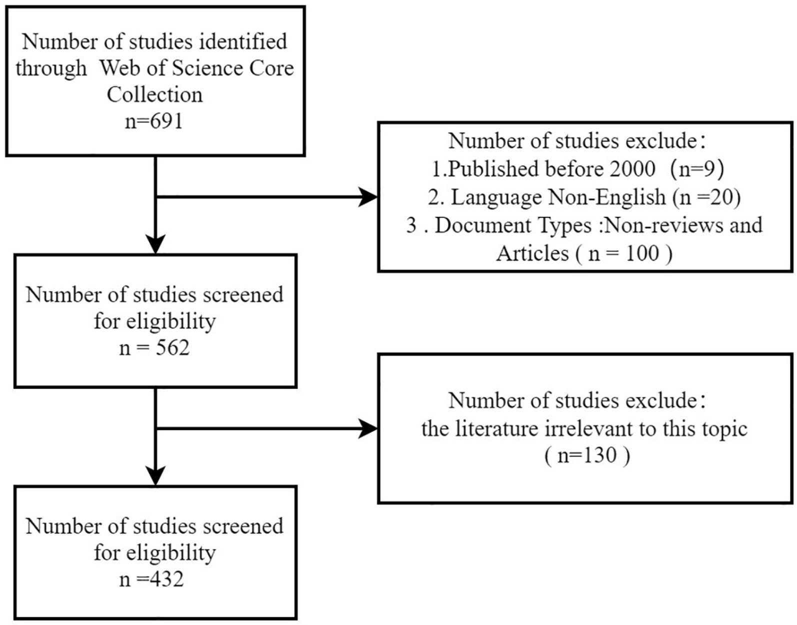

FIGURE 1
Flow diagram of literature search and screening.

is a free and available program, which has greater advantages in intuitively catching up the research hotspots and evolutionary processes of various fields in the knowledge system and predicting the development trends of various fields.

Results

Analysis of annual publications

Figure 2 shows the number of published in the field of traditional Chinese exercises for musculoskeletal disorders. From 2000 to 2006, there were few publications on the treatment of musculoskeletal disorders by traditional Chinese exercises. The number of articles was no more than five which indicated that this research field has not received attention. The number of publications from 2007 to 2014 was significantly higher than that before 2006, but the number of publications during the period did not change much, indicating that this field has gradually attracted attention. From 2014 to 2021, the number of publications was increased. Although the number of documents issued will decrease after 2020, this may be because the arrival of COVID-19 has hindered the traditional Chinese exercises, which is mainly clinical research. This trend is consistent with what has been observed in other areas of research. From the trend of Figure 2, It is found that more research on traditional Chinese exercises for musculoskeletal disorders is being conducted.

Analysis of journal

A total of 432 publications related to Chinese traditional exercise for musculoskeletal disorders were published in 209 journals. Table 1 shows the top 10 journals in terms of number of publications. Most of the publishers of these journals are located in the USA or England. The top three journals in terms of the number of publications are Evidence Based Comprehensive and Alternative Medicine, Medicine and Journal of Alternative and Comprehensive Medicine.

The analysis of co-citation journals shows that important knowledge sources are distributed in a specific field. Our statistical analysis results show that 4,113 articles published in Chinese traditional exercise for musculoskeletal disorders have been co-cited.

Table 2 shows the top 10 cited journals in terms of number of publications. The most frequently cited journal is Cochrane Database of Systematic Reviews, followed by Journal of Rheumatology and Pain. We found that most of the top 10 journals cited were in Q1, indicating that the research in this field mainly cited high-quality journals. According to the citation analysis of journals, the most cited journal is Annals of Internal Medicine, a high-level journal in the medical field, with a total of six articles, a single article was cited 75.83 times. This shows that the quality of the articles published in this journal is high and have received extensive attention in this research field.

Figure 3 is a dual-map superposition of the references in traditional Chinese exercises for musculoskeletal disorders research. Cited journals are on the left and co-cited journals are on the right. The reference link comes from the journal on the left side of the map and points to the journal on the right side of the map. The green path indicates that documents published in "medicine, medical clinical" journals are often cited by "health, nursing, medicine, sports, rehabilitation, sport" and "psychology, education, social" journals. Pink path indicates that documents published in journals are often cited by "health, nursing, medicine, sports, rehabilitation, sport" journals.

Analysis of country and institutions

VOSviewer is used to generate a network visualization map. In order to make the network clear, 16 countries/regions that publish at

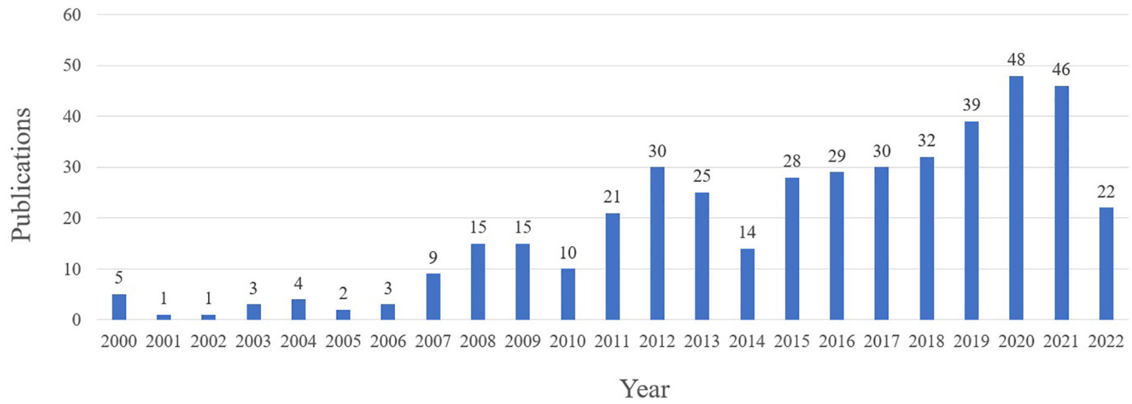

FIGURE 2
The number of annual publications on traditional Chinese exercises for musculoskeletal disorders research from 2000 to 2022.

TABLE 1 Top 10 journals with the highest frequency with traditional Chinese exercises for musculoskeletal disorders.

Rank	Journal	Publications	Country	Citations (WoS)	Average citation/ publication	Impact factor (2021)	Categories	Quartile (JCR)	OA
1	Evidence-Based Complementary and Alternative Medicine	20	England	342	17.10	2.650	Integrative and complementary medicine	Q3	Yes
2	Medicine	18	USA	38	2.11	1.817	Medicine, general, and internal	Q3	Yes
3	Journal of Alternative and Complementary Medicine	17	USA	390	22.94	2.381	Integrative and complementary medicine	Q3	No
4	Complementary Therapies in Medicine	10	England	172	17.20	3.335	Integrative and complementary medicine	Q2	Yes
5	Bmc Musculoskeletal Disorders	7	England	185	26.43	2.562	Orthopedics rheumatology	Q3; Q4	Yes
5	Cochrane Database of Systematic Review	7	England	767	109.57	11.874	Medicine, general, and internal	Q1	No
5	Osteoarthritis and Cartilage	7	England	245	35.00	7.507	Orthopedics rheumatology	Q1; Q1	No
5	Pain Medicine	7	USA	245	35.00	3.637	Anesthesiology medicine, general, and internal	Q2; Q2	No
5	Trials	7	England	56	8.00	2.728	Medicine, general, and internal	Q4	Yes
10	Arthritis Care and Research	6	USA	2,132	355.33	5.178	Rheumatology	Q2	No
10	British Journal of Sports Medicine	6	England	657	109.50	18.479	Sport sciences	Q1	No
10	Current Pain and Headache Reports	6	USA	290	48.33	3.904	Clinical neurology	Q2	No
10	Journal of Physical Therapy Science	6	Japan	92	15.33	0.392	Rehabilitation	Q4	No
10	PLoS One	6	USA	333	55.50	3.752	Multidisciplinary sciences	Q2	Yes

least five articles are visualized. The size of the node is determined by the number of published articles (the more the number, the larger the node). The lines between nodes represent the cooperation between countries/regions (the stronger the cooperation, the wider the lines). The number of total link strength reflects the strength of cooperation between countries/regions. From 2000 to 2022, articles on traditional Chinese exercises for musculoskeletal disorders came from 38 different countries/regions independently or cooperatively.

TABLE 2 Top 10 cited journals with the highest frequency with traditional Chinese exercises for musculoskeletal disorders.

Rank	Journal	Citations	Country	IF (2021)	Categories	Quartile (JCR)
1	Cochrane Database of Systematic Reviews	758	England	11.874	Medicine, general and internal	Q1
2	Journal of Rheumatology	556	Canada	5.346	Rheumatology	Q2
3	Pain	502	USA	7.926	Neurosciences clinical neurology anesthesiology	Q1; Q1; Q1
4	Arthritis & Rheumatism-Arthritis Care & Research (Arthritis and Rheumatism)	489	USA	/	Rheumatology	/
5	Archives of Physical Medicine and Rehabilitation	453	USA	4.06	Rehabilitation sport sciences	Q1; Q1
6	Journal of Alternative and Complementary Medicine	408	USA	2.381	Integrative and complementary medicine	Q3
7	Spine	402	USA	3.269	Orthopedics clinical neurology	Q3; Q2
8	Journal of the American Geriatrics Society	392	USA	7.538	Gerontology geriatrics and gerontology	Q1; Q1
9	Annals of Internal Medicine	329	USA	51.598	Medicine, general, and internal	Q1
10	Osteoarthritis and Cartilage	327	England	7.507	Orthopedics rheumatology	Q1; Q1

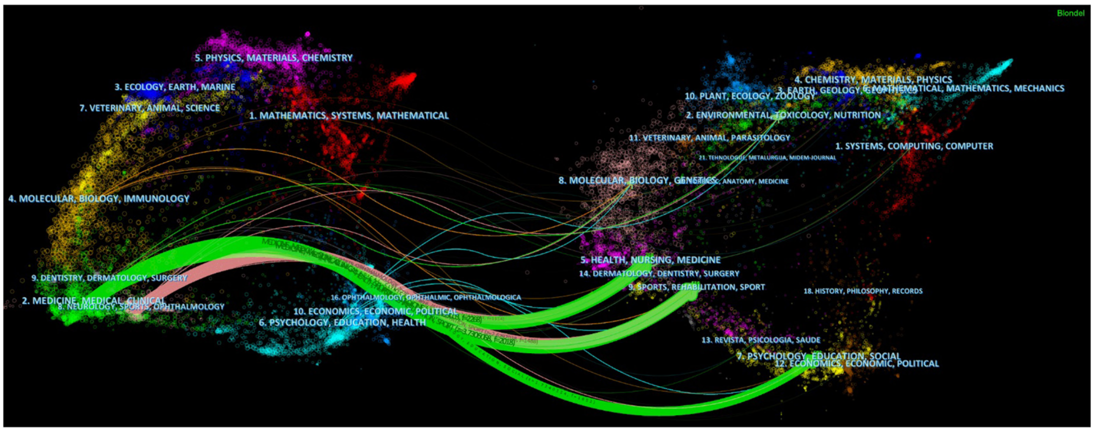

FIGURE 3
The dual-map overlay of journals.

TABLE 3 Top 10 countries for publications of traditional Chinese exercises for musculoskeletal disorders.

Rank	Country	Publications	Citations	Average citations/ publication
1	USA	183	9,308	50.86
2	China	129	2,151	16.67
3	Canada	41	4,602	112.24
4	Australia	31	1,761	56.81
5	Germany	25	828	33.12
6	England	23	1,129	49.09
7	South Korea	16	568	35.5
8	Italy	12	107	8.92
9	Spain	11	222	20.18
9	Sweden	11	422	38.36

Table 3 shows top 10 countries for publications of traditional Chinese medicine in musculoskeletal disorder. The publications authors are mainly from the USA, with 183 articles published, followed by China (129). Canada (41), Australia (31), and Germany (25) also made considerable contributions to the research of Chinese traditional exercise for musculoskeletal disorders.

Table 4 shows top 10 institutions with the highest frequency of traditional Chinese exercises for musculoskeletal disorders. In order to make the network clear, 36 institutions that publish at least five articles are visualized (Figure 4). The top 10 institutions with the largest number of publications have been identified, including 4 from China, 3 from the USA, 2 from Australia, 1 from Canada and 1 from Germany. The distribution of the top 10 organizations in terms of the number of documents issued is consistent with the distribution characteristics of each country. Among them, Harvard University contributed 31 articles to the largest number of publications in the USA. Shanghai University of Traditional Chinese Medicine contributed 17 articles to the largest number of publications in China. From the time line of articles published by institutions generated by VOSviewer, around 2020, university of traditional Chinese medicine, especially Shanghai University of Traditional Chinese Medicine and Chengdu University of Traditional Chinese Medicine paid more attention to the research of traditional Chinese exercises on musculoskeletal treatment.

TABLE 4 Top 10 Institutions with the highest frequency of traditional Chinese exercises for musculoskeletal disorders.

Rank	Country	Publications	Citations	Average citations/ publication
1	Harvard University	31	972	31.35
2	Tufts University	22	1,616	73.45
3	Shanghai University of Traditional Chinese Medicine	17	139	8.18
4	Shanghai University of Sport	15	255	17.00
5	University of Ottawa	13	2,077	159.77
6	The Chinese University of Hong Kong	12	456	38.00
7	University of Duisburg-Essen	12	427	35.58
8	Fujian University of Traditional Chinese Medicine	11	161	14.64
9	North Carolina University	11	970	88.18
10	The University of Sydney	10	961	96.10
10	University of Toronto	10	1,180	118.00

Analysis of authors

Table 5 shows the top ten authors in this field. Among the authors in the field of traditional Chinese exercises for musculoskeletal disorders, Wang CC published the most articles (Zhang et al., 2017), which were cited 946 times, with an average of 52.56 times. Three of the top five articles cited in total are published by Wang CC. The top five active authors all published at least 10 articles. Mcalindon Timothy is the researcher who has cited the most per article, with an average of 93.86 times for each article.

TABLE 5 Top 10 authors for publications on traditional Chinese exercises for musculoskeletal disorders.

Rank	Author	Publications	Citations	Average citations/ publication
1	Wang, Chenchen	18	946	52.56
2	Harvey, William F	11	356	32.36
3	Driban, Jeffrey B	10	401	40.10
3	Price, Lori Lyn	10	401	40.10
3	Zou, Liye	10	330	33.00
6	Wayne, Peter M	9	248	27.56
7	Dobos, Gustav	8	290	36.25
8	Cramer, Holger	7	138	19.71
8	Mcalindon, Timothy	7	657	93.86
8	Rones, Ramel	7	655	93.57

Analysis of cited reference and co-cited reference

Table 6 shows the most cited articles in the field of traditional Chinese exercises for musculoskeletal disorders. Among the top 10 most cited publications on traditional Chinese exercises for musculoskeletal disorders, there was five systematic reviews, three guideline literature, one clinical randomized controlled trial and one review. The results show that high quality systematic review can sort out the evidence of clinical research in this field and get higher level evidence.

Co-citation means that two articles appear in the citation of the third cited article at the same time, thus forming a co-citation relationship. Co-citation indicates that the cited literature is related to the corresponding research in terms of content and the literature usually contains high-quality content with significant influence in a specific research field. In addition, the relationship between literature co-citations may change over time. The study of the influence of network on literature co-citation can facilitate the investigation of the development and evolution of specific disciplines.

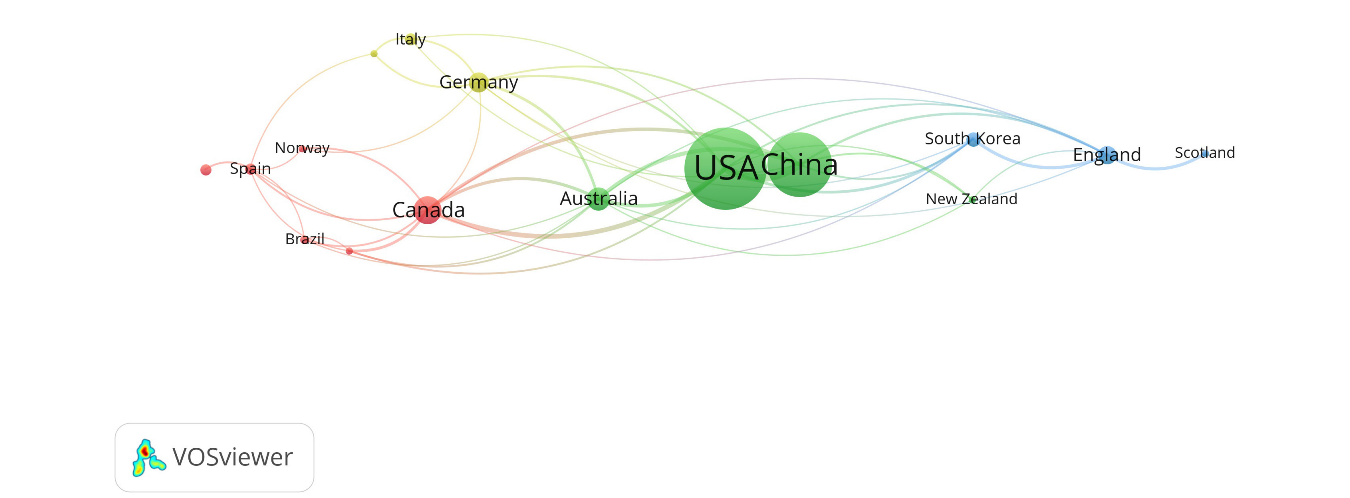

FIGURE 4
Map of countries with publications in traditional Chinese exercises for musculoskeletal disorders research from 2000 to 2022.

TABLE 6 The top 10 references based on the number of citations traditional Chinese exercises for musculoskeletal disorders.

Rank	Citations		First author	Corresponding author	Document type	Year	Journal	IF (2021)
1	1,817	American College of Rheumatology 2012 recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee	Hochberg, Marc C.	Hochberg, Marc C	Article	2012	Arthritis Care and Research	5.178
2	911	Non-invasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians	Qaseem, Amir	Qaseem, Amir	Article	2017	Annals of Internal Medicine	51.598
3	626	2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee	Kolasinski, Sharon L.	Kolasinski, Sharon L	Article	2020	Arthritis and Rheumatology	15.483
4	341	Non-pharmacologic therapies for low back pain: A systematic review for an American College of Physicians Clinical Practice Guideline	Chou, Roger	Chou, Roger	Review	2017	Annals of Internal Medicine	51.598
5	308	Exercise for osteoarthritis of the knee: A Cochrane systematic review	Fransen, Marlene	Van der Esch, Martin	Review	2015	British Journal of Sports Medicine	18.479
6	299	The effect of Tai Chi on health outcomes in patients with chronic conditions–A systematic review	Wang, CC	Wang, CC	Review	2004	Archives of Internal Medicine	/
7	260	Effects of Tai Chi exercise on pain, balance, muscle strength, and perceived difficulties in physical functioning in older women with osteoarthritis: A randomized clinical trial	Song, R	Bae, SC	Article	2003	Journal of Rheumatology	5.346
8	255	Physical activity and exercise for chronic pain in adults: An overview of cochrane reviews	Geneen, Louise J	Geneen, Louise J.	Review	2017	Cochrane Database of Systematic Reviews	11.874
9	247	A review of the clinical evidence for exercise in osteoarthritis of the hip and knee	Bennell, Kim L.	Bennell, Kim L.	Review	2011	Journal of Science and Medicine in Sport	4.597
10	209	Tai Chi: Physiological characteristics and beneficial effects on health	Li, JX	Li, JX	Review	2001	British Journal of Sports Medicine	18.479

Table 7 shows the most frequently cited articles published in the field of traditional exercise exercises for musculoskeletal disorders. Among the top 10 most cited publications on traditional Chinese exercises for musculoskeletal disorders, there were seven clinical randomized controlled trials, two reviews, one guideline literature and one systematic review. The results show that high quality clinical research is the focus of researchers in this field, which is helpful for the research in the field of traditional Chinese exercises for musculoskeletal disorders.

Analysis of co-occurrence keyword

Keywords with high frequency can reveal hot spots in past research and keywords with strong burst power can predict future research frontiers. By August 2022, the top 10 keywords of frequency were Tai Chi, Exercise, Pain, Older Adult, Randomized Controlled Trial, Osteoarthritis, Quality of Life, Knee Osteoarthritis, Management and Low Back Pain (Table 8). According to the high-frequency keywords, we can infer that knee osteoarthritis is the most frequently studied musculoskeletal disorder in this field, and Tai Chi is the most frequently studied traditional Chinese exercises in this field.

In this study, 432 articles were merged and classified by VOSviewer, 83 keywords that were used more than 10 times were clustered and analyzed. The results are shown in Figure 5 and Table 9. In the VOSviewer keyword network visualization, 83 keywords are grouped into clusters and different clusters are labeled with different colors. As shown in Figure 5, The clusters of red, green and blue were found. The red and green clusters are relatively independent, while the blue clusters are associated with both red and green clusters. The main keywords in the red cluster are Randomized Controlled Trial; Low Back Pain; Meta Analysis; Rheumatoid Arthritis; The main keywords of green cluster Tai Chi; Exercise; Older Adult; Osteoarthritis; Quality of Life. The main keyword of blue cluster is Pain; Knee Osteoarthritis; Management.

The VOSviewer keyword symbiosis visualization hotspot map can identify hotspots in the field of traditional Chinese exercises for musculoskeletal research where most of the research was conducted.

TABLE 7 The top 10 co-cited references based on the number of citations traditional Chinese exercises for musculoskeletal disorders.

Rank	Citations	Title	First author	Corresponding author	Document type	Year	Journal	IF (2021)
1	91	Tai Chi is effective in treating knee osteoarthritis: A randomized controlled trial	Wang, CC	Wang, CC	Article	2009	Arthritis and Rheumatism	/
2	82	Effects of Tai Chi exercise on pain, balance, muscle strength, and perceived difficulties in physical functioning in older women with osteoarthritis: A randomized clinical trial	Song, R	Bae, SC	Article	2003	Journal of Rheumatology	5.346
3	67	Physical activity for osteoarthritis management: A randomized controlled clinical trial evaluating hydrotherapy or Tai Chi classes	Fransen, Marlene	Fransen, Marlene	Article	2007	Arthritis and Rheumatism	/
4	65	A randomized trial of Tai Chi for fibromyalgia	Wang, CC	Wang, CC	Article	2010	New England Journal of Medicine	176.082
5	63	Group and home-based Tai Chi in elderly subjects with knee osteoarthritis: A randomized controlled trial	Brismee, Jean-Michel	Shen, Chwan-Li	Article	2007	Clinical Rehabilitation	2.884
6	61	The effect of Tai Chi on health outcomes in patients with chronic conditions–A systematic review	Wang, CC	Wang, CC	Review	2004	Archives of Internal Medicine	/
7	51	Effects of t'ai chi training on function and quality of life indicators in older adults with osteoarthritis	Hartman, CA	Hartman, CA	Article	2000	Journal of The American Geriatrics Society	7.538
8	49	Tai chi Qigong for the quality of life of patients with knee osteoarthritis: A pilot, randomized, waiting list controlled trial	Lee, HJ	Lee, HJ	Article	2009	Clinical Rehabilitation	2.884
9	34	Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American rheumatism association	R. Altman	R. Altman	Review	1986	Arthritis and Rrheumatism	/
10	33	Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee	N Bellamy	N Bellamy	Review	1988	Journal of Rrheumatology	5.346
10	33	Challenges inherent to t'ai chi research: Part I–t'ai chi as a complex multicomponent intervention	Wayne, PM	Wayne	Review	2008	Journal of Alternative and Complementary Medicine	2.381

Keywords were clustered in the heat map, keywords with different frequencies presented different colors, such as the high density (red) among the above keywords.

Analysis of keyword burst

Keyword burst is a valuable indicator reflecting the most active research topic in this field. It can not only reflect research hotspots in this field, but also reflect changes in hotspots and predict future research trends. As shown in **Figure 6**, the top 15 keywords with the strongest strength of burst are presented. The changes in keyword outbreaks over the past 22 years have proved the evolution of the hotspots of traditional Chinese exercises for musculoskeletal disorders. The keyword "cardiorespiratory function" had a strength of 3.41 from 2000 to 2011. The keyword "self-efficiency" has the longest cycle, which is 12 years and the strength is 3.31. The remaining eight keywords which have received more attention since 2016 are the focus of current research in this field. The keywords of explosion include "outcome" (strength = 4.13), "physical therapy" (strength = 3.9), "neck pain" (strength = 3.2), "people" (strength = 3.24), "systematic review" (strength = 7.26), "disease" (strength = 3.99), "meta-analysis" (strength = 3.32) and "prevention" (strength = 3.25).

Discussion

General information

From 2000 to 2022, the number of publications on traditional Chinese exercises for musculoskeletal disorders showed an increasing

TABLE 8 Top 20 keywords in the treatment of traditional Chinese exercises for musculoskeletal disorders.

Rank	Keyword	Frequence
1	Tai chi	231
2	Exercise	152
3	Pain	112
4	Older adult	105
5	Randomized controlled trial	103
6	Osteoarthritis	85
6	Quality of life	85
8	Knee osteoarthritis	80
9	Management	80
10	Low back pain	71
11	Physical activity	58
12	Meta analysis	53
13	Balance	51
14	Rheumatoid arthritis	50
15	Health	49
16	Qigong	48
17	Clinical trials	46
18	Efficacy	43
19	Fibromyalgia	42
20	Arthritis	39

trend. This research field has attracted more and more scholars' attention and become a new hot field. This phenomenon may be related to the clinical effect of Chinese traditional exercise as complementary alternative medicine and sports medicine in the treatment of musculoskeletal disorders.

The top 10 journals published 130 articles, accounting for 30.09% of the total number of articles published, indicating that the top 10 academic journals have a strong interest in the articles on musculoskeletal research of traditional Chinese exercises. Among them, Medicine, evidence-based complementary and alternative medicine and other journals belong to OA journals, indicating that the strong development of open-access journals in recent years has greatly promoted the research progress in this field. Most of the journals belong to the category of complementary and alternative medicine, indicating that the field of complementary and alternative medicine is more interested in the musculoskeletal disorders research of traditional Chinese exercises.

The USA is the first country to study this field. Meanwhile, two of the top five institutions are from the USA, led by Harvard University. All these indicate that the USA is the most influential country in the field of traditional Chinese exercises treatment of musculoskeletal disorders. In recent years, China's influence in this field has gradually increased and there is a good development trend in this field in the future. Two of the top five are from China, with Shanghai University of Traditional Chinese Medicine and Shanghai University of Physical Education published 17 and 15 papers respectively. In addition to China and the USA, many countries have carried out research in this field, indicating that research attention in this field has increased in recent years. Therefore, there should be a stronger network of collaboration between more countries, institutions and authors, especially in China.

Although the traditional Chinese exercises originated in China, there are more than 20 universities of traditional Chinese exercises for China, which do not publish as many publications as other institutions. This may be related to the fact that most Chinese physicians pay more attention to the cultural attributes of traditional Chinese exercises. Interestingly, universities of traditional Chinese medicine are increasingly aware of this phenomenon and are gradually devoting themselves to the research of traditional Chinese exercises for musculoskeletal disorders.

According to the keyword frequency, we found that Tai Chi is the most commonly used traditional Chinese exercise for musculoskeletal diseases, which we believe may be related to the following reasons: (1) Tai Chi has been practiced in China for centuries. At present, Tai Chi has about 150 million practitioners in more than 150 countries and regions around the world. It is the most widely spread traditional Chinese exercises; (2) There are large body of evidence on the health effects of Tai chi, with more than 500 articles and 120 systematic reviews of the health benefits of Tai chi published. Based on such evidence-based advice, more researchers will focus on Tai Chi in their research; (3) Modern researchers have developed many simplified forms of Tai Chi, which shorten the learning time of practitioners and promote the spread of Tai Chi.

Global trend and research hotspots

Frequently keywords and burst keywords are the core content of the research literature topic. Cluster analysis was carried out based on keywords and finally three colors clusters were formed. Then, according to the keyword burst analysis, the research hotspots and development frontiers in the field are identified. The main contents are as follows: The efficacy evaluation of traditional Chinese exercises for the treatment of musculoskeletal disorders; the efficacy of traditional Chinese exercises for the treatment of musculoskeletal disorders dysfunctions; the pain improvement of traditional Chinese exercises for musculoskeletal disorders.

Cluster one keywords in this cluster can be divided into two categories. One focuses on research methods, such as randomized controlled trial, systematic review, and Meta-analysis. This cluster focused on the evaluation of the efficacy of traditional Chinese exercises for musculoskeletal disorders. The other type focuses on clinical diseases such as low back pain, rheumatoid arthritis, fibromyalgia and neck pain. In early studies, researchers focused on the therapeutic effects of Tai Chi on knee arthritis, fibromyalgia and other diseases. In 2000, Yocum suggested that Tai Chi might relieve pain and stress in rheumatoid arthritis patients, based on the link between stress and neuronal immune function (Yocum et al., 2000). The hypothesis that Chinese traditional exercises can alleviate musculoskeletal diseases was put forward. In 2003, Song conducted a randomized controlled trial study to explore the effects of Tai Chi on pain, balance, muscle strength in elderly women with osteoarthritis (Song et al., 2003). According to Astin's research, mindfulness meditation combined with Qigong can alleviate pain and depression in patients with fibromyalgia. Astin et al. (2003) randomized controlled trial will provides high-level evidence for the effectiveness of traditional Chinese exercises for musculoskeletal disorders. In 2010, Wang CC published "A Randomized Trial of Tai

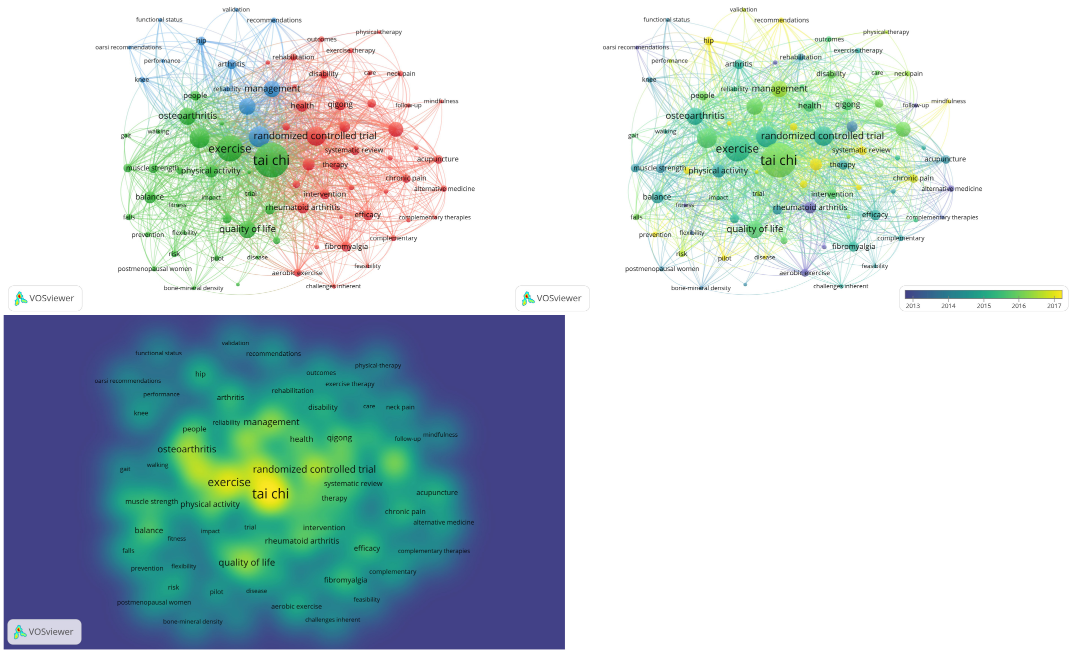

FIGURE 5
Co-occurrence network of high-frequency keywords of traditional Chinese exercises for musculoskeletal disorders.

TABLE 9 Cluster of keywords in the traditional Chinese exercises for musculoskeletal disorders.

Cluster	Color	Keywords
1	Red	Randomized controlled trial; Low back pain; meta analysis; rheumatoid arthritis; health; qigong; efficacy; fibromyalgia; intervention; therapy; systematic review; chronic pain; disability; prevalence; acupuncture; aerobic exercise; toga; quality; alternative medicine; complementary; outcomes; depression; neck pain; exercise therapy; recommendations; double-blind; care; complementary and alternative medicine; controlled-trial; challenges inherent; cognitive-behavioral therapy; follow-up; mindfulness meditation; self-efficacy; symptoms; complementary therapies; feasibility; mindfulness; physical-therapy; self-management
2	Green	Tai chi; exercise; older adult; osteoarthritis; quality of life; physical activity; balance; people; muscle strength; program; women; strength; adult; physical function; risk; falls; pilot; prevention; trial; postmenopausal women; impact; risk factors; walking; bone-mineral density; gait; classification; disease; flexibility; fitness; individuals
3	Blue	Pain; knee osteoarthritis; management; clinical trials; arthritis; hip; rehabilitation; knee; reliability; oarsi recommendations; performance; functional status; validation

Chi for Fibromyalgia" in The New England Journal of Medicine, a top medical journal, confirmed the therapeutic effect of Tai Chi on patients with fibromyalgia (Wang et al., 2010). This is the first article on traditional Chinese exercises published in the top journal in the medical field. High quality randomized controlled trial will promote research in the field, with the number of articles published in the following years more than doubling the number of articles published in 2010. In the subsequent study, besides Tai Chi, yi jin jing and baduanjin were also added to the research in this field. For example, An's research in 2013 found that 1-year baduanjin is an effective and safe exercise method for the treatment of knee osteoarthritis (An et al., 2013). In 2011, Hall found that 10 weeks of Tai Chi practice improved pain and disability outcomes in patients with low back pain (Hall et al., 2011). In 2016, Lauche Romy's study showed that 12 weeks of Tai Chi and traditional neck exercises were effective in improving neck pain and quality of life (Lauche et al., 2016). The number of diseases studied in this field has increased, such as low back pain, hip arthritis and neck pain. According to the keyword burst, neck pain was a hot research topic in this field from 2016 to 2018. In 2022, Kong published an article in Frontiers in Aging Neuroscience, which showed that traditional Chinese exercises significantly improved neck pain and disability in patients with neck pain and Baduanjin was the most effective (Kong et al., 2022). In recent years, there has also been a Chinese randomized controlled trial protocol on the intervention of neck pain with traditional exercise (Cheng et al., 2021). We suspect that neck pain may be a continuing research focus in the future.

Meta-analysis is a systematic review of quantitative analysis, which can synthesize the research results of multiple small samples on the same topic and improve the statistical efficiency of the original results. According to keywords burst systematic review and meta-analysis broke out from 2017 to 2020. Systematic review, published by Roger Chou in the annals of internal medicine in 2017, provides evidence that Tai Chi is effective for chronic low back pain, but the strength of the evidence is low (Rogers et al., 2010). Meta-analysis of comprehensive high-quality randomized controlled trials has been regarded as the highest level of evidence in evidence-based medicine, which can provide support for clinical guidelines. 2017 Qaseem incorporates Tai Chi into Non-invasive Treatments for Acute, Subacute, and Chronic Low Back Pain: Guideline from

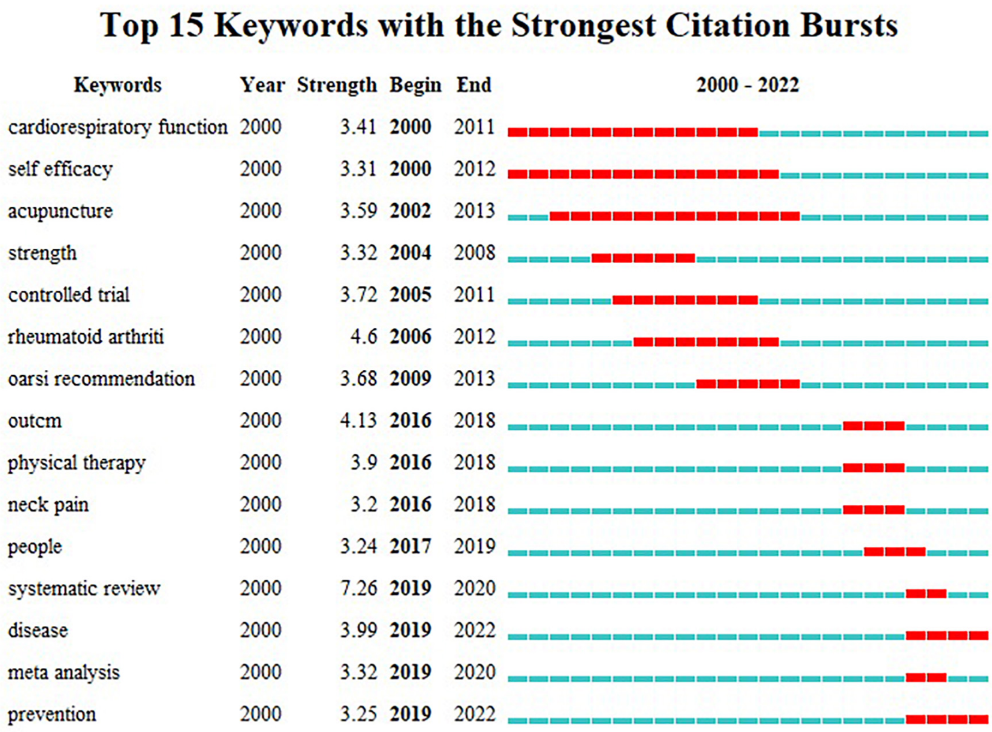

FIGURE 6
Top 15 keywords with the strongest citation bursts.

the American College of Physicians (Qaseem et al., 2017). The high level of clinical guidelines promote the clinical application of traditional Chinese techniques However, many Meta analysis points out that RCT in this field has shortcomings such as small sample size. Therefore, we speculate that on the basis of high-quality RCT studies in the future, the effectiveness of traditional Chinese exercises for musculoskeletal disorders will be further clarified.

Cluster two Keywords include Tai Chi; Exercise; Older Adult; Osteoarthritis; Quality of Life; Physical Activity; Balance; Muscle Strength. This cluster focused on the efficacy of traditional Chinese exercises for the treatment of musculoskeletal disorders dysfunctions. The main clinical manifestations of musculoskeletal disorders are pain and dysfunction, which seriously affect patients' physical function (Balance and Muscle Strength) and quality of life. Traditional Chinese exercises can improve muscle strength, enhance balance and prevent falls. Hartman, published in the Journal of the American Geriatrics Society in 2000, has demonstrated that 12 weeks of Tai Chi can improve self-efficacy, quality of life indicators and functional activity in elderly patients with knee arthritis (Hartman et al., 2000). Studies have shown that Tai Chi can improve balance and abdominal strength by improving joint pain, stiffness and sensory difficulties. An's study in 2008 found that Baduanjin can improve pain, stiffness and disability in patients with knee osteoarthritis and improve quadriceps strength (An et al., 2008). Runhaar's 2015 study suggested that exercises including Tai Chi, increased thigh strength in patients with osteoarthritis, reduced stretching difficulties and improved proprioception (Runhaar et al., 2015). Song's 2010 study found that 6 months of Tai Chi improved muscle strength around the knees, increased bone mineral density and reduced the fear of falling (Song et al., 2010). According to a systematic review in Age and Ageing, Tai Chi improves balance and fall risk in elderly people with knee arthritis (Mat et al., 2015). In 2020 Zhang's found that the effect of Tai Chi on balance and fall prevention in patients with knee arthritis may be related to the enhancement of lower limb strength and reduction of foot load by Tai Chi (Zhang et al., 2020b). Tai Chi gait significantly increases external knee adduction moment and long-term practice may be harmful to patients with knee osteoarthritis (Simic et al., 2011). Therefore, Tai Chi gait is best used as an intermittent exercise for balance and stability, which can significantly improve the deep minor muscle group strength of knee flexors in the elderly. These studies are from the perspective of muscle strength and balance to explain the mechanism of traditional Chinese exercise in the treatment of knee osteoarthritis. According to the keyword burst, "prevention" is a hot research topic in this field from 2019 to 2022. The improvement of muscle strength and balance in Tai Chi is mainly explained in terms of clinical symptoms and biomechanics. Future studies may reveal the mechanism of Tai Chi in treating musculoskeletal and joint diseases from a biomechanical perspective.

Cluster three keywords included Pain; Knee Osteoarthritis; Management; Clinical Trials; Arthritis. This Cluster focused on Pain management for musculoskeletal disorders. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or an experience similar to it. It is usually an important concomitant symptom of musculoskeletal disorders and profoundly affects the quality of life of patients. In 2009, Wang conducted a randomized controlled trial to explore the therapeutic effect of Tai Chi on knee osteoarthritis (KOA) and found that Tai Chi can not only effectively improve the physical function and quality of life of KOA patients, but also reduce the pain, anxiety and depression of KOA patients and improve self-efficacy (Wang et al., 2009). In 2016, it was confirmed that Tai Chi relieved KOA pain as much as standard physical therapy and showed greater improvement in quality of life and anxiety and depression than physical therapy (Wang et al., 2016). This evidence suggests that traditional Chinese exercises can play an important role as a mind-body therapy for the management of pain in musculoskeletal disorders.

Some researchers have explored the mechanism of Tai Chi in alleviating the pain of musculoskeletal disorders from neuroimaging. In 2019, Kong found that the effect of Tai Chi on pain improvement in fibromyalgia patients may be related to the enhancement of the cognitive control network and the resting-state functional connectivity of bilateral rostral anterior cingulate cortex (rACC)/medial prefrontal cortex (mPFC) (Kong et al., 2021). Chwan observed the changes of Tai Chi on KOA patient brain function by MRI and found that the improvement of Tai Chi on knee osteoarthritis pain pair was closely related to the increased resting-state functional magnetic resonance imaging connectivity observed between bilateral mPFC and amygdala seed regions (Shen et al., 2022). More studies have compared the specific changes of knee joint brain function with different Chinese traditional exercises. Studies have shown that both Tai Chi and Baduanjin can increase the resting state functional connectivity (rsFC) between supplementary motor area and bilateral dorsolateral prefrontal cortex (DLPFC), but there are differences in the changes of DLPFC rsFC between Tai Chi and Baduanjin (Shen et al., 2022). Current research into the mechanisms of musculoskeletal disorders has focused on knee arthritis. We believe that future studies will continue to reveal the specific effects of different traditional Chinese exercises on pain in musculoskeletal disorders from a neuroimaging perspective.

Limitations

The limitations of the traditional Chinese exercises for musculoskeletal disorders study should be considered in further studies. First of all, our study did not search other academic databases and was limited to science Web, which may have missed some influential articles. Second, we aimed to study global trends in traditional Chinese exercises for musculoskeletal disorders, but the language range was limited. This may have led to selection bias. Third, this study includes articles and reviews, so there may be some bias in reflecting the academic impact of articles by the number of citations.

Conclusion

We conducted a bibliometric analysis of the literature related to traditional Chinese exercises for musculoskeletal disorders over the past 22 years. We find a gradual increase in the number of annual publications, most of which appear in Medicine. The United States and China are the most published countries. The most relevant papers were published by Harvard Medical School, followed by Shanghai University of Traditional Chinese Medicine. But cooperation between different countries and institutions has been insufficient. Therefore, contact and communication should be strengthened to promote the application of traditional Chinese exercises for musculoskeletal disorders. According to the cited references and keywords, the main disease treated is osteoarthritis. At present, the focus of research in this field is still the safety and effectiveness of traditional Chinese exercises for the treatment of musculoskeletal disorders. At the same time, more research began to explore how traditional Chinese exercises played a role in the treatment of musculoskeletal disorders. Revealing the mechanism of traditional Chinese exercises from the interdisciplinary perspective of biomechanics and neuroimaging is the focus of research in this field and also the hotspot of future research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

CG and FY conceived the idea. CG and YG collected the literature. CG, YG, and FX conducted the data analysis. CG drafted the manuscript. YG, FX, ZC, and FY revised the manuscript. All authors have read and approved the final article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1096789/full#supplementary-material

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A neural circuit for gastric motility disorders driven by gastric dilation in mice

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Introduction: Symptoms of gastric motility disorders are common clinical manifestations of functional gastrointestinal disorders (FGIDs), and are triggered and exacerbated by stress, but the neural pathways underpinning them remain unclear.

Methods: We set-up a mouse model by gastric dilation (GD) in which the gastric dynamics were assessed by installing strain gauges on the surface of the stomach. The neural pathway associated with gastric motility disorders was investigated by behavioral tests, electrophysiology, neural circuit tracing, and optogenetics and chemogenetics involving projections of the corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus (PVN) to acetylcholine (ChAT) neurons in the dorsal motor nucleus of the vagus (DMV).

Results: We found that GD induced gastric motility disorders were accompanied by activation of PVN^{CRH} neurons, which could be alleviated by strategies that inhibits the activity of PVN^{CRH} neurons. In addition, we identified a neural pathway in which PVN^{CRH} neurons project into DMV^{ChAT} neurons, modulated activity of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway to alleviate gastric motility disorders induced by GD.

Discussion: These findings indicate that the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway may mediate at least some aspects of GD related gastric motility, and provide new insights into the mechanisms by which somatic stimulation modulates the physiological functions of internal organs and systems.

KEYWORDS

gastric motility disorders, neural circuit, paraventricular nucleus of the hypothalamus, dorsal motor nucleus of the vagus, corticotropin-releasing hormone

1. Introduction

Functional gastrointestinal disorders (FGIDs) are widespread, and constitute a major personal and socio-economic burden (Drossman, 2016). A recent global epidemiological study (Sperber et al., 2021) has found that over 40% of the world's population suffers from FGIDs. The disease is characterized by chronic abdominal discomfort without structural or biochemical causes, and its etiology and pathophysiology are multifactorial and still incompletely defined. Stress is widely relevant to the pathophysiology and treatment of digestive disorders. The latest Rome IV guidelines identify FGIDs as a disorder of gut–brain interaction (Drossman and Hasler, 2016), and stress contributes dynamically to various pathways of brain–gut communication, including the autonomic nervous system, the HPA axis, the local immune system, and brain mechanisms (Labanski et al., 2020). Changes in brain–gut interactions may underlie the symptoms of several FGIDs, including functional dyspepsia (FD) and irritable bowel syndrome (Mayer et al., 2006; Drossman, 2016).

The gastrointestinal tract and its enteric nervous system are innervated by the autonomic nervous system, which provides an efferent pathway for the stress-induced modulation of the gastrointestinal sensorimotor function, with the role of the vagus nerve in gastrointestinal sensitivity and motility having interesting clinical implications (Bonaz et al., 2018). From a neuro-gastrointestinal perspective, the functions of the upper gastrointestinal tract, including gastric tone and motility, are regulated by the activity of pacing neurons in the dorsal motor nucleus of the vagus (DMV), and its activity is regulated in turn by the tonic GABAergic input from the adjacent nucleus tractus solitarius (NTS) (Travagli and Anselmi, 2016) as well as inputs from higher centers, including projections from the paraventricular nucleus of the hypothalamus (PVN) (Browning and Travagli, 2014). PVN is an important autonomous control center due to the secretion of multiple peptides (Ferguson et al., 2008), and is closely related to the stomach. Peptidergic neurons in PVN release related transmitters after activation, and take part in the adjustment of physiological functions of the stomach by nerve conduction and neuro-endocrine systems (Benarroch, 2005). The corticotropin-releasing hormone (CRH, also known as the corticotropin-releasing factor, CRF) is a typical stress neuropeptide that is mainly distributed in the PVN. It coordinates the autonomic response of the gastrointestinal tract to stress (Czimmer and Tache, 2017).

Resolving the interactions between peripheral alterations and brain changes remains a challenging task. In recent years, optogenetic and chemogenetic techniques have provided high spatial and temporal resolutions, and have been used to target the manipulation of the activity of specific types of neurons. This provides a more comprehensive and precise understanding of the nervous system involved in regulating various organismal functions. In this study, we established a mouse model of stress-induced gastric motility disorder by using gastric dilation (GD). We dissected the functional organization of the PVN → DMV pathway, and investigated the principles of pathway acclimation in a mouse model of GD-induced gastric motility disorder *via* behavioral tests, neural circuit tracing, and electrophysiological, optogenetic, and chemogenetic techniques.

2. Materials and methods

2.1. Resting-state functional magnetic resonance imaging (rS-fMRI) trial

We recruited 24 healthy subjects for the study, of which 12 were males and 12 females. They were all 20–25 years of age, with a mean of 22.7 ± 1.9 years. The exclusion criterion for all participants was related to any contraindications to FMRI scanning. The procedures followed were in accordance with the World Medical Association's Declaration of Helsinki and the Clinical Experimentation Ethics Committee of Anhui University of Chinese Medicine (ChiCTR2200055920).

All subjects were treated with acupuncture interventions performed at the abdomen and stomach (Cai et al., 2018) for 20 min under water-loaded GD conditions. rS-fMRI (GE 3.0T, GE Medical System, Milwaukee, Wisconsin) and gastric electromyography (Abbreviated as EGG, EGEG-2D6B type, Hefei Huake Electronic Technology Research Institute) were performed before and after acupuncture. For water-loaded GD (van Dyck et al., 2016), all subjects fasted for 6–8 h, then drank 100 ml of water within 20 s, and continued to drink pure water at about 37°C until they began to feel full. They continued to drink water in this mode until they felt completely full or could not continue owing to epigastric symptoms. We recorded the water intake at this time, that is, the maximum threshold of gastric satiety.

The Data Processing Assistant for rS-fMRI (DPARSF) 4.2 software based on the MATLAB R2013b platform and Statistical Parametric Mapping (SPM) 12 software were used to pre-process the raw data. In this study, the correlation analysis method based on the seed point region of interest (ROI) was used. By using the built-in WFU-Pick-Atlas tool in SPM12 software, two spherical seed points with a radius of 2 mm were constructed as bilateral hypothalamic ROIs based on the Montreal Neurological Institute (MNI) coordinates defined in the literature (Lips et al., 2014). The coefficients of functional connectivity between the ROI and the brain voxels were obtained by REST 1.8 software and voxel-wise analysis. The calculated values of the coefficient of functional connectivity r were converted into Z-values by Fisher's Z, and statistically significant changes in functional connectivity were presented as images by using Alphasim correction.

2.2. Ethical approval and animals

We used 8–10-week-old C57BL/6J and CRH-Cre male mice, obtained from the Charles River or The Jackson Laboratory. The mice were housed in groups of five per cage in a stable environment (23–25°C, 50% humidity, 12-h light–dark cycles) for rearing, except for the mice used for surgery. After gastric balloon implantation, the mice were provided with liquid food. All experiments were conducted in accordance with the ARRIVE guidelines (Percie du Sert et al., 2020) and the Animal Experimentation Ethics Committee of Anhui University of Chinese Medicine (Reference no. AHUCM-mouse-2021-85).

2.3. Animal models

The mice were anesthetized with 1.5–3.0% isoflurane, and the surgical area was shaved and disinfected. Mice were fasted for 24 h prior to gastric surgery (with water provided). A catheter with a balloon (7 cm long, 0.6 mm outer diameter, 0.3 mm inner diameter) was used. A skin incision approximately 5 mm long was made at the head–neck junction on the back of the mouse, and a skin incision was made below the xiphoid cartilage at an intersection of 0.5 cm next to the midline of the abdomen. The two incisions were connected by inserting a sterile catheter. The stomach was exposed along the abdominal incision, the balloon was placed in the stomach, and then the gastric wall, abdominal muscles, and skin incisions were sutured in sequence. The other end of the catheter was passed from the abdominal incision to the neck incision, and was fixed at the neck incision with sutures. After surgery, mice were housed individually access to liquid diet. To avoid surgical stress reactions, GD and related experiments were performed 3 days after surgery.

In the GD experiment, 500 μl of 37°C saline was injected into the balloon with a rate of 0.5 mL/s for GD (McConnell et al., 2008; Liu et al., 2019; Kim et al., 2020) and lasting 20 min. Control mice receive the same gastric surgery (placement of the balloon in the stomach) as the GD group mice, but without GD. We checked the connection between the balloon and catheter at the end of the experiment. If leakage had occurred, the relevant data were excluded.

2.4. Animal electroacupuncture (EA) process

The site of animal electroacupuncture intervention was consistent with those used in previous experiments (Wang et al., 2015). Zhong-wan-acupoint (RN12) was located on the intersection of the upper 1/3 and lower 2/3 of the line connecting the xiphoid process and the upper border of the pubic symphysis, wei-shu-acupoint (BL21) was 2 mm adjacent to the spinous process of the 12th thoracic vertebra. Using disposable sterile acupuncture needles (0.25*13 mm, Yunlong Medical Co., Ltd., China) and electrical stimulator (G6805, Qingdao Xinsheng, China). A 20 min EA procedure was performed at a frequency of 2/100 Hz by using current with an intensity of 0.1–1 mA.

2.5. Virus microinjection

An intraperitoneal injection of pentobarbital (20 mg per kg) was used to induce anesthesia for stereotaxic brain injection by using a stereotactic frame (RWD Co., Ltd., China). Throughout the procedure, a heating pad was used to maintain the animals' body temperature at 36°C.

Through calibrated glass microelectrodes connected to an infusion pump (micro4, WPI Co., Ltd., USA), 200 nl of the virus was injected (depending on the virus titer and expression strength) at a rate of 35 nl min^{-1} (unless otherwise stated). Virus overflow was prevented by leaving the pipette for a minimum of 10 min at the injection site. Three coordinates were used: anterior–posterior (AP) from the bregma, medial–lateral (ML) from the midline, and dorsal–ventral (DV) from the brain surface. All viruses used in this study were obtained from BrainVTA Co., Ltd. (Wuhan, China).

2.5.1. Anterograde tracing

To allow EYFP expression in the downstream fibers, rAAV-Ef1α-DIO-hChR2 (H134R)-EYFP-WPRE (abbreviation rAAV-DIO-ChR2-EYFP, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd) was injected into the PVN (−0.62 mm AP, ± 0.25 mm ML, −4.55 mm DV) of the CRH-Cre mice. After 3 weeks, their brain slices were co-stained with acetylcholine-specific antibodies (abbreviation ChAT) to track $EYFP^{+}$ signals in the DMV.

2.5.2. Retrograde tracing

The C57BL/6J mice were injected with scAAV2/R-hSyn-EGFP-WPREs (AAV2R, 5.09E + 12 vg/mL, BrainVTA Co., Ltd) into the DMV (−7.83 mm AP, ± 0.24 mm ML, −3.6 mm DV), this virus could be absorbed by the terminals at the injection site and transported retrogradely to the soma to express the EGFP. After 3 weeks of virus injection, the brain sections were prepared to follow the $EYFP^{+}$ signals and co-stained with CRH-specific antibodies.

2.5.3. Optogenetic manipulation

Two Cre-dependent viruses were delivered to the PVN of the CRH-Cre mice, respectively: rAAV-Ef1α-DIO-hChR2(H134R)-EYFP-WPRE-hGh-pA (abbreviation rAAV-DIO-ChR2-EYFP, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd) and rAAV-Ef1α-DIO-eNpHR3.0-EYFP-WPRE-hGh-pA (abbreviation rAAV-DIO-eNpHR3-EYFP, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd), rAAV-DIO-EYFP-WPRE-pA (abbreviation rAAV-DIO–EYFP, AAV2/9, 1.95 × 1,012 vgml/mL, BrainVTA Co., Ltd) viruses were used as the controls. Optical fibers (200 μm OD,0.37 NA, Inper Co., Ltd., Hangzhou, China) were embedded in the ipsilateral DMV after injection of optogenetic activation virus in the right PVN; two optical fibers (200 μm OD,0.37 NA, Inper Co., Ltd., Hangzhou, China) were embedded in the bilateral DMV after injection of optogenetic suppression virus in bilateral PVN, and fixed with dental cement.

2.5.4. Chemogenetic manipulation

The Cre-dependent viruses rAAV-Ef1α-DIO-hM3d(Gq)-mCherry-WPREs (abbreviation rAAV-DIO-hM3Dq-mCherry, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd) and rAAV-Ef1α-DIO-hM4D(Gi)-mCherry-WPREs (abbreviation rAAV-DIO-hM4Di-mCherry, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd) were delivered to the PVN of the CRH-Cre mice, respectively. The virus rAAV-Ef1α-DIO-mCherry-WPRE-pA (abbreviation rAAV-DIO–mCherry, AAV2/8, 8.93 × 1012 vgml/mL, BrainVTA Co., Ltd) were used as controls for the chemogenetic virus (rAAV-DIO-hM4Di-mCherry/rAAV-DIO-hM3Dq-mCherry, BrainVTA Co., Ltd), and the chemogenetic virus + saline group was used as a control for the chemogenetic virus + Clozapine-N-oxide (CNO) group.

For this part of the experiment, activating viruses were injected into the right PVN and inhibiting viruses were injected into both PVNs. Confocal microscopy (LSM880, Zeiss, Germany) was used to acquire signals associated with virus injection in regions of the mouse brain.

2.6. *In vivo* optogenetic and chemogenetic manipulations

2.6.1. Optogenetic manipulation

Optogenetic activation or inhibition experiments were performed 3 weeks after viral expression. Chronically implantable fibers were connected to a laser generator using optic fiber sleeves. A Master-8 pulse stimulator (Shanghai Fiblaser Technology Co., Ltd., China) was used to deliver a 5-min pulse of blue (473 nm, 10 Hz, 5–8 mW) or yellow light (594 nm, 5–8 mW, constant). In optogenetic inhibition experiments, yellow light was given immediately after establishing the GD model and gastric motility was recorded for 20 min; The control group was not given yellow light after establishing the GD model. In the optogenetic activation experiment, gastric motility was recorded for 20 min immediately after the application of blue light in the light group and in the absence of light in the control group; in the EA group, electroacupuncture was performed for 20 min immediately after the blue light and gastric motility was recorded at the end of the electroacupuncture treatment.

2.6.2. Chemogenetic manipulations

Chemogenetic activation or inhibition experiments were performed 3 weeks after viral expression. In chemogenetic inhibition experiments, after clozapine-N-oxide (CNO, 5 mg/kg, Sigma) or saline was injected intraperitoneally for 40 min, the GD model was established and maintained 20 min, within which time (20 min) the gastric motility was detected. In chemogenetic activation experiments, after 40 min of CNO/saline injection, gastric motility was recorded (**Supplementary Figure 1**).

2.7. Optical fiber-based Ca^{2+} signal recording

A total of 200 nL of rAAV-CRH-GCaMP6s-WPRE-hGH (abbreviation rAAV-CRH-GCaMP6s, AAV2/9, 2.0E + 12 vg/mL, BrainVTA Co., Ltd) was microinjected unilaterally into the PVN of the C57BL/6J mice. An optical fiber (200 μm OD,0.37 NA, Inper) was implanted roughly 0.2 mm above the site of viral injection. 3 weeks after the mice had received the viral injection and optical fiber implantation, they were subjected to fiber photometry recording. A special balloon catheter was implanted in the stomach (refer to Method 2.3) of the mice 2 days prior to recording.

GCaMP6s fluorescence intensity was recorded before and during mechanical stimuli (GD). The values of fluorescence change $\Delta F/F$ (%) were derived by calculating $\Delta F/F$ (%) $= (F_{signal}\text{-}F_{baseline})/F_{baseline} \times 100$, where $F_{baseline}$ is the mean of the GCaMP6s signal for 5 s before time zero (stimulus initiation), F_{signal} is the GCaMP6s signal for the entire session (Zhu et al., 2021). Typical Ca^{2+} traces and thermograms were generated with InperPlot software (Inper Technology). We retroactively validated the reliability of fiber optic insertion and viral infection.

2.8. *In vitro* electrophysiological recordings

2.8.1. Brain section preparation

The pentobarbital-anaesthetized mice were intracardially perfused with 20–30 ml of ice-cold oxygenated N-methyl-d-Glucosamine artificial cerebrospinal fluid (NMDG ACSF) (solution components provided in the **Supplementary Data 1**). Coronal sections (300 μm) containing PVN or DMV were sectioned on a vibrating microtome (VT1200s, Leica, Germany) at a speed of 0.14 mm/s. The brain sections were first incubated in NMDG ACSF at 33°C for 12 min and then transferred to N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES) ACSF (solution components provided in the **Supplementary Data 1**) at 25°C for 1 h. The brain sections were then placed in a sectioning chamber (Warner Instruments, USA) for whole-cell recording while being continuously perfused with standard ACSF (solution components in the **Supplementary Data 1**) at 2.5–3 ml/min at 32°C.

2.8.2. Whole-cell patch-clamp recordings

Whole-cell patch-clamp recordings were performed on visualized PVN and DMV neurons using an infrared-differential interference contrast (IR/DIC) microscope (BX51WI, Olympus, Japan) with a 40x water-immersion objective. Patch pipettes (3–5 MΩ) were pulled from borosilicate glass capillaries (VitalSense Scientific Instruments Co., Ltd) using a four-stage horizontal micropipette puller (P1000, Sutter Instruments, USA), patch pipettes were filled with intracellular solution (solution components in the **Supplementary Data 1**) were used for voltage-clamp recording. Signals were amplified with a Multiclamp 700B amplifier, low-pass filtered at 2.8 kHz, digitized at 10 kHz, and recorded in a computer for offline analysis using Clampfit 10.7 software (Molecular Devices) (Zhou et al., 2022).

The current-evoked firing of PVN^{CRH} neurons was recorded in current-clamp mode ($I = 0$ pA). The threshold current of the action potential was defined as the minimum current to elicit an action potential. To visualize the PVN neurons, we injected rAAV-DIO-EYFP into the CRH-Cre mice so that green fluorescent EYFP was expressed only in the CRH neurons.

For validation of chemogenetic virus function. After 3 weeks of chemogenetic virus expression, electrophysiological brain slices were prepared by the above process. The PVN neurons expressing m-Cherry were visualized by using a vertical microscope in Mercury lamp mode, and neuronal responses were recorded before and after CNO administration.

In the vitro electrophysiological recordings of light-evoked response, brain slices were prepared by the above process after 3 weeks of optogenetic virus expression, blue light was delivered through an optical fiber (diameter of 200 μm, Inper) that was positioned 0.2 mm above the surface of the target areas. To characterize the function of rAAV-DIO-ChR2-EYFP in the PVN, $ChR2\text{-}EYFP^{+}$ neurons in PVN were visualized by a vertical microscope in Mercury lamp mode, and the responses elicited by different frequencies of blue light stimulation (473 nm, 5–8 mV, pulse width 10 Mm, stimulation frequencies 5 Hz, 10 Hz, 20 Hz) were recorded. For recording light-evoked postsynaptic currents (Fang et al., 2020; Zhou et al., 2022), DMV expressing $ChR2\text{-}EYFP^{+}$ fibers were visualized by a vertical microscope in Mercury lamp mode. The membrane potentials were held at −70 mV for recording the excitatory postsynaptic currents and at 0 mV for recording inhibitory postsynaptic currents, and these recordings were immediately terminated once the series resistance changed more than 10%. To eliminate the polysynaptic components, tetrodotoxin (TTX; 1 μM, Dalian Refine Biochemical Items Co., Ltd.) and 4-aminopyridine (4-AP; 2 mM, Sigma) were added to the standard ACSF to block sodium channels and augment light-induced postsynaptic currents, respectively.

2.9. Immunohistochemistry and imaging

Mice were deeply anesthetized with an intraperitoneal injection of pentobarbital sodium and then perfused with ice-cold 0.9% saline followed by 4% PFA. The brain tissue was embedded into dehydrated paraffin and cut into 5 μm-thick sections, alternatively, coronal sections were cut to a thickness of 40 μm using a cryostat (CM1860, Leica). For immunofluorescence, the sections were incubated with blocking buffer (0.3% Triton X-100, 10% donkey serum in phosphate buffer saline) for 1 h at room temperature, and then they were treated with primary anti-bodies diluted with blocking solution, including anti-c-Fos (1:100, mouse, Santa Cruz), anti-CRH (1:500, rabbit, Abcam), anti-acetylcholine (1:500, goat, Merck), anti-GABA (1:500, rabbit, Sigma), anti-c-Fos (1:500, goat, Santa Cruz), at 4°C for 24 h. The sections were treated for 2 h at room temperature with the matching fluorophore-coupled secondary anti-body (1:500, Invitgen), or secondary anti-body sheep anti-mouse IgG (1:500, Beyotime). After rinsing, the slices were treated with 4,6-diamidino-2-phenylindole (DAPI; 1:2,000, Sigma) at the last stage. To display the fluorescent signals, the sections were photographed and scanned using the confocal microscopy (LSM880, Zeiss).

2.10. *In vivo* gastric recordings

Following the same surgical procedure as was performed on the model group, two incisions were made in the scapula and the abdomen, and they were connected by inserting a sterile catheter. The stomach was exposed and a custom strain gauge transducer (120 Ω, GuangCe Co., Ltd) was sticked on the surface of the gastric wall on the gastric antrum (Kawachi et al., 2011; Gao et al., 2021; **Supplementary Figure 2**). Another skin incision is made along the dorsal midline. The lead from the transducer is passed through the abdominal wall and extended posteriorly under the skin. Strain gauge signals were amplified by a bridge (ML-301, AD Instruments) and digitizer (Powerlab 26/04, AD Instruments) to provide automatic collection of gastric motility data. Each mouse was recorded for at least 20 min and the average amplitude and frequency were automatically calculated using Labchart 8 software (AD Instruments) with low-pass filtering and high-pass filtering. After surgery, mice were housed individually access to liquid diet.

2.11. Statistical analysis

The data were analyzed by investigators blind to the treatments. Owing to missing targets, such as the injection of the viruses or the positioning of the optical fiber, the viral tracing, *in vivo* recording, and behavioral data on some animals were removed from subsequent examination. The paired t-test was used to compare the results before and after the treatment of the same subject. For experimental groups with multiple comparisons, the data were analyzed by using one-way and two-way analysis of variance (ANOVA). Tukey's method was used for comparisons between groups within multiple groups. The data were reported as the mean ± standard deviation and significance was defined as $p < 0.05$.

3. Results

3.1. Functional connectivity between hypothalamus and brainstem increased in subjects with water-loaded GD state following EA

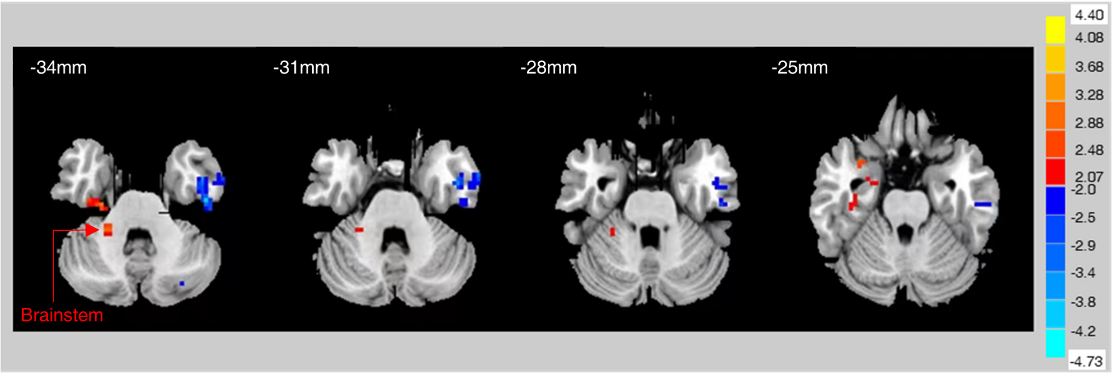
The correlation between changes in the functional connectivity of the brain regions and changes in gastric motility was analyzed based on the seed points (regions of interest). The hypothalamus was used as the ROI and its functional connectivity with other brain regions was examined. Interestingly, it was found that the fMRI in water-loaded GD subjects showed enhanced functional connectivity between the hypothalamus and the brainstem after EA intervention (**Figures 1A, B**) and the changes in this functional connectivity were positively correlated with changes in EGG amplitude ($r = 0.583$, Correlation Analysis) (**Figure 1C**). This phenomenon suggests an association between hypothalamic–brainstem connectivity and gastric motility in water-loaded GD subjects.

3.2. GD increased PVN^{CRH} neuronal activity in mice

The CRH neurons are mainly distributed in the PVN, and coordinate the autonomic response of the gastrointestinal tract to stress. We focused on the PVN^{CRH} neurons (Rosenberg, 1989). To investigate whether they were sensitive to GD stimulation, we performed fiber optic photometric recordings in mice receiving the infusion of a fluorescent Ca^{2+} indicator in the PVN for the CRH promoter (rAAV-CRH-GCaMP6s) (**Figures 2A, B**). The Ca^{2+} signals increased rapidly following GD stimulation (**Figures 2C, D**). The immunofluorescence experiments (**Figures 2G, H**) showed an increased co-labeling rate of CRH and C-fos within PVN in the GD group compared with the normal mice ($t = 6.581$, $^{****}P < 0.0001$, one-way ANOVA). Whole-cell recordings of the PVN^{CRH} neurons were performed in acute brain sections, and we found increased current-evoked action potentials in the GD mice [$F_{(1,18)} = 13.50$, $^{**}P = 0.0017$, two-way ANOVA]. These results suggest that the excitability of the PVN^{CRH} neurons is enhanced in GD situations (**Figures 2I, J**).

Meanwhile, we found that EA intervention inhibited PVN^{CRH} neuronal excitability in GD mice. Ca^{2+} fiber optic recording showed a rapid decrease in Ca^{2+} signal in GD mice after acupuncture stimulation (**Figures 2E, F**); immunofluorescence showed a decrease in co-labeling rate in the GD + EA group compared with the GD group ($t = 2.524$, $^{*}P = 0.0226$, one-way ANOVA; **Figures 2G, H**); and membrane clamp recording showed a decrease in current-evoked action potentials in GD + EA mice compared with the GD group [$F_{(1,18)} = 4.703$, $^{*}P = 0.0438$, two-way ANOVA]. Hence, EA intervention reduces excitability of PVN^{CRH} neurons activated by GD (**Figures 2I, J**).

A



B

Brain area	BA Partition	Voxel (n)	Z	MNI coordinates		
				X	Y	Z
Brainstem(R)		81	4.31	24	-33	-36

C

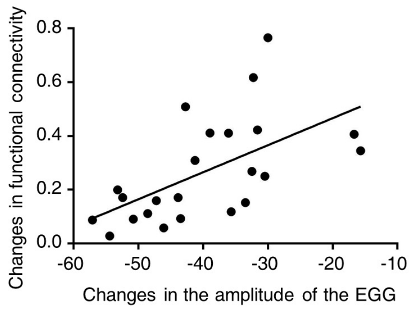


FIGURE 1
Functional connectivity between hypothalamus and brainstem was increased in subjects with water-loaded-GD state following EA. **(A)** Representative images of brain regions (brainstem) with changes in hypothalamic functional connectivity before and after EA. **(B)** The specific values of changes in hypothalamic-brainstem functional connectivity before and after EA. **(C)** EA-induced hypothalamic-brainstem ($r = 0.583$, $P = 0.004$) was positively correlated with changes in EGG amplitude, EGG, electrogastrogram.

3.3. Gastric motility disorders induced by GD were alleviated by inhibition of PVN^{CRH} neuronal activity in mice

The above experiments revealed that the excitability of PVN^{CRH} neurons was closely related to GD. We modulated the neuronal activity for further observation.

We injected the Cre-dependent inhibitory chemogenetic virus (rAAV-DIO-hM4Di-mCherry) into the bilateral PVN of the CRH-Cre mice to selectively inhibit PVN^{CRH} neurons (**Figures 3A, B**). Prior to behavioral assays, the function of the chemogenetic virus was verified by the membrane clamp of the brain slice, and its combination with CNO was effective in inhibiting PVN^{CRH} neurons [$F_{(1,8)} = 48.89$, $^{***}P = 0.0001$, two-way ANOVA; **Figure 3C**; **Supplementary Figure 3A**]. After 40 min of the intraperitoneal injection of CNO, the GD mice showed a significant increase in the amplitude of gastric motility ($t = 4.064$, $^{*}P = 0.0181$, one-way ANOVA). However, no significant changes in this amplitude were observed in the mCherry + CNO group or the hm4Di-mCherry + saline group (**Figures 3D, E**). These results suggest that the inhibition of PVN^{CRH} neuronal activity alleviates gastric motility disorders in mice under stressful conditions.

Given the increased excitability of PVN^{CRH} neurons in the GD model mice, we injected the Cre-dependent excitatory chemogenetic virus (rAAV-DIO-hM3Dq-mCherry) into the blank CRH-Cre mice to activate PVN^{CRH} neurons (**Figures 3F, G**). Prior to behavioral experiments, the function of the chemogenetic activation virus was verified, and its combination with CNO was effective in activating PVN^{CRH} neurons [$F_{(1,8)} = 45.52$, $^{***}P = 0.0001$, two-way ANOVA; **Figure 3H**; **Supplementary Figure 3B**]. After 40 min of intraperitoneal injection, this manipulation of activation of the PVN^{CRH} neurons reduced the amplitude of gastric motility in the mice ($t = 3.901$, $^{*}P = 0.023$, one-way ANOVA; **Figures 3I, J**). These results provide evidence of the functional causal relationship between the PVN^{CRH} neurons and gastric motility.

3.4. Dissecting the PVN^{CRH}-to-DMV^{ChAT} pathway

The DMV is one of the key centers of gastrointestinal regulation, and past evidence (Sawchenko, 1983; Llewellyn-Smith et al., 2012) suggests a direct fiber link between the PVN and the DMV. Moreover, more than 90% of the DMVs are cholinergic neurons (Travagli and Anselmi, 2016). To confirm the PVN^{CRH} → DMV projection, we applied a cell type-specific anterograde tracking system and injected the anterograde rAAV-DIO-ChR2-EYFP virus into the PVN of the CRH-Cre mice (**Figure 4A**). 3 weeks later, neurons positive for the yellow fluorescent protein (EYFP^{+}) were observed in the PVN (**Figure 4B**). EYFP^{+} signals were observed in the DMV, which

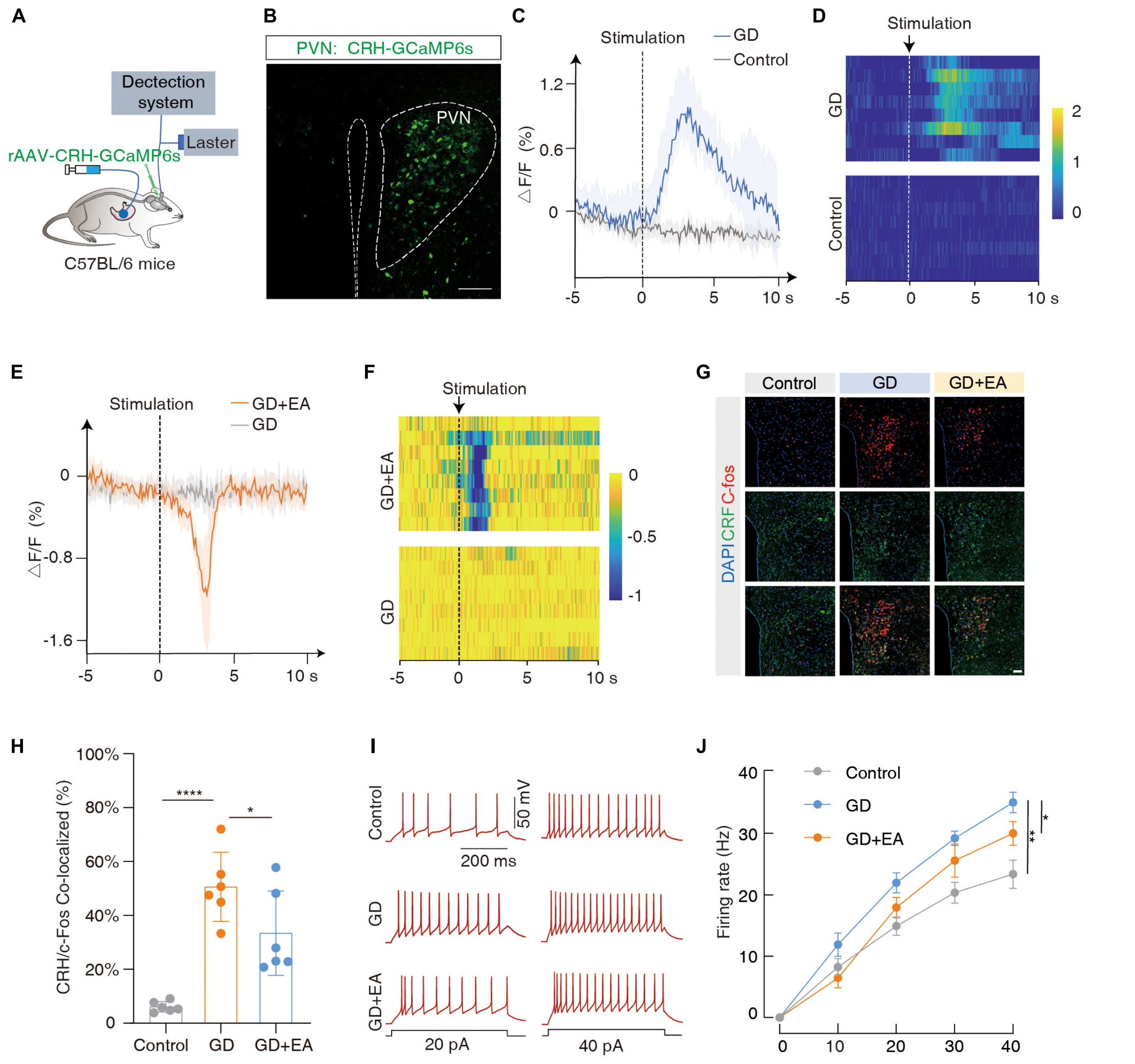


FIGURE 2

GD increases PVN^{CRH} neuronal activity in mice. **(A)** Schematic of the fiber photometry setup. Ca^{2+} transients were recorded from GCaMP6s-expressing PVN^{CRH} neurons in mice. **(B)** Typical images showing the injection site within the PVN by rAAV-CRH–GCaMP6s, scale bar 100 μm. **(C,D)** The mean (left) and the heatmaps (right) show that Ca^{2+} signals rapidly increased in gastric dilation (GD) state compared with normal state in mice. The colored bar on the right indicates ΔF/F (%). Each line in the heat map represents one experiment with one mouse. **(E,F)** The mean (left) and heat map (right) show that the Ca^{2+} signal decreases rapidly in GD mice upon acupuncture stimulation. EA is the abbreviation for acupuncture stimulation. **(G)** Representative images of C-fos and corticotropin-releasing hormone (CRH) expression in the PVN of various groups of mice. GD: gastric dilation group; EA: electroacupuncture group, scale bar 50 μm. **(H)** The C-fos and CRH co-labeling rate statistics for each group, $n = 6$ mice per group, one-way ANOVA, Control vs. GD ($t = 6.581$, $P < 0.0001$); EA vs. GD ($t = 2.524$, $P = 0.0226$). **(I,J)** Sample traces **(I)** and data **(J)** of firing rates recorded from PVN^{CRH} neurons of mice treated in control group, GD group and EA group. $n = 10$ cells from six mice per group, two-way ANOVA, Control vs. GD [$F_{(1,18)} = 13.50$, $P = 0.0017$]; EA vs. GD [$F_{(1,18)} = 4.703$, $P = 0.0438$]. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

surrounded the acetylcholine-positive (ChAT^{+}) neurons with red fluorescence (Figure 4C). To further resolve the PVN^{CRH}-to-DMV^{ChAT} connection, we injected a broad-spectrum retrograde non-trans-synaptic virus (scAAV2/R-hSyn-EGFP) into the DMV (Figure 4D). 3 weeks later, EGFP^{+} fibers and EGFP^{+} neurons were found on the DMV, and the results of immunofluorescence showed that most of the EGFP^{+} neurons were cholinergic (red fluorescence in Figure 4E). In addition, a large number of EGFP^{+} neurons appeared in the PVN, and the results of immunofluorescence revealed multiple EGFP^{+} neurons co-labeled as CRH^{+} neurons (Figure 4F). These findings suggest a PVN^{CRH} → DMV^{ChAT} pathway.

To examine the functional connections of the PVN^{CRH} → DMV^{ChAT} pathway, optogenetic experiments were performed. We first verified the activity of rAAV-DIO-ChR2-EYFP viruses by the membrane clamp, and then recorded action potentials induced by irradiation from 473 nm blue light (5, 10, and 20 Hz) in CRH neurons expressing the ChR2-EYFP^{+} in the PVN region of the brain slice (Figures 4G–I). All CRH neurons in the PVN of the injection site were found to exhibit action potentials as induced

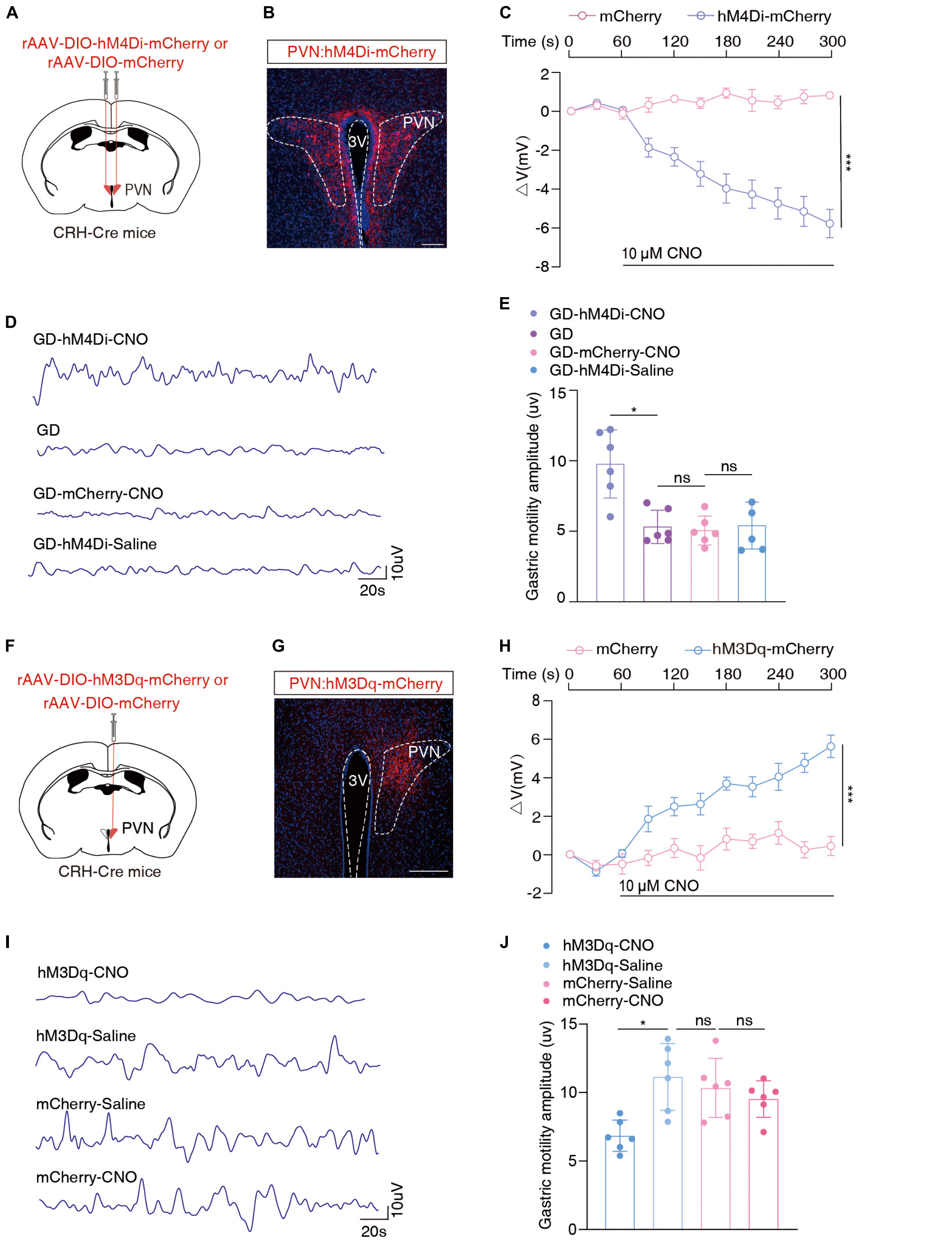


FIGURE 3

Chemogenetic inhibition of PVN^{CRH} neuronal activity alleviates GD-induced gastric motility disorders. **(A)** Schematic of chemogenetic experiments in CRH-Cre mice. **(B)** Typical images showing the injection site within the PVN by inhibition chemogenetic virus. Scale bars, 100 μm. **(C)** Membrane potential change induced by CNO, $n = 5$ cells from five mice for each group, two-way ANOVA, $F_{(1,8)} = 48.89$, $P = 0.0001$. Action potentials induced by CNO in neurons with red fluorescence in the PVN region were recorded on brain slices containing hm4Di-mCherry and those containing mCherry, respectively. **(D)** Representative graphs of gastric motility in various groups of mice. **(E)** Effects of chemogenetic inhibition of PVN^{CRH} neurons on gastric motility in GD mice, $n = 6$ mice in each group, one-way ANOVA, $t = 4.064$, $P = 0.0181$. **(F)** Schematic of chemogenetic experiments in CRH-Cre mice. **(G)** Typical images showing the injection site within the PVN by activated chemogenetic virus. Scale bars, 100 μm. **(H)** Membrane potential change induced by CNO, $n = 5$ cells from five mice per group, two-way ANOVA, $F_{(1,8)} = 45.52$, $P = 0.0001$. **(I)** Representative graphs of gastric motility in various groups of mice. **(J)** Effect of chemogenetic activation of PVN^{CRH} neurons on gastric motility in normal mice. $n = 6$ mice in each group, one-way ANOVA, $t = 3.901$, $P = 0.023$. *$P < 0.05$, ***$P \leq 0.0001$.

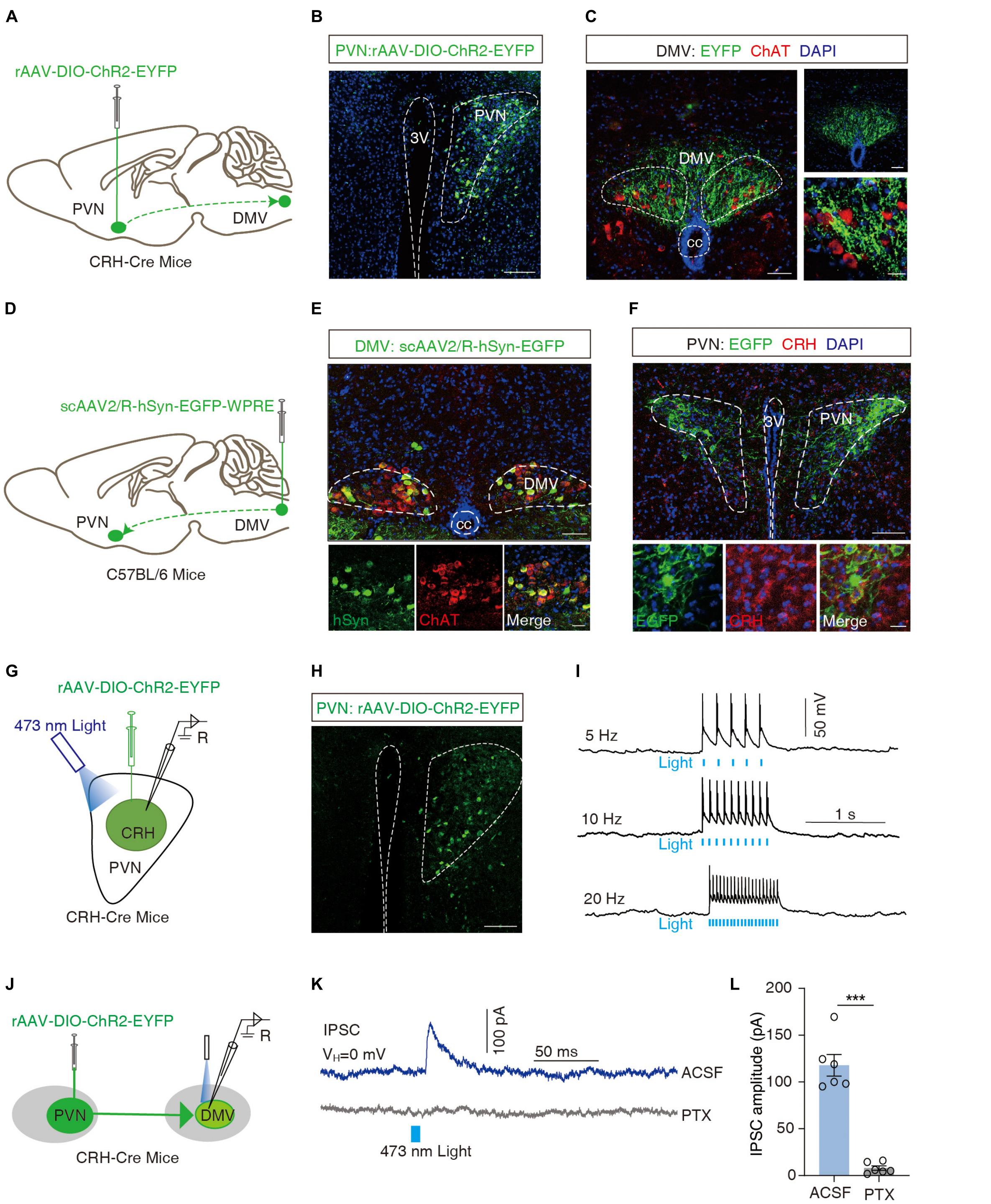


FIGURE 4

Dissection of the PVN^{CRH} to DMV^{ChAT} pathway. **(A)** Schematic of PVN injection of rAAV-DIO-ChR2-EYFP in CRH-Cre mice. **(B)** Representative image of EYFP labeling neurons by PVN infusion of rAAV-DIO-ChR2-EYFP. Scale bar, 100 μm. **(C)** Images representative of ChR2-EYFP^{+} fibers in DMV of CRH-Cre mice with PVN injection of rAAV-DIO-ChR2-EYFP (left) and ChR2-EYFP^{+} fibers co-localized with acetylcholine neuronal markers (ChAT) immunofluorescence within the DMV (right). Scale bars, 50 μm (left) or 50 μm (right-top) or 20 μm (right-bottom). **(D)** Schematic of DMV injection of scAAV2/R-hSyn-EGFP in C56BL/6 mice. **(E)** Representative image of scAAV2/R-hSyn-EGFP^{+} neurons and fibers, which co-localized with acetylcholine neuronal markers (ChAT) immunofluorescence in DMV. Scale bars, 100 μm (top) or 50 μm (bottom). **(F)** Representative image of EGFP^{+} neurons in PVN, which co-localized with CRH immunofluorescence. Scale bars, 100 μm (top) or 20 μm (bottom). **(G)** Schematic of PVN injection of rAAV-DIO-ChR2-EYFP and the recording configuration in acute slices. **(H)** Representative image injection site and viral expression within the PVN of CRH-Cre mice with PVN infusion of rAAV-DIO-ChR2-EYFP. Scale bar, 100 μm. **(I)** Sample traces of action potentials evoked by blue light (473 nm, 5–8 mV, pulse width 10 Mm, stimulation frequencies 5 Hz, 10 Hz, 20 Hz) recorded from PVN EYFP^{+} neurons in acute brain slices. **(J)** Schematic of PVN injection of rAAV-DIO-ChR2-EYFP in CRH-Cre mice and the recording configuration in acute slices. **(K)** Representative traces of light-evoked currents (473 nm, 20 ms, blue bar) before and after PTX (10 μM) treatment recorded from the DMV neurons. **(L)** Summarized data of light-evoked currents (473 nm, 20 ms) before and after PTX (10 μM) treatment recorded from the DMV neurons, $n = 6$ cells from six mice per group, paired t-test, $t = 9.997$, $P = 0.0002$. ***$P < 0.001$.

by the blue light. As shown by the whole-cell membrane clamp combined with the optogenetic techniques, the brief stimulation of efferent fibers of ChR2-containing PVN neurons by blue light in the DMV elicited inhibitory postsynaptic currents in the DMV neurons that were eliminated by the GABA receptor antagonist picronectin [picro-toxin (PTX)] ($t = 9.997$, $^{***}P = 0.0002$, paired t-test; **Figures 4J–L**). After whole-cell membrane clamp recording, we performed immunofluorescence detection on the brain slice and found that PVN^{CRH} neurons labeled with ChR2-EYFP were co-localized with GABAergic antibodies (**Supplementary Figure 4A**), and $ChAT^{+}$ neurons in DMV were encapsulated by $EYFP^{+}$ fibers (**Supplementary Figure 4B**). These data support the hypothesis that PVN^{CRH} neurons send monosynaptic projections to DMV^{ChAT} neurons.

3.5. PVN^{CRH} neurons control the DMV^{ChAT} neurons to alleviate gastric motility disorder induced by GD

To investigate the role of the PVN → DMV pathway in GD-induced gastric motility disorders, optogenetics experiments were performed. We injected the cre-dependent inhibitory optogenetic virus rAAV-DIO-eNpHR3-EYFP into the bilateral PVN and buried optical fibers in the bilateral DMV (**Figures 5A, B**). The optical inhibition of DMV-carrying eNpHR3 in the GD mice led to a significant increase in the amplitude of gastric motility [$F_{(1,10)} = 13.33$, $^{**}P = 0.0045$, two-way ANOVA; **Figures 5C, D**], which suggests that the optogenetic inhibition of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway significantly promoted gastric motility in the GD mice.

In light of the findings of the previous step, we injected Cre-dependent rAAV-Ef1a-DIO-ChR2-EYFP in naïve CRH-Cre mice and optically activated the end of the ChR2-containing PVN^{CRH} fiber in the DMV (**Figures 5E, F**). We found that the activation of this pathway attenuated gastric motility in the mice [$F_{(1,10)} = 20.51$, $^{**}P = 0.0011$, two-way ANOVA; **Figures 5G, H**]. Based on this, the amplitude of gastric motility increased after 20 min of EA intervention ($t = 2.683$, $^{*}P = 0.0437$, paired t-text; **Figures 5G, I**). This result also proved, inversely, that EA may improve gastric motility by inhibiting the activity of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway. Interestingly, this result is consistent with findings from human fMRI.

4. Discussion

This study defined the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway, which is involved in the generation of gastric motility disorders in case of GD and plays an important role in the regulation of gastric motility. Central to these processes are mechanisms of the neural pathway that involve increased excitability of PVN^{CRH} neurons and increased inhibition from them to DMV^{ChAT} neurons under acute stress-related conditions.

The PVN is a key node in the regulation of physiological stress responses, and receives multiple afferent messages about external stress and internal physiological states. It plays an important role in the regulation of gastrointestinal functions under stress. The PVN contains many stress-responsive neuron types, with a dense distribution of the CRH as a central player in the stress response (Sawchenko, 1983; Browning et al., 2014). These CRF neurons are thought to be glutamatergic or GABAergic (Tache et al., 2001). Some evidence has shown that the acute release of CRF, such as in response to a stressful event, induces plasticity within neural circuits of the vagal brainstem, which has the potential to alter the vagal output to the gastrointestinal tract (Browning et al., 2014). Moreover, pre-treatment through the injection of CRF peptide receptor antagonists into the ventricles blocks the inhibition of the gastric motor function induced by various stressors (Tache et al., 2001). The central role of the CRF in delaying gastric transit is mediated not by the stimulation of the associated HPA axis, but instead by the autonomic nervous system, as gastric inhibition of motor responses is still observed in adrenalectomized or hypophysectomized rats, but not in vagotomized rats (Lenz et al., 1988). The major structures affecting the autonomous flow to the stomach, namely, the PVN and the dorsal vagal complex (DVC) of the brain stem, were identified as the brain nuclei responsible for CRF-induced gastric emptying and motor inhibition in rats (Monnikes et al., 1992). In line with previous reports, we confirmed that GD mice exhibited significant deficits in gastric motility with activation of CRH neurons in the PVN.

The DMV is the origin of vagal efferent fibers that regulate gastric motility and other visceral functions (e.g., the vagal circuit and its effect on gastric motility) (Travagli and Anselmi, 2016). The efferent fibers of the DMV form synapses with postganglionic neurons located in the stomach to regulate gastric motility (Travagli and Anselmi, 2016), and the DMV has a direct fiber connection to the gastrointestinal tract. The vast majority of neurons in the DMV are cholinergic, and activate nicotinic cholinergic receptors on postganglionic neurons within the target organ (Browning and Travagli, 2010). There is a well-known projection between the PVN and the DMV (Willett et al., 1987), and we verified this result with anterograde and retrograde monosynaptic tracing. In line with previous reports (Browning et al., 2014), the CRF increased inhibitory GABAergic synaptic transmission to the identified corpus-projecting DMV neurons. In this study, we observed that subjects with water-loaded GD state following EA showed enhanced functional connectivity between hypothalamus and brainstem in fMRI, and the change in this functional connectivity was positively correlated with the change in EGG amplitude, then we mapped the PVN → DMV pathway in animal experiments, found through optogenetic techniques that PVN^{CRH} neurons projecting to acetylcholine neurons in the DMV were inhibitory, and alleviated gastric motility disorders in GD mice by inhibiting $PVN^{CRH} \rightarrow DMV^{ChAT}$ excitability.

Owing to the complex and multifactorial pathophysiology of FGIDs, the effectiveness of current treatments is still unsatisfactory. In this case, nearly 50% of FGIDs patients have exhibited a tendency to seek complementary and alternative medicine (Lahner et al., 2013). Many clinical studies and evidence-based evaluations have shown that acupuncture treatment alleviates the symptoms of FGIDs (Yuan-yuan et al., 2019; Guo et al., 2020; Wang et al., 2021) and mitigates symptoms and anxiety in FD patients. The central nervous system is an important site for the integration of acupuncture information and disease-related information. Acupuncture treatment involves the insertion of fine needles into the skin and underlying muscle layers, where the methods of

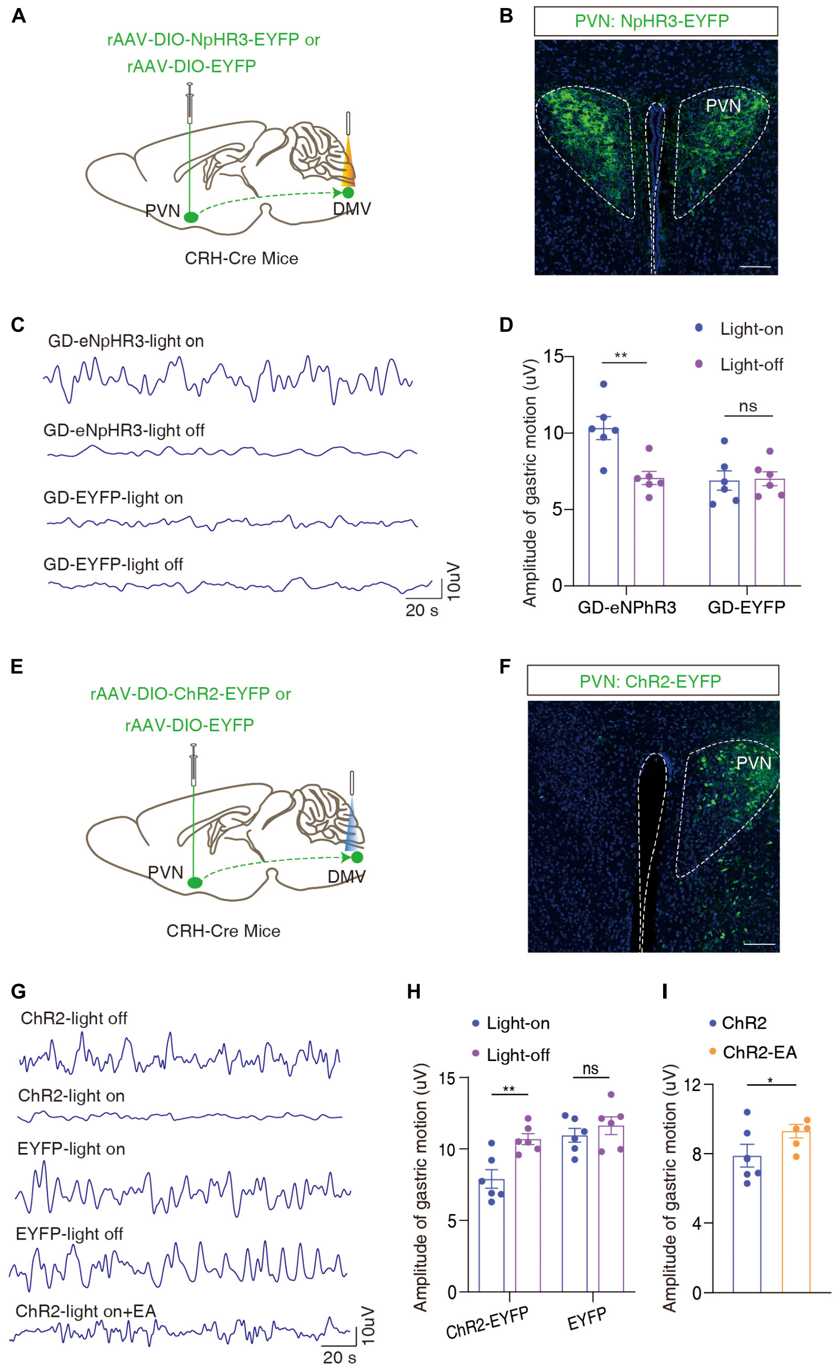


FIGURE 5
Optogenetic modulation of the PVN^{CRH} → DMV^{ChAT} pathway alleviates GD-mediated gastric motility disorders. **(A)** Schematic of optogenetic experiments in CRH-Cre mice. **(B)** Representative image of EYFP^{+} neurons by PVN infusion of rAAV-DIO-NpHR3-EYFP or rAAV-DIO-EYFP. Scale bar, 100 μm. **(C)** Representative graphs of gastric motility in various groups of mice. **(D)** Effects of optogenetic inhibition of PVN^{CRH} neurons on gastric motility in GD mice, $n = 6$ mice in each group, two-way ANOVA, $F_{1,10} = 13.33$, $P = 0.0045$. **(E)** Schematic of optogenetic experiments in CRH-Cre mice. **(F)** Representative image of EYFP^{+} neurons by PVN infusion of rAAV-DIO-ChR2-EYFP or rAAV-DIO-EYFP. Scale bar, 100 μm. **(G)** Representative graphs of gastric motility in various groups of mice. **(H)** Effects of optogenetic activation of PVN^{CRH} neurons on gastric motility in normal mice, $n = 6$ mice in each group, two-way ANOVA, $F_{(1,10)} = 20.51$, $P = 0.0011$. **(I)** Effect of EA intervention on gastric motility based on optogenetic activation of PVN^{CRH} neurons in normal mice. $n = 6$ mice in each group, paired *t*-text, $t = 2.683$, $P = 0.0437$. *$P < 0.05$, **$P < 0.01$.

stimulation may be manual or electric. Many previous studies (Koizumi et al., 1980; Kagitani et al., 2005, 2010; Takahashi, 2013) have reported that acupuncture stimulates somatic afferent nerves in the skin and muscles, when the mechanical force generated by acupuncture directly or indirectly acts on the acupoint area. Mechanical stimulation is transformed into neurochemical signals that induce afferent signals from the body. Many experiments have shown that the effect of acupuncture may be achieved by somatosensory autonomic reflexes or the modulation of the nervous system (Yu, 2020; Liu et al., 2021). The neural mechanisms

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involved in the modulation of gastrointestinal movement by acupuncture feature several aspects of acupuncture signaling, the sympathetic and parasympathetic nervous systems, the enteric nervous system, and the central nervous system (Wang et al., 2021). With the development of neuroimaging technology, the study of the acupuncture effect is not limited to animal experiments, non-invasive and high spatial and temporal resolution techniques, such as fMRI, support acupuncture effect based on human beings. Several neuroimaging studies have shown that acupuncture treatment improves not only clinical symptoms (postprandial fullness, epigastric distention, etc.) but also significantly modulates abnormal brain functions such as medial prefrontal cortex, brainstem, thalamus, caudate, and hippocampus in FD patients (Zeng et al., 2015; Teng et al., 2022; Yin et al., 2022). The central neural mechanism of the acupuncture effect is closely related to its modulation of neural circuits or neural networks, our study found after EA intervention, fMRI in GD subjects showed changes in functional connectivity between hypothalamus and brainstem. It also reflects the central nervous system provides exogenous neural input to control gastrointestinal motility in a broader and more integrated manner involving the spinal cord, medulla oblongata, thalamus, and so on.

The modulatory effects of acupuncture on gastrointestinal motility require the involvement of the CNS by altering the activity of nuclei associated with gastrointestinal motility, including the DMV, the NTS, the nucleus of the middle suture, the lateral hypothalamic area (LHA), and the PVN. All of these have been identified following the injection of neuro-anatomical tracers into the stomach and ST36 (Lee et al., 2001; Wang et al., 2013). The NTS and DMN form the main neuro-anatomical structure of the vagus nerve, the DVC, the role of which in acupuncture-mediated regulation of gastrointestinal function is supported by multiple pieces of evidence from several studies. The electro-acupuncture points ST36 and ST37 modulate the electrical activity of the stomach while regulating the firing of NTS and DMV neurons (Liu et al., 2004; Wang et al., 2007; Gao et al., 2012). The PVN is particularly important in the regulation of the gastrointestinal function, especially in case of stress-induced changes in gastrointestinal dynamics. Our previous study (Wang et al., 2015) found that the RN12 and BL21 signals of electroacupuncture converge in the PVN, and increase the expression of gastrointestinal hormones as well as their receptors in the PVN and the gastric antrum. Previous studies (Zhao et al., 2021) have suggested that the improvement in stress-induced jejunal motility disorders by the EA of ST36 may be related to the deregulation of CRF-R_2. However, information on the acupuncture-mediated regulation of gastric motility by the CRH function is scarce. In this study, we found that EA modulates gastric motility by inhibiting the excitability of PVN^{CRH} neurons in GD mice. We used viral tracking nuclear electrophysiology to identify an inhibitory neural circuit of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway. Following this, the activity of this circuit was modulated by using optogenetics, and the results suggested that EA possibly improves gastric motility by inhibiting the activity of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway. This result also proved, inversely, that EA may improve gastric motility by inhibiting the activity of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway. Interestingly, this result is consistent with findings from human fMRI.

In summary, this study explored the significance of the $PVN^{CRH} \rightarrow DMV^{ChAT}$ pathway in GD-induced gastric motility disorders. We found that the alleviation of its symptoms through the inhibition of the pathway may involve a hypothalamic paraventricular nucleus-mediated system of autonomic control. As options for the pharmacological treatment for functional gastric motility disorders remain limited, these findings suggest the potential for non-pharmacological therapeutic approaches, and provide new insights into the mechanisms by which somatic stimulation modulates the physiological function of internal organs and systems.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Experimentation Ethics Committee of Anhui University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study. This animal study was reviewed and approved by Animal Experimentation Ethics Committee of Anhui University of Chinese Medicine.

Author contributions

G-MS and X-YW: conceptualization. X-YW, R-LC, and HW: methodology and formal analysis. X-YW, G-QW, and X-QC: software, validation, and writing—original draft preparation. X-YW, G-QW, SH, HW, and X-QP: investigation. R-LC, H-TW, and G-MS: resources. X-YW, G-QW, X-QC, X-QP, and H-TW: data curation. R-LC, HW, and G-MS: writing—review and editing. X-QP, M-TZ, and H-TW: visualization. G-MS: supervision and project administration. G-MS, M-TZ, and X-YW: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1069198/full#supplementary-material

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Acupuncture for carpal tunnel syndrome: A systematic review and meta-analysis of randomized controlled trials

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Background: The evidence for the effectiveness of acupuncture for patients with carpal tunnel syndrome (CTS) is insufficient. Therefore, this systematic review and meta-analysis aimed to evaluate the effectiveness of acupuncture on CTS through a comprehensive literature search.

Methods: English and Chinese databases were searched from their inceptions until 27 October 2022 to collect randomized controlled trials (RCTs) that investigated the effect of acupuncture on CTS. Two reviewers independently selected studies that met the eligibility criteria, extracted the required data, assessed the risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2), and evaluated the quality of reporting for acupuncture interventions using the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). The primary outcomes were symptom severity and functional status, while secondary outcomes included pain intensity, responder rate, and electrophysiological parameters. Review Manager software (version 5.4.1) was used for data analysis. The certainty of the evidence was rated with GRADEpro (version 3.6) software.

Results: We included 16 RCTs with a total of 1,025 subjects. The overall risk of bias was rated as low in one RCT, some concerns in 14, and high in one. Compared with night splints, acupuncture alone was more effective in relieving pain, but there were no differences in symptom severity and functional status. Acupuncture alone had no advantage over medicine in improving symptom severity and electrophysiological parameters. As an adjunctive treatment, acupuncture might benefit CTS in terms of symptom severity, functional status, pain intensity, and electrophysiological parameters, and it was superior to medicine in improving the above outcomes. Few acupuncture-related adverse events were reported. The above evidence had a low or very low degree of certainty.

Conclusion: Acupuncture as an adjunctive treatment may be effective for patients with CTS. Additionally, more rigorous studies with objective outcomes are needed to investigate the effect of acupuncture in contrast with sham acupuncture or other active treatments.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=329925, identifier CRD42022329925.

KEYWORDS

acupuncture, carpal tunnel syndrome, systematic review, meta-analysis, randomized controlled trial

1. Introduction

Carpal tunnel syndrome (CTS), the common peripheral nerve entrapment syndrome, is caused by compression of the median nerve at the level of the wrist. The prevalence of CTS is 1–5% in the general population (Atroshi et al., 1999) and 7–10% in the working-age population (Spahn et al., 2012b; Feng et al., 2021). CTS can occur in one or both hands and is characterized by pain, numbness, and tingling in the median nerve distribution. In advanced cases, muscle atrophy may develop (Wipperman and Goerl, 2016). Being female, being obese, having to overuse the wrists, those who are pregnant, and those who are in perimenopausal age pose a greater risk of being affected by CTS (Spahn et al., 2012a; Graham et al., 2016). Patients with CTS frequently awaken from sleep due to worsening symptoms and have a lower quality of life. In addition, CTS is associated with reduced work time, decreased productivity, and disability (Daniell et al., 2009). Patients with CTS miss an average of 27 days of work per year, and the costs of CTS are estimated to exceed $2 billion annually in the United States (Palmer and Hanrahan, 1995).

Treatment strategies for CTS include non-surgical and surgical approaches. Given the invasive nature of the surgery, patients with CTS prefer to choose non-surgical management as an initial treatment (Shi and MacDermid, 2011; Calandruccio and Thompson, 2018). According to the American Academy of Orthopaedic Surgeons (AAOS) (Graham et al., 2016), there are various non-surgical treatments for CTS, such as immobilization (brace/splint/orthosis), steroid injections, and oral steroids. However, the evidence for the effectiveness of these non-surgical approaches is insufficient (Page et al., 2012; Padua et al., 2016). Moreover, certain undesirable adverse reactions limit the usage of treatments, such as splints and braces, which may influence sleep when used nightly (Manente et al., 2001), and steroid injections, which can lead to skin thinning, changes in pigmentation, and other adverse reactions (Chesterton et al., 2018). Therefore, it is necessary to explore effective and safe non-surgical interventions for patients with CTS.

Acupuncture is gaining popularity and acceptance worldwide and is widely used in neuro-musculoskeletal disorders (Qiao et al., 2020). Randomized controlled trials (RCTs) have investigated the effect of acupuncture as a monotherapy or adjuvant intervention on CTS, but their findings have been inconsistent. Previous systematic reviews of acupuncture for CTS were conducted by Sim et al. (2011) (6 RCTs), Choi et al. (2018) (12 RCTs), and Wu et al. (2020) (10 RCTs), and these systematic reviews suggested that there was not sufficient and convincing evidence to support the effectiveness of acupuncture on CTS. To further investigate this, we updated the systematic review and meta-analysis to include more objective outcomes and recent RCTs.

2. Methods and analysis

2.1. Study registration

We registered this systematic review and meta-analysis at PROSPERO: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=329925 (Registration ID: CRD42022329925). This systematic review and meta-analysis was conducted according to A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) (Shea et al., 2017) and reported in light of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (Page et al., 2021).

2.2. Inclusion criteria

We included studies that met all of the following criteria:

2.2.1. Type of studies

Our systematic review and meta-analysis included RCTs that evaluated the effectiveness of acupuncture in treating CTS and were published in either English or Chinese.

2.2.2. Type of participants

Our study included adult patients (≥18 years old) with CTS diagnosed using electrophysiological assessment (e.g., nerve conduction studies) and/or a combination of symptoms history and physical examination (as per Erickson et al., 2019). There were no limitations on gender, ethnicity, severity, or duration of CTS among the study participants.

2.2.3. Types of interventions

Experimental group: acupuncture alone or acupuncture plus other treatment(s) (e.g., wrist splinting, drugs, corticosteroid injection, and other non-traditional Chinese medicine). There were no restrictions on the types of acupuncture.

Control group: no treatment, sham acupuncture alone, other treatment, or sham acupuncture combined with other treatment(s).

Presence of cointerventions: cointerventions were required to be equal between the experimental and control groups.

2.2.4. Types of outcomes

2.2.4.1. Primary outcomes

Primary outcomes were symptom severity and functional status. Symptom severity was measured using the Boston Carpal Tunnel Questionnaire's symptom severity scale (CTQ-SSS) and the global symptoms score (GSS), while functional status was assessed with the CTQ's functional status scale (CTQ-FSS) and the disabilities of the arm, shoulder, and hand questionnaire (DASH).

2.2.4.2. Secondary outcomes

Secondary outcomes included the following:

(1) Pain intensity: the visual analog scale (VAS) or the numerical rating scale (NRS);
(2) Electrophysiological parameters: compound muscle action potential (CMAP), sensory nerve action potential (SNAP), distal motor latency (DML), distal sensory latency (DSL), motor nerve conduction velocity (MNCV), and sensory nerve conduction velocity (SNCV);
(3) Responder rate: responder (symptom improved or greatly improved) and non-responder (symptom did not change or worsened); and
(4) Adverse events.

2.3. Exclusion criteria

Studies were excluded if they met one of the following conditions:

(1) Studies including patients with CTS from a special population, such as those with diabetes, who were pregnant, and those with rheumatoid arthritis;
(2) Patients who had surgery for CTS;
(3) Experimental and/or control group included other interventions of traditional Chinese medicine (e.g., Tuina and Chinese herbs);
(4) Studies that provided no details of control intervention;
(5) Studies with duplicate data; and
(6) If full texts were unavailable through all practical approaches.

2.4. Search strategy

The following databases were searched from their inceptions until 27 October 2022: PubMed, EMbase, the Cochrane Library, the Chinese Biomedical Literature Database (CBM), the China National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP), and the Wanfang database (Wanfang Data). We utilized Medical Subject Headings (MESH) and free terms related to acupuncture and CTS to build search strategies. The search strategies for the above databases are provided in **Supplementary material 1**. We manually searched gray literature, reference lists of relevant reviews, and trial registers (ClinicalTrials.gov and the Chinese Clinical Trials Registry). Meanwhile, relevant experts were consulted for potentially eligible studies.

2.5. Study selection

EndNote X9 was used to manage the literature. Two independent reviewers (PY and GC) conducted the study selection. After removing duplicates, irrelevant records which were screened according to titles or abstracts were excluded. Then, the rest records with full text were scrutinized to identify eligible studies. The two reviewers cross-checked their identified studies and discussed any disputes.

2.6. Data extraction

The data on the following aspects were extracted by two reviewers (JL and JD) independently:

(1) Study's information: first author, year of publication, country, sample size, and information related to the risk of bias (e.g., randomization and blinding);
(2) Participants' (study level) characteristics: age, gender, diagnostic criteria, duration, and severity of CTS;
(3) Experimental group's details: protocol of acupuncture (type, acupoint selection, frequency, duration, etc.) and/or other cointervention(s) (type, frequency, duration, etc.);
(4) Control group's details: protocol of comparators and/or other cointervention(s) (type, frequency, duration, etc.); and
(5) Outcomes' information: primary and secondary outcomes, adverse events.

If there are multiple-arm RCTs, we included only data from the arms with interventions relevant to this study. Two reviewers cross-checked the extracted information. Any discrepancy was resolved through discussion. The authors would be contacted if there was missing information.

2.7. Assessment of risk of bias

Two independent reviewers (QD and XL) assessed the risk of bias in the included studies using version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2). According to ROB 2, five domains of bias were evaluated: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain of individual study and all included studies were rated as "low risk," "some concerns," or "high risk." Any disagreements were resolved with a third reviewer (RJ).

2.8. Assessment of the reporting quality of the intervention

Two independent reviewers (HF and QD) utilized the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) to evaluate the reporting quality of interventions for each included study based on the following six items (17 sub-items) (MacPherson et al., 2010): acupuncture rationale, details of needling, treatment regimen, other components of treatment, practitioner background, and control or comparator interventions. The third reviewer (RJ) participated in resolution of discrepancies.

2.9. Certainty of evidence assessment

Two independent reviewers (FW and YY) assessed the certainty of the evidence with the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system. Each outcome was assessed based on five aspects: limitations, inconsistency, indirectness, imprecision, and publication bias, and categorized as high, moderate, low, or very low evidential certainty. GRADEpro (Version 3.6) software was used to evaluate the evidence and summarize the findings.

2.10. Data analysis

We evaluated acupuncture's effects as monotherapy and adjunctive treatment, respectively. If feasible, meta-analyses were conducted using post-intervention data when clinical homogeneity existed between studies. We calculated the mean difference (MD) with 95% confidence intervals (CIs) for continuous data measured by uniform standards. Otherwise, standardized mean differences (SMDs) and 95% CIs were evaluated. For dichotomous data (e.g., responder rate), we calculated the risk ratios (RRs) and 95% CIs. The Chi-square test with a significance level of $P < 0.10$ and I^2 statistic were used to detect and quantify heterogeneity, respectively. The random-effects model (REM) was applied in meta-analyses if there was substantial heterogeneity ($P < 0.1$ or I^2 value > 50%). Otherwise, the fixed-effects model (FEM) was used. We conducted descriptive analyses when meta-analyses were not appropriate or possible. Review Manager software (version 5.4.1) was used for data synthesis.

3. Results

3.1. Study inclusion and characteristics

We obtained a total of 1,486 records in the literature search. After removing 550 duplicates, we excluded 880 irrelevant records based on their title and abstract. The full text of 56 remaining records was then evaluated, and 16 eligible studies (Kumnerddee and Kaewtong, 2010; Jin and Lang, 2011; Li, 2011; Yang et al., 2011; Yao et al., 2012; Ramin, 2013; Xiang et al., 2014; Hadianfard et al., 2015; Chung et al., 2016; Maeda et al., 2017; Ural and Özturk, 2017; Xie et al., 2018; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020; Xiong, 2020; Huang and Lin, 2022) were included in the final analysis. A list of excluded records with reasons is provided in **Supplementary material 2**. The PRISMA flow chart presents the selection procedure (**Figure 1**). Of the included studies, eight were conducted in China (Jin and Lang, 2011; Li, 2011; Yang et al., 2011; Xiang et al., 2014; Chung et al., 2016; Xie et al., 2018; Xiong, 2020; Huang and Lin, 2022), two in the USA (Yao et al., 2012; Maeda et al., 2017), three in Iran (Ramin, 2013; Hadianfard et al., 2015; Bahrami-Taghanaki et al., 2020), two in Turkey (Ural and Özturk, 2017; Tezel et al., 2019), and one in Thailand (Kumnerddee and Kaewtong, 2010). The sample size of the studies ranged from 27 to 181, with a total of 1,025 participants. The mean age of participants varied between 36.4 and 53.6 years. Fifteen studies included patients with mild to moderate CTS, and one study (Jin and Lang, 2011) did not specify the severity of CTS. Five studies used acupuncture as monotherapy, while 11 studies investigated its adjunctive effect. **Table 1** show the characteristics of the included studies.

3.2. Risk of bias

During the randomization process, 11 studies specified the randomization method (Kumnerddee and Kaewtong, 2010; Yang et al., 2011; Yao et al., 2012; Xiang et al., 2014; Hadianfard et al., 2015; Chung et al., 2016; Maeda et al., 2017; Ural and Özturk, 2017; Xie et al., 2018; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020). Two studies (Yang et al., 2011; Chung et al., 2016) implemented appropriate methods to conceal the allocation sequence. All studies reported that there were comparable baselines between groups. Two studies (Yao et al., 2012; Maeda et al., 2017) blinded patients by conducting sham comparisons between the groups. Additionally, several outcomes, including symptom severity, functional status, and pain intensity, were participant-reported outcomes, which meant outcome assessors were blinded in the studies (Yao et al., 2012; Maeda et al., 2017). Seven studies (Kumnerddee and Kaewtong, 2010; Yang et al., 2011; Yao et al., 2012; Chung et al., 2016; Maeda et al., 2017; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020) described dropouts rate with 1.6–18.3%; among these studies, four trials (Chung et al., 2016; Maeda et al., 2017; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020) did not give the detailed reason of dropouts, and three studies (Yang et al., 2011; Yao et al., 2012; Chung et al., 2016) used intent-to-treat analysis. Four trials (Yang et al., 2011; Chung et al., 2016; Maeda et al., 2017; Bahrami-Taghanaki et al., 2020) provided the registration number or published protocol, and all of them reported planned outcomes. Overall, 1 RCT (Yang et al., 2011) was rated as having a low risk of bias, 14 (Kumnerddee and Kaewtong, 2010; Jin and Lang, 2011; Li, 2011; Yao et al., 2012; Ramin, 2013; Xiang et al., 2014; Hadianfard et al., 2015; Chung et al., 2016; Maeda et al., 2017; Ural and Özturk, 2017; Xie et al., 2018; Tezel et al., 2019; Xiong, 2020; Huang and Lin, 2022) had some concerns, and 1 (Bahrami-Taghanaki et al., 2020) was a high risk of bias. The results of the risk of bias in individual studies and the overall risk of bias are shown in **Figure 2**.

3.3. Acupuncture protocols included trials

There were different acupuncture techniques, among which manual acupuncture was applied in seven studies (Yang et al., 2011; Yao et al., 2012; Hadianfard et al., 2015; Ural and Özturk, 2017; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020; Huang and Lin, 2022) and electroacupuncture in nine (Kumnerddee and Kaewtong, 2010; Jin and Lang, 2011; Li, 2011; Ramin, 2013; Xiang et al., 2014; Chung et al., 2016; Maeda et al., 2017; Xie et al., 2018; Xiong, 2020), respectively. All studies reported the selected acupoints, and the frequency of all acupoints is shown in **Figure 3**. The most used acupoints were Daling (PC7, 100%), Neiguan (PC6, 75.0%), Hegu (LI 4, 50.0%), Quchi (LI 11, 50.0%), and Laogong (PC 8, 37.5%). Thirteen included studies (Kumnerddee and Kaewtong, 2010; Jin and Lang, 2011; Yang et al., 2011; Yao et al., 2012; Ramin, 2013; Xiang et al., 2014; Hadianfard et al., 2015; Chung et al., 2016; Ural and Özturk, 2017; Tezel et al., 2019; Bahrami-Taghanaki et al., 2020; Xiong, 2020; Huang and Lin, 2022) applied the fixed acupoint protocol and 3 (Li, 2011; Maeda et al., 2017; Xie et al., 2018) used individualized acupoint

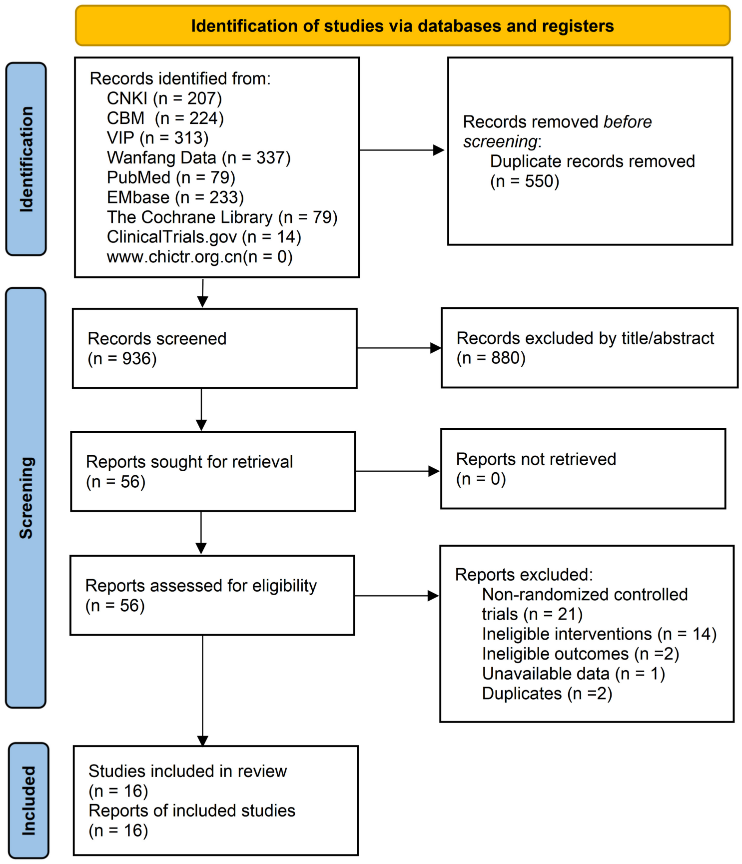

FIGURE 1
PRISMA flow diagram.

protocol (fixed main acupoints plus acupoints based on syndrome differentiation). In addition, the retention time was mainly 20 or 30 min, and the total sessions ranged from 6 to 36 sessions within 20 days to 17 weeks of treatment duration.

3.4. STRICTA checklist for the included studies

According to the STRICTA checklist, the items with more than 70% of reporting rates were item 3a (number of treatment sessions, 100%), item 2e (needle stimulation, 100%), item 3b (frequency and duration of treatment sessions, 93.8%), item 6b (precise description of the control or comparator, 87.5%), item 2d (response sought, 81.3%), item 2f (needle retention time, 81.3%), and item 2g (needle type, 81.3%). Item 4b (setting and context of treatment) and 1c (the extent to which treatment was varied) were not reported in the included studies. Detailed information on the STRICTA checklist is provided in **Supplementary material 3**.

3.5. Primary outcomes

3.5.1. Acupuncture as monotherapy

3.5.1.1. Acupuncture vs. sham acupuncture

Maeda et al. (2017) found no difference in the improvement of symptom severity (CTQ-SSS) or functional status (CTQ-FSS) between the electroacupuncture and sham electroacupuncture groups.

3.5.1.2. Acupuncture vs. night splints

Kumnerddee and Kaewtong (2010) found no difference in symptom severity (CTQ-SSS) or functional status (CTQ-FSS) between the electroacupuncture and night splints groups.

3.5.1.3. Acupuncture vs. medicine

Yang et al. (2011) observed that manual acupuncture was not superior to prednisolone in reducing symptom severity as measured by CSS.

3.5.2. Acupuncture as an adjunctive treatment

3.5.2.1. Acupuncture plus night splints vs. sham acupuncture plus night splints

Yao et al. (2012) reported that there was no difference between the manual acupuncture plus night splints group and the sham acupuncture plus night splints group in symptom severity (CTQ-SSS) or functional status (CTQ-FSS).

3.5.2.2. Acupuncture plus night splints vs. medicine plus night splints

Compared with medicine plus night splints, manual acupuncture plus night splints showed lower symptom severity (CTQ-SSS/GSS: SMD = −1.51, 95% CI −1.58 to −0.72, I^2 = 47%) (**Figure 4**), but

TABLE 1 Characteristics of included studies.

References	Sample size (randomized/ analyzed)	Number of patient (randomized/ analyzed)	Age (E/C)	Gender (F/M)	Duration of CTS	Intervention			Control			Outcomes
						Type	Frequency	Duration	Type	Frequency	Duration	
Kumnerddee and Kaewtong, 2010	61/60	E: 30/30 C: 31/30	E: 50.37 ± 9.01 C: 51.73 ± 8.92	E: 26/4 C: 28/2	E: 12.12 ± 15.71 m C: 8.32 ± 7.68 m	EA	30 min/session 2 sessions/week	5 weeks	Night splints	Every night	5 weeks	CTQ-SSS CTQ-FSS VAS
Jin and Lang, 2011	50/50	E: 25/25 C: 25/25	E: 44 ± 6 C: 44 ± 4	E: 14/11 C: 12/13	E: 3.51 ± 0.5 m C: 3.65 ± 1.5 m	EA	30 min/session 1 session/day	20 days	Mecobalamin tablets	0.5 mg/time, tid	20 days	CAMP DML SNCV Responder rate
Li, 2011	80/80	E: 40/40 C: 40/40	E: 42.25 ± 9.73 C: 41.03 ± 10.07	E: 29/11 C: 31/9	NI	EA + medicine	40 min/session 5 sessions/week	4 weeks	Medicine (diclofenac sodium + mecobalamin tablets + vitamin B1 + vitamin B6 + dibazol tablets)	Diclofenac sodium: 25 mg, tid; Mecobalamin tablets: 500 µg, tid; Vitamin B1: 20 mg, tid; Vitamin B6: 20 mg, tid; Dibazol tablets: 10 mg, tid.	Diclofenac Sodium: 2 weeks; Mecobalamin/ vitamin B1/vitamin B6/dibazol tablets: 4 weeks	CTQ-SSS CTQ-FSS CMAP SNAP SNCV DML
Yang et al., 2011	77/77	E: 38/38 C: 39/39	E: 49.3 ± 8.9 C: 49.9 ± 10.3	E: 32/6 C: 30/9	E: 7.6 ± 3.8 m C: 7.7 ± 3.2 m	MA	30 min/session 2 sessions/week	4 weeks	Prednisolone	1–2 weeks: 20 mg daily; 3–4 weeks: 10 mg daily	4 weeks	GSS CMAP SNAP MNCV SNCV DML DSL
Yao et al., 2012	41/41	E: 21/21 C: 20/20	E: 53.6 ± 7.65 C: 48.5 ± 10.5	E: 14/7 C: 16/4	E: 74.4 ± 65.4 m C: 49.6 ± 53.7 m	MA + night splints	20 min/session 1 session/week	6 weeks	Sham acupuncture + night splints	Sham acupuncture: 20 min/session 1 session/week; Night splints: every night	6 weeks	CTQ-SSS CTQ-FSS
Ramin, 2013	52/52	E: 26/26 C: 26/26	47.61 ± 11.53	46/6	4.02 ± 4.84 m	EA	30 min/session 3 sessions/week	4 weeks	Prednisolone	5 mg daily	4 weeks	CMAP SNAP MNCV SNCV DML DSL

(Continued)

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TABLE 1 (Continued)

References	Sample size (randomized/ analyzed)	Number of patient (randomized/ analyzed)	Age (E/C)	Gender (F/M)	Duration of CTS	Intervention			Control			Outcomes
						Type	Frequency	Duration	Type	Frequency	Duration	
Xiang et al., 2014	60/60	E: 30/30 C: 30/30	E: 45.78 ± 9.05 C: 46.02 ± 8.93	E: 22/8 C: 21/9	E: 4.25 ± 1.02 m C: 3.92 ± 1.25 m	EA + mecobalamin tablets	30 min/session 6 sessions/week	4 weeks	Mecobalamin tablets	0.5 mg/time, tid	4 weeks	GSS NRS CMAP SNAP SNCV DML
Hadianfard et al., 2015	50/50	E: 25/25 C: 25/25	E: 44.5 ± 8.5 C: 42.5 ± 7.6	E: 24/1 C: 23/2	NI	MA + night splints	20 min/session 2 sessions/week	4 weeks	Ibuprofen + night splints	Ibuprofen: 400 mg/time, tid; Night splints: NI	Ibuprofen: 10 days; Night splints: 4 weeks	CTQ-SSS CTQ-FSS VAS MNCV DSL DML
Chung et al., 2016	181/181	E: 90/90 C: 91/91	E: 51 ± 10.2 C: 51 ± 8.7	E: 77/13 C: 81/10	E: 50 ± 52.7 m C: 51 ± 59.9 m	EA + night splints	20 min/session 1–2 sessions/week	17 weeks	Night splints	8 h/night, every night	17 weeks	CTQ-SSS CTQ-FSS DASH VAS
Maeda et al., 2017	51/43	E: 28/22 C: 23/21	E: 48.5 ± 10.1 C: 50.6 ± 7.8	E: 22/6 C: 20/3	E: 9.9 ± 8.9 y C: 9.4 ± 9.3 y	EA	20 min/session 1–3 weeks: 3 sessions/week 4–5 weeks: 2 sessions/week 6–8 weeks: 1 session/week	8 weeks	Sham acupuncture	20 min/session 1–3 weeks: 3 sessions/week 4–5 weeks: 2 sessions/week 6–8 weeks: 1 session/week	8 weeks	CTQ-SSS CTQ-FSS
Ural and Özturk, 2017	27/27	E: 14/14 C: 13/13	E: 50.5 ± 6.1 C: 51.5 ± 4.5	E: 14/0 C: 13/0	E: 18.3 ± 6.6 m C: 19.3 ± 11.1 m	MA + night splints	25 min/session 2–3 sessions/week	4 weeks	Night splints	NI	4 weeks	VAS DASH CMAP SNAP MNCV SNCV DML

(Continued)

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TABLE 1 (Continued)

References	Sample size (randomized/ analyzed)	Number of patient (randomized/ analyzed)	Age (E/C)	Gender (F/M)	Duration of CTS	Intervention			Control			Outcomes
						Type	Frequency	Duration	Type	Frequency	Duration	
Xie et al., 2018	86/86	E: 43/43 C: 43/43	E: 41.26 ± 6.78 C: 41.78 ± 6.49	E: 25/18 C: 24/19	E: 5.17 ± 3.48 m C: 4.89 ± 3.52 m	EA + medicine	40 min/session 5 sessions/week	4 weeks	Medicine (diclofenac sodium + mecobalamin tablets + vitamin B1 tablets + vitamin B6 tablets + bendazol tablets)	Diclofenac sodium: 25 mg/time, tid; Mecobalamin tablets: 0.5 mg/time, tid; Vitamin B1 tablets: 10 mg/time, tid; Vitamin B6 tablets: 10 mg/time, tid; Bendazol tablets: 10 mg/time, tid	Diclofenac sodium: 2 weeks; Mecobalamin/ vitamin B1/vitamin B6 tablets: 4 weeks	CTQ-SSS CTQ-FSS CMAP SNAP SNCV DML Responder rate
Tezel et al., 2019	51/44	E: 26/24 C: 25/20	E: 47.1 ± 7.7 C: 46.6 ± 8.1	E: 23/1 C: 19/1	NI	MA + night splints	20 min/session 2 sessions/week	5 weeks	Night splints	NI	5 weeks	CTQ-SSS CTQ-FSS VAS CAMP DML MNCV SNCV
Bahrami-Taghanaki et al., 2020	60/49	E: 30/25 C: 30/24	36.36 ± 7.74	NI	NI	MA + night splints	30 min/session 3 sessions/week	4 weeks	Celebrex tablets + night splints	Celebrex tablets: 100 mg/time, tid	4 weeks	GSS
Xiong, 2020	48/48	E: 24/24 C: 24/24	E: 46.3 ± 11.1 C: 49.2 ± 12.5	E: 16/8 C: 14/10	E: 2.7 ± 1.8 m C: 2.9 ± 1.5 m	EA + ultrashort wave therapy	30 min/session 6 sessions/week	6 weeks	Ultrashort wave therapy	20 min/session 6 sessions/week	6 weeks	CTQ-SSS Responder rate
Huang and Lin, 2022	50/50	E: 25/25 C: 25/25	E: 43.6 ± 6.5 C: 42.7 ± 7.6	E: 24/1 C: 23/2	NI	MA + night splints + ibuprofen	20 min/session 2 sessions/week	4 weeks	Night splints + ibuprofen	Ibuprofen: 400 mg, tid; Night splints: NI	Ibuprofen: 10 days; Night splints: 4 weeks	CTQ-SSS CTQ-FSS VAS DSL DML

E, experimental group; C, control group; min, minutes; m, months; h, hours; y, years; NI, no information; F, female; M, male; MA, manual acupuncture; EA, electroacupuncture; CTQ-SSS, Boston Carpal Tunnel Questionnaire-symptom severity scale; CTQ-FSS, CTQ-functional status scale; GSS, global symptoms score; DASH, disabilities of the arm, shoulder, and hand questionnaire; VAS, visual analog scale; NRS, numerical rating scales; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; DML, distal motor latency; DSL, distal sensory latency; MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

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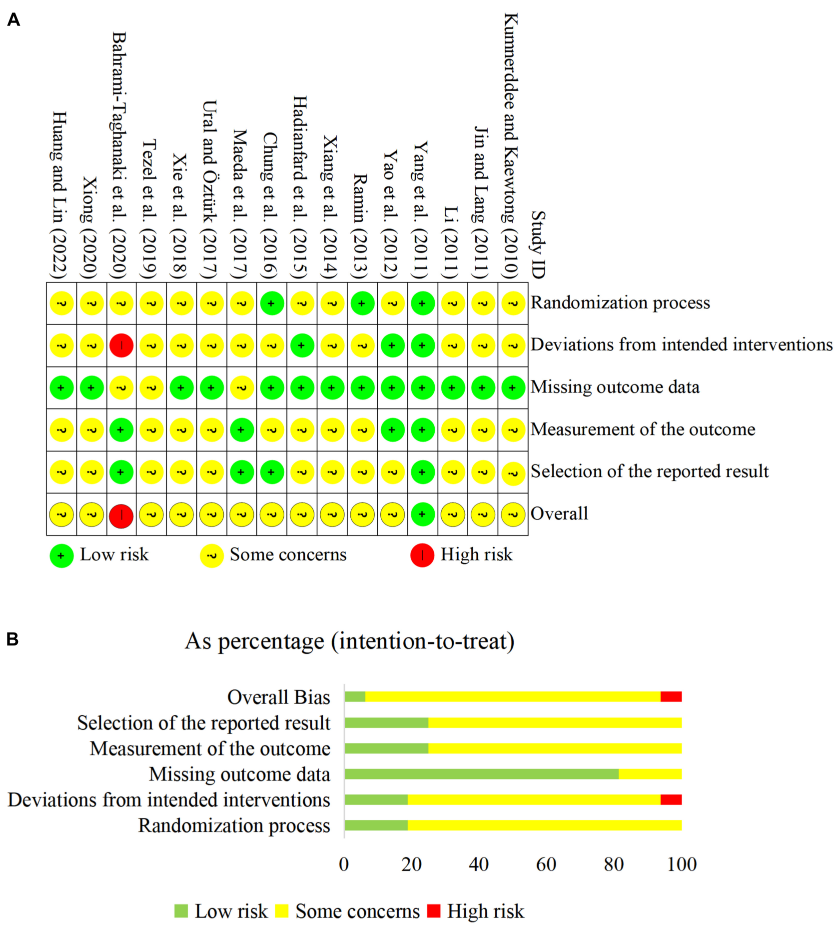

FIGURE 2
The results of risk of bias assessment. **(A)** Risk of bias of individual study; **(B)** overall risk of bias.

Hadianfard et al. (2015) found there was a greater effect of manual acupuncture plus night splints on functional status (CTQ-FSS).

3.5.2.3. Acupuncture plus night splints vs. night splints

The results of the meta-analysis showed that neither symptom severity (CTQ-SSS: SMD = −0.13, 95% CI −0.59 to 0.32, I^2 = 52%) nor functional status (CTQ-FSS: SMD = −0.20, 95% CI −0.87 to 0.46, I^2 = 76%) was significantly different between the acupuncture plus the night splints group and the night splints group (**Figure 5A**). However, the improvement of functional status measured by DASH was greater in the acupuncture plus night splints group than in the night splints group (change of DASH: SMD = −0.40, 95% CI −0.68 to −0.13, I^2 = 0%) (**Figure 5B**).

3.5.2.4. Acupuncture plus medicine vs. medicine

According to pooled results, the acupuncture plus medicine group had lower symptom severity (CTQ-SSS/GSS: SMD = −1.17, 95% CI −2.31 to −0.03, I^2 = 93%) than the medicine group (**Figure 6A**), but the functional status (CTQ-FSS: MD = −2.17, 95% CI −6.45 to 2.10, I^2 = 98%) was not significantly different between the two groups (**Figure 6B**).

3.5.2.5. Acupuncture plus ultrashort wave therapy vs. ultrashort wave therapy

Xiong (2020) observed that patients who received acupuncture plus ultrashort wave therapy had lower symptom severity (CTQ-SSS) compared with those who received ultrashort wave therapy alone.

3.5.2.6. Acupuncture plus medicine plus night splints vs. medicine plus night splints

One RCT (Huang and Lin, 2022) found that adjunctive manual acupuncture in addition to night splints and ibuprofen treatment could improve symptom severity (CTQ-SSS) and functional status (CTQ-FSS) better than night splints plus ibuprofen treatment.

3.6. Secondary outcomes (pain intensity)

3.6.1. Acupuncture as monotherapy

Kumnerddee and Kaewtong (2010) reported that the electroacupuncture group showed a greater reduction in VAS than the night splints group.

3.6.2. Acupuncture as adjuvant treatment

3.6.2.1. Acupuncture plus night splints vs. medicine plus night splints

Hadianfard et al. (2015) observed that manual acupuncture plus night splints had a better effect than medicine plus night splints in decreasing VAS.

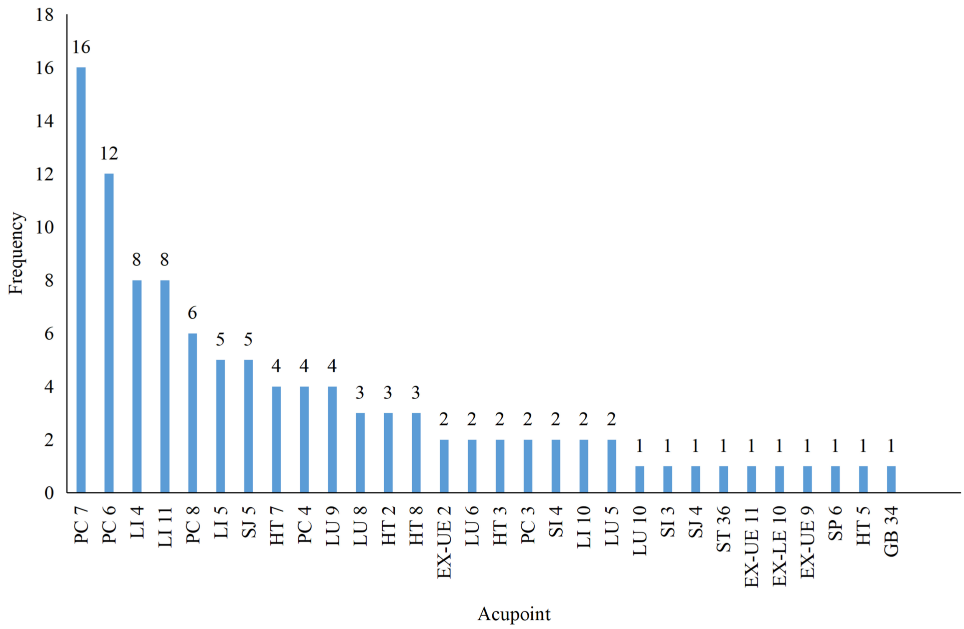

FIGURE 3
The frequency of acupoints selection.

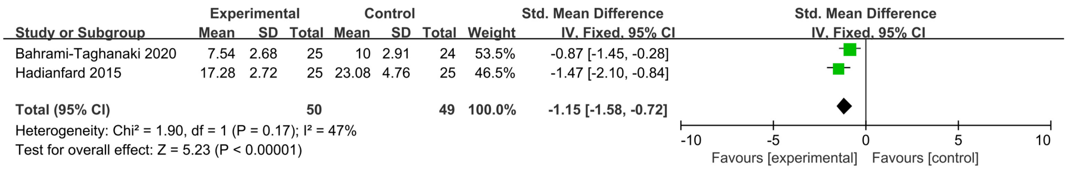

FIGURE 4
A meta-analysis of symptom severity of acupuncture plus night splints vs. medicine plus night splints.

3.6.2.2. Acupuncture plus night splints vs. night splints

Meta-analysis results from three studies (Chung et al., 2016; Ural and Özturk, 2017; Tezel et al., 2019) showed that the acupuncture plus night splints group had lower pain intensity than the night splints group (VAS: MD = −1.65, 95% CI −3.05 to −0.26, I^2 = 91%) (**Figure 7**).

3.6.2.3. Acupuncture plus medicine vs. medicine

Xiang et al. (2014) suggested that electroacupuncture plus medicine treatment was superior to medical treatment in relieving pain as measured by the NRS.

3.6.2.4. Acupuncture plus medicine plus night splints vs. medicine plus night splints

Huang and Lin (2022) found that manual acupuncture plus medicine and night splints were more effective in improving VAS scores than medicine plus night splints.

3.7. Secondary outcomes (electrophysiological parameters)

The results for electrophysiological parameters are shown in **Table 2**.

3.7.1. Acupuncture as monotherapy

Compared with medicine, the acupuncture group had a lower CMAP (MD = −1.02, 95% CI −2.02 to −0.03, I^2 = 46%). No differences were found in DML, DSL, MNCV, SNAP, and SNCV between the two groups.

3.7.2. Acupuncture as an adjunctive treatment

3.7.2.1. Acupuncture plus night splints vs. medicine plus night splints

Hadianfard et al. (2015) found a faster MNCV and shorter DSL in the acupuncture plus night splints group than in the medicine plus night splints group. However, no difference in DML existed between the two groups.

3.7.2.2. Acupuncture plus night splints vs. night splints

There were no differences between the acupuncture plus night splints group and the night splints group in CMAP, DML, MNCV, SNCV, and SNAP.

3.7.2.3. Acupuncture plus medicine vs. medicine

Compared with the medicine group, the acupuncture plus medicine group showed higher CMAP (MD = 2.30, 95% CI 0.84 to 3.77, I^2 = 81%) and SNAP (MD = 2.53, 95% CI 1.63 to 3.44, I^2 = 0%), shorter DML (MD = −0.47, 95% CI −0.66 to −0.28, I^2 = 32%), and faster SNCV (MD = 4.02, 95% CI 2.44 to 5.59, I^2 = 0%).

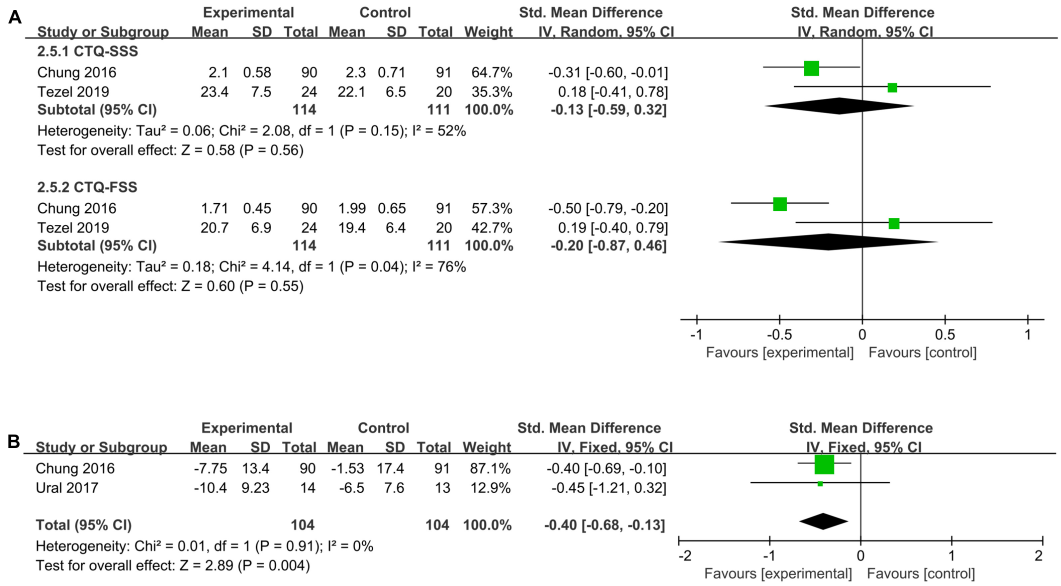

FIGURE 5
A meta-analysis of symptom severity and functional status of acupuncture plus night splints vs. night splints. **(A)** CTQ-SSS and CTQ-FSS; **(B)** change of DASH.

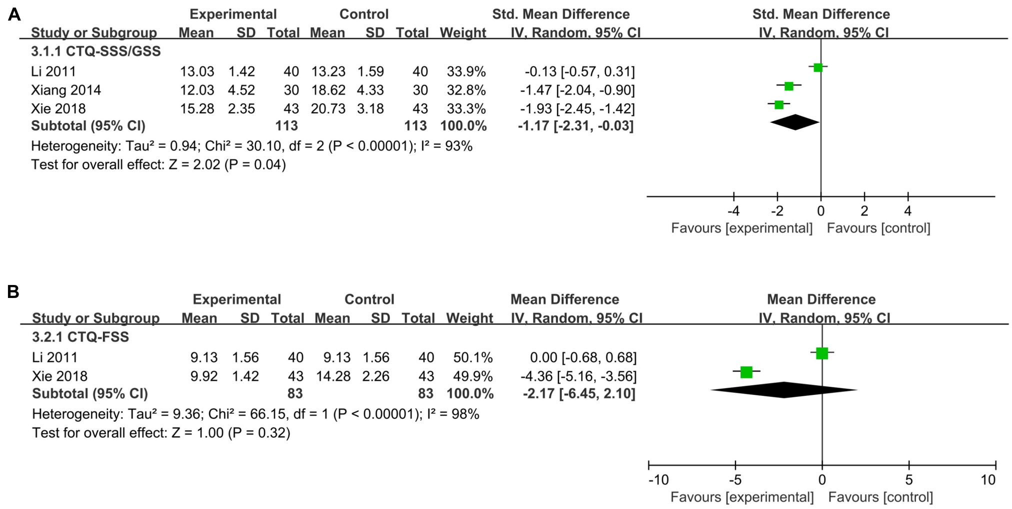

FIGURE 6
A meta-analysis of symptom severity and functional status of acupuncture plus medicine vs. medicine. **(A)** CTQ-SSS/GSS; **(B)** CTQ-FSS.

3.7.2.4. Acupuncture plus medicine and night splints vs. medicine plus night splints

Huang and Lin (2022) found that the DML showed no significant difference between the acupuncture plus medicine and night splints group and the medicine plus night splints group, but the DSL was shorter in the acupuncture plus medicine and night splints group.

3.8. Responder rate

Three studies (Jin and Lang, 2011; Xie et al., 2018; Xiong, 2020) provided the responder rate. Jin and Lang (2011) reported a comparable responder rate between the acupuncture group and the medicine group. Xie et al. (2018) reported a superior responder rate in the acupuncture plus medicine group than the medicine group. Xiong (2020) observed that acupuncture plus ultrashort wave therapy had no better than ultrashort wave therapy in responder rate.

3.9. Adverse events

Four studies (Jin and Lang, 2011; Yang et al., 2011; Yao et al., 2012; Tezel et al., 2019) found no adverse events or serious adverse events related to acupuncture treatment occured. Kumnerddee and Kaewtong (2010) observed 6 of 30 cases in electroacupuncture group experienced skin bruises but no serious complication took place. Another study (Chung et al., 2016) reported electroacupuncture-related adverse events, including

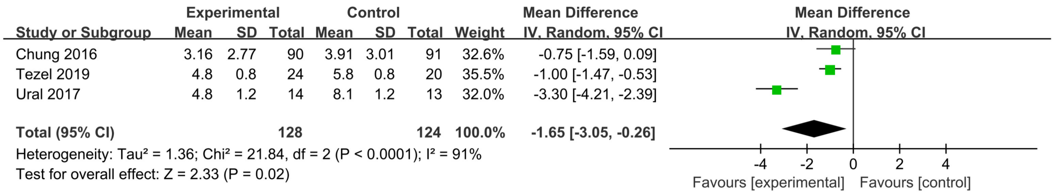

FIGURE 7
A meta-analysis of pain intensity of acupuncture plus night splints vs. night splints.

TABLE 2 The results of electrophysiological parameters for all comparisons.

Comparison	Experimental group vs. control group	Outcomes	Number of studies	Intergroup differences		Heterogeneity (I^2)
				MD (95% CI)	*P*	
Acupuncture as monotherapy	Acupuncture vs. medicine	CMAP (mv)	3	−1.02 (−2.02 to −0.03)	0.04	46%
		DML (ms)	3	−0.31 (−0.96 to 0.34)	0.35	75%
		MNCV (m/s)	2	−3.57 (−13.79 to 6.65)	0.49	92%
		SNAP (μv)	2	−3.14 (−6.84 to 0.56)	0.10	0%
		SNCV (m/s)	3	−1.12 (−6.39 to 4.14)	0.68	79%
		DSL (ms)	2	−0.05 (−0.78 to 0.69)	0.90	84%
Acupuncture as adjunctive therapy	Acupuncture plus medicine vs. medicine	CMAP (mv)	3	2.30 (0.84 to 3.77)	0.002	81%
		DML (ms)	3	−0.47 (−0.66 to −0.28)	<0.00001	32%
		SNCV (m/s)	3	4.02 (2.44 to 5.59)	<0.00001	0%
		SNAP (μv)	3	2.53 (1.63 to 3.44)	<0.00001	0%
	Acupuncture plus night splints vs. night splints	CMAP (mv)	2	1.31 (−1.04 to 3.66)	0.27	58%
		DML (ms)	2	0.05 (−0.33 to 0.43)	0.79	0%
		MNCV (m/s)	2	1.81 (−0.55 to 4.18)	0.13	0%
		SNCV (m/s)	2	0.24 (−2.20 to 2.67)	0.85	0%
		SNAP (μv)	1	3.20 (−0.73 to 7.13)	0.11	–
	Acupuncture plus medicine plus night splints vs. medicine plus night splints	DML (ms)	1	−0.22 (−0.48 to 0.04)	0.09	–
		DSL (ms)	1	−0.53 (−0.75 to −0.31)	<0.00001	–
	Acupuncture plus night splints vs. Medicine plus night splints	DML (ms)	1	−0.20 (−0.43 to 0.03)	0.09	–
		MNCV (m/s)	1	1.76 (0.68 to 2.84)	0.001	–
		DSL (ms)	1	−0.26 (−0.37 to −0.15)	<0.00001	–

CMAP, compound muscle action potential; SNAP, sensory nerve action potential; DML, distal motor latency; DSL, distal sensory latency; MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

bruises at acupoints (4/90), mild local dermatitis around acupoints (3/90), increased pain (2/90), and numbness and tingling after electroacupuncture treatment (2/90), and the above adverse events disappeared within a week. The rest of the 10 studies provided no information on the adverse events.

3.10. Certainty of evidence

There was low and very low certainty of evidence attributed to some concern risk of bias, imprecision, and strongly suspected publication bias. A summary of the finding table is provided in **Supplementary material 4**.

4. Discussion

4.1. Summary of main results

We included 16 RCTs with 1,025 subjects and explored the effect of acupuncture as monotherapy and adjunctive therapy on CTS. Compared with night splints, acupuncture alone was more effective in relieving pain, but there were no differences in symptom severity and functional status. Acupuncture had no advantage over medicine in improving symptom severity or electrophysiological parameters. As an adjunctive treatment, acupuncture might effectively alleviate symptom severity, functional status, pain intensity, and electrophysiological parameters.

Meanwhile, acupuncture as adjunctive therapy was more effective than medicine to ameliorate symptom severity, functional status, pain intensity, and electrophysiological parameters. According to narrative analysis, acupuncture as monotherapy or adjunctive therapy, showed no superiority to sham acupuncture. Few acupuncture-related adverse events were reported. The above evidence had low or very low certainty.

4.2. Compared with previous reviews

Sim et al. (2011) included six RCTs and published the first systematic review of acupuncture for CTS, but three of the RCTs they identified were excluded from our study because the participants received other traditional Chinese medicine in one RCT (Shi et al., 2006) and cointerventions between groups were not comparable in the other two RCTs (Hu et al., 2000; Cai, 2007). Limited by insufficient RCTs, Sim et al. (2011) summarized the evidence of acupuncture for CTS as encouraging but not convincing. Choi et al. (2018) also found insufficient evidence to assess the effect of acupuncture and related interventions on CTS with 12 identified RCTs. Wu et al. (2020) conducted the latest systematic review involving 10 RCTs. Except for manual and electroacupuncture, they included laser acupuncture, moxibustion, and transcutaneous electrical nerve stimulation treatment. They drew the conclusion that acupuncture and related therapies appeared to be effective in improving symptoms, function, and pain in CTS, and emphasized that the validity of such a conclusion was limited. We included 16 RCTs to update the evidence and investigate the effect of acupuncture as monotherapy or adjunctive therapy for CTS.

4.3. The effect of acupuncture on CTS

The narrative analysis showed that neither acupuncture alone nor acupuncture as a adjunctive treatment had superiority over sham acupuncture. However, these results were derived from two independent studies, respectively (Yao et al., 2012; Maeda et al., 2017). Given the limited studies and risk of the underrated effect of acupuncture in sham-control trials with a small sample size (Lundeberg et al., 2008; Birch et al., 2022a,b), we failed to identify the advantage of acupuncture over sham acupuncture for CTS, which should continue to be explored in future studies.

One included RCT showed that 10-session acupuncture alone might be more effective than night splints in relieving pain intensity but not symptom severity or functional status. Night splints are recommended for CTS to improve short-term symptoms and function (Erickson et al., 2019). Whether there is a different long-term effect between acupuncture and night splints is unknown. No clear advantages of acupuncture as a monotherapy were observed compared with medicine. Among comparative medicines used in included studies, such as prednisolone (Yang et al., 2011; Ramin, 2013) and oral vitamin B12 (Jin and Lang, 2011), only prednisolone was recommended by the AAOS. Yang et al. (2011) found that patients with CTS who received acupuncture had a lower recurrence rate than those who received prednisolone in the 1-year follow-up period, which indicated acupuncture might have a better long-term effect than prednisolone. Due to insufficient studies, we were unable to compare the effect of acupuncture with other active treatments. More relevant head-to-head trials should be conducted in the future to focus on clinical and cost effects.

Patients with CTS who received acupuncture plus other treatment(s) showed more improvement in symptoms, function, or pain. However, these positive findings of acupuncture as adjunctive therapy came from open-label RCTs, which could be influenced by the patients' subjective intentions. Based on the results of electrophysiological parameters, we found acupuncture combined with medicine could improve median nerve function better than medicine alone, which provided objective evidence for the adjunctive effect of acupuncture. However, the adjunctive effect of acupuncture should be further investigated in clinical trials with objective outcomes.

4.4. Implications for future research

The outcomes that were measured by subjective tools, such as CTQ, GSS, DASH, and VAS, relied on participants' self-reports, which might induce measurement bias favoring acupuncture in open-label studies. Therefore, studies using objective outcomes are vital to build convincing evidence of acupuncture for CTS. According to the ROB 2 assessment, allocation concealment and advanced registration, or protocol, should be improved to enhance the credibility of the evidence. Meanwhile, in compliance with the STRICTA, authors should take care to report the details of the intervention, especially in items of acupuncture rationale, cointerventions, practitioner background and control or comparator interventions.

4.5. Limitations

Our systematic review and meta-analysis included the latest RCTs and assessed the effect of acupuncture on CTS. However, several limitations exist and should be considered. In the present review, the small sample size, substantial heterogeneity, and potential risk of bias of the included studies reduced the certainty of the evidence. Thus, the findings should be treated with caution. Owing to limited RCTs and data, we failed to investigate the advantages of different acupuncture techniques, identify the optimal parameters of the acupuncture protocol, or explore the follow-up effect of acupuncture.

5. Conclusion

Acupuncture as an adjunctive treatment may be effective for patients with CTS. In addition, more rigorous studies with objective outcomes are needed to investigate the effect of acupuncture in contrast with sham acupuncture or other active treatments.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

RJ and HF conceptualized the study and provided methodological support. PY and GC selected the studies. JL and JD extracted the data. QD and XL assessed the risk of bias and wrote and edited the manuscript. HF and QD assessed the reporting quality of the intervention. FW and YY evaluated the grade. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1097455/full#supplementary-material

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A bibliometric analysis of traditional Chinese non-pharmacological therapies in the treatment of knee osteoarthritis from 2012 to 2022

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Objective: The benefits of traditional Chinese non-pharmacological therapies in the treatment of Knee osteoarthritis (KOA) are receiving increasing attention. Therefore, this study aims to systematically analyze the global research on the treatment of KOA by Chinese traditional non-pharmacological therapies using bibliometric analysis and present the results with a knowledge map form.

Methods: Literature related to traditional Chinese non-pharmacological therapies used in the treatment of KOA from 2012 to 2022 was searched from the Web of Science core database and PubMed database. CiteSpace, SCImago Graphica and VOSviewer were used to extract nations, institutions, journals, authors, references, keywords, as well as the most widely used acupoints, therapies and evaluation indexes.

Results: A total of 375 literature have been included. 32 countries around the world have participated in the research. China, the United States, and Europe were at the center of the global cooperation network. The most prolific institutions and authors were from China represented by Cun-zhi Liu and Jian-feng Tu of Beijing University of Chinese Medicine, the institution with the highest cited frequency was University of York, and "Osteoarthritis Cartilage" was the most frequently cited journal. The most frequently cited literature was "OARSI guidelines for the non-surgical management of knee, hip, and poly articular osteoarthritis." 22 kinds of Chinese non-pharmacological therapies were used to treat KOA, among which acupuncture was the most commonly used one, and ST36 (Zusanli) and WOMAC were the most commonly selected acupoint and evaluation index.

Conclusion: In the past decade, the value of Chinese non-pharmacological therapies in the treatment of KOA has received widespread attention. It was a common concern of global researchers to relieve the pain of KOA patients and restore the quality of life. Under the background that acupuncture accounts for a relatively high proportion, the next step may consider how to make the balanced development of a variety of Chinese non-pharmacological therapies. In addition, the problem of how to eliminate the placebo effect maybe the direction of future research.

KEYWORDS
non-pharmacological therapy, traditional Chinese medicine, bibliometric, knee osteoarthritis, knowledge map

Introduction

Knee osteoarthritis (KOA) is a common chronic joint disease characterized by articular cartilage damage, osteophyte formation, and synovial hyperplasia accompanied by knee pain, and limited function. It was the osteoarthritis with the highest disability rate (Chen et al., 2021), with approximately 14 million patients suffering from KOA in the United States and facing high surgical costs (Deshpande et al., 2016). The Osteoarthritis Research Society International (OARSI) and the U.S. Department of Defense (DoD) have noted the benefits of non-surgical management for the treatment of KOA (Bannuru et al., 2019; Krishnamurthy et al., 2021), however, there is currently no treatment that can reverse the joint damage caused by KOA. KOA is mainly treated to relieve pain and improve joint mobility.

Traditional Chinese non-pharmacological therapies refers to a series of external therapies under the guidance of traditional Chinese medicine theory. Many studies support the benefits of traditional Chinese non-pharmacological therapies including acupuncture, Tai Chi, moxibustion, and many others, which not only improves pain, depression (Zhang and Yuan, 2020; Ho et al., 2021), and sleep quality (Lu et al., 2017), but also helps reduce the operation rates (Gang et al., 2020) and the financial burden on patients. A survey shows that acupuncture as an intervention method of KOA was expected to save 100,000 pounds per year (White A. et al., 2012). The 2014 guidelines for the management of hip and knee osteoarthritis by the National Institute of Health and Clinical Excellence (NICE) recommends non-pharmacological intervention as core intervention (National Institute for Health and Care Excellence, 2014). In summary, traditional Chinese non-pharmacological therapies is a safe, effective, and low side effect option.

Bibliometrics using quantitative methods to describe published studies according to a scientific cartography program that allows researchers to visually find out the evolution process and classical literature of a discipline. It provides an important quantitative basis for macroscopically understanding the key topics and research trends of a discipline. Recently an increasing number of bibliometric analyses have shown potential therapeutic effects of traditional Chinese non-pharmacological therapies in facial palsy (Zhang X. et al., 2012), post-stroke rehabilitation (Sun et al., 2012), cognitive impairment (Li et al., 2021), and cardiac disease (Li et al., 2022), suggesting that bibliometric has been widely used in clinical and basic studies. However, a bibliometric analysis of the use of traditional Chinese non-pharmacological therapies in KOA has not been conducted as far as we know. Therefore, the purpose of this work was to use bibliometric visualization tools to analyze the research status, hotspots, and future trends of Chinese non-pharmacological therapies used in KOA treatment from 2012 to 2022, the results will be displayed in the form of knowledge map.

Materials and methods

From September 2012 to 2022, literature related to the use of traditional Chinese non-pharmacological therapies in KOA was searched in the core database of the Web of Science and PubMed database. The data were searched according to "Knee Osteoarthritis" and "traditional Chinese non-pharmacological therapy," and the specific retrieval formula is shown in **Table 1**. Data retrieval was not limited to the literature type and language. Initially 546 papers were obtained. Then, the repeated literature were further deleted manually, and only the literature related to the treatment of KOA with Chinese non-pharmacological therapy were included. Data collection and analysis were done independently by YL, SJ and MZ, and any differences were resolved through discussion or seeking the help of other authors. Finally, 375 articles were included.

CiteSpace (version6.1.R3) is a software designed to identify the scientific literature and present new trends and developments in the discipline (Chen and Song, 2019). It presents the structure, rule and distribution of subject knowledge in the form of scientific knowledge map that allows the discovery of advances and research frontiers in a given field. VOSviewer (Version1.6.14) is a software for building visual bibliometric networks, constructed by a team of Leiden University (van Eck and Waltman, 2010). Using VOSviewer and SCImago Graphica, we completed studies on national geographic distribution, publication trends of literature, commonly used acupoints, evaluation indexes, and intervention methods. In order to ensure consistency, the top 50 of each element were selected for analysis. The results will be systematically reviewed in accordance with PRISMA guidelines.

Results

Number of published literature and annual trends

From 2012 to 2022, the number of literature on traditional Chinese non-pharmacological therapies in the treatment of KOA showed an overall fluctuating trend, with 375 literature published, or an average of 34 literature per year. After 2019, the number of publications increased significantly. In the same year, China promulgated the "opinions on promoting the inheritance and innovative Development of Traditional Chinese Medicine," clearly pointing out that to promote the inheritance, openness and innovative development of TCM (Huang, 2019), the number of literature on KOA and other TCM treatments was expected to continue to grow in the future (**Figure 1**).

Document type analysis

There were five types of literature in total, of which, 268 "Articles" were the largest type of literature (71.4%), indicating that a large number of clinical and basic trials have been conducted in the past decade to verify the efficacy of traditional Chinese non-pharmacological therapies in the treatment of KOA. This was followed by "Review" with 82 articles, indicating that retrospective research was also valued by researchers, while 25 articles (6.5%) were of other types (**Table 2**).

TABLE 1 Search queries.

Set	Result	Search query
#1	36,538	{TS = [(Knee Osteoarthritis) OR (gonarthritis) OR (gonitis)]}
#2	15,010	{TS = [(baduanjin) OR (qigong) OR (taichi) OR (acupuncture) OR (tuina) OR (Acupotomy) OR (electro-acupuncture) OR (auricular needle) OR (Moxibustion) OR (acupoint) OR (catgut embedding) OR (Yi Jin Jing) OR (acupressure) OR (cupping therapy) OR (fuming-washing therapy) OR (needle knife therapy) OR (wax therapy) OR (bloodletting therapy) OR (intermediate frequency therapy) OR (gua sha)]}
#3	546	Indexes = WoS Core Collection, PubMed
		Editions = SCI Expanded–1900-present
		Timespan = 2012–2022
		#1 AND #2

National analysis

According to the national analysis, a total of 32 countries involved in the research of traditional Chinese non-pharmacological therapies on KOA from 2012 to 2022. China published 252 articles and was the most active country, the United States was the second (71), England (Wang et al., 2021) and South Korea (Vickers et al., 2012). Among them, China and the United States had the strongest correlation, indicating close cooperation among the regions. From the perspective of centrality, the United States ranked first (0.68), followed by Australia (0.21) and China (0.19). The top three most-cited countries were the United States (2363), China (1688), and England (1664; **Table 3**). Regionally, Asia and Europe were the research centers, with a clear clustering phenomenon. For example, China, Japan, South Korea, and Singapore were the major contributors to Asian research, while Spain, England, and Germany were the main drivers of European research (**Figure 2**).

Institutional analysis

According to the analysis of 557 institutions participating in studies of traditional Chinese non-pharmacological therapies on KOA over the past decade, 36 institutions published more than five articles (**Figure 3**), with Beijing University of Chinese Medicine (Tu et al., 2021) published the most, followed by Shanghai University of Chinese Medicine (National Institute for Health and Care Excellence, 2014), and Capital Medical University (White A. et al., 2012), which noted that traditional Chinese non-pharmacological therapies helped to improve pain and restore the knee function in KOA patients (Wang M. et al., 2020; Zhang Y. et al., 2020; Tu et al., 2021), suggesting that this effect may be achieved through the changes of inflammatory cytokines TNG-α, IL-1β, and IL-13 (Shi et al., 2020), which have received more attention in recent years. In terms of centrality, Beijing University of Chinese Medicine (0.1) ranked the top one, followed by Capital Medical University (0.1), and Korea Medical College of Oriental Medicine (0.08). The top three most frequently cited universities were University of York (1314), University of Southampton (1237), and Memorial Sloan-Kettering Cancer Center (1185, **Table 4**). Through the close collaboration with Klee University and Charite, their study indicated that the effect of acupuncture on KOA was related to the amount and duration of acupuncture (MacPherson et al., 2013; Vickers et al., 2018), and the effect was long-lasting (MacPherson et al., 2017), suggesting that acupuncture was a recommended therapy for KOA (Vickers et al., 2012).

Author analysis

Over the past decade, 2,021 authors participated in the study of traditional Chinese non-pharmacological therapies for KOA, among which, 27 authors have published more than five articles. The three authors with the most published literature were Cun-Zhi Liu (Li et al., 2021), Jian-Feng Tu (Li et al., 2021), and Li-Qiong Wang (Zhang X. et al., 2012), who concluded that acupuncture

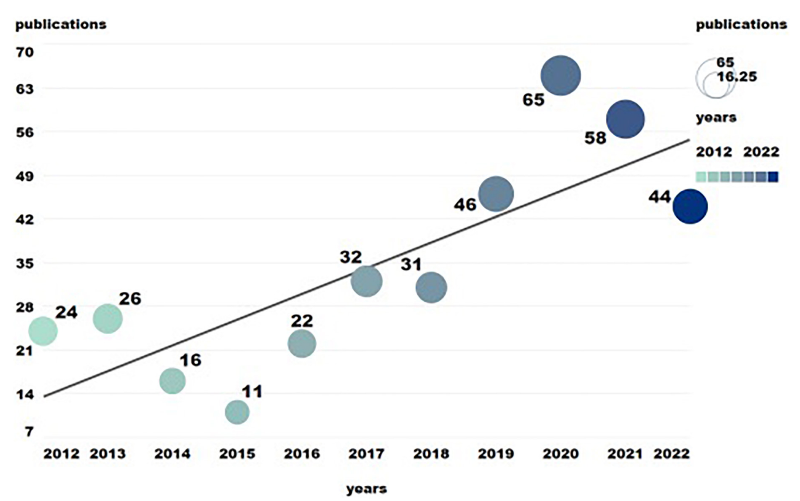

FIGURE 1
The annual number of publications related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

TABLE 2 Document types related to Chinese non-pharmacological therapy on KOA.

Ranking	Type	Counts (%)
1	Article	268 (71.4%)
2	Review	82 (21.8%)
3	Meeting abstract	13 (3.4%)
4	Editorial material	7 (1.8%)
5	Letter	5 (1.3%)

was an effective method by observing specific changes in the brain function in patients with KOA (Zhang N. et al., 2020). They also found that intestinal flora was a possible target (Wang et al., 2021), and improving the frequency of treatment may lead to better outcomes (Lin et al., 2020). The three authors with the highest centrality were Wang X (0.11), Li X (0.08), and Li Y (0.08). The most frequently cited author was Lewith G (1153; Table 5), who draws a negative conclusion on traditional Chinese non-pharmacological therapies, suggesting that acupuncture and Qi Gong were not particularly effective compared to controls and that patient's confidence in the physician and treatment method had a significant effect on the outcome (Macfarlane et al., 2012; White P. et al., 2012). Macpherson H (1128) and Vickers A (1066) also had high citation frequency (Table 5). The authors with the purple outer circles indicate a high between centrality and were core researchers in the research field. The authors with the red mark represent a prominent frequency over a period of time. For example, Macpherson H, Cun-Zhi Liu, and Li-Qiong Wang were the most active authors in the last decade (Figure 4).

Journal analysis

Journal analysis showed that a total of 2,994 journals were cited, of which 107 journals were cited more than 20 times. The most frequently cited journal in total was *Osteoarthritis Cartilage* (560), followed by *Pain* (409), and *Acupuncture in Medicine* (365). The top three journals in terms of centrality were *Arthritis Rheumatism* (0.1), *Arthritis Care Research* (0.08), and *Complementary Therapies*

TABLE 3 Top 10 countries related to Chinese non-pharmacological therapy on KOA.

Rank	Publications	Countries	Centrality	Countries	Citations	Countries
1	252	China	0.68	USA	2363	USA
2	71	USA	0.21	Australia	1688	China
3	27	England	0.19	China	1664	England
4	25	South Korea	0.14	England	1218	Germany
5	19	Australia	0.13	Spain	434	Swizerland
6	11	Germany	0.03	Brazil	407	Australia
7	9	Brazil	0.02	Germany	227	South Korea
8	7	Spain	0.02	Canada	194	Canada
9	6	Canada	0.01	Iran	129	Spain
10	4	Swizerland	0.01	Italy	99	Brazil

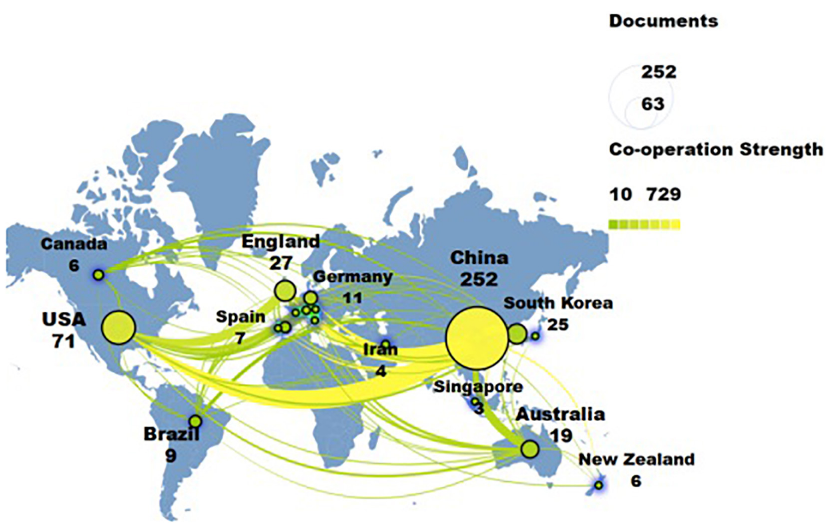

FIGURE 2
The collaboration network of countries researching traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

FIGURE 3
The collaboration map of institutions related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

TABLE 4 Top 10 institutions related to Chinese non-pharmacological therapy on KOA.

Rank	Publications	Institutions	Centrality	Institutions	Citations	Institutions
1	20	Beijing Univ Chinese Med	0.1	Beijing Univ Chinese Med	1314	Univ York
2	10	Shanghai Univ Tradit Chinese Med	0.1	China Acad Chinese Med Sci	1237	Univ Southampton
3	9	Capital Med Univ	0.08	Korea Inst Oriental Med	1185	Mem Sloan Kettering Canc Ctr
4	9	Chengdu Univ Tradit Chinese Med	0.07	Capital Med Univ	1102	Keele Univ
5	8	China Acad Chinese Med Sci	0.06	Fujian Univ Tradit Chinese Med	505	Charite
6	8	Fujian Univ Tradit Chinese Med	0.05	Shanghai Univ Tradit Chinese Med	435	Univ Maryland
7	8	Univ Hong Kong	0.04	Harvard Med Sch	269	Univ Melbourne
8	7	Korea Inst Oriental Med	0.04	Chengdu Univ Tradit Chinese Med	248	Beijing Univ Chinese Med
9	7	Kyung Hee Univ	0.03	Univ Hong Kong	223	Massachusetts Gen Hosp
10	6	Shanghai Jiao Tong Univ	0.02	Massachusetts Gen Hosp	193	China Acad Chinese Med Sci

TABLE 5 Top 10 authors related to Chinese non-pharmacological therapy on KOA.

Rank	Publications	Author	Centrality	Author	Citation	Author
1	13	Cun-Zhi Liu	0.11	Wang X	1153	Lewith G.
2	13	Jian-Feng Tu	0.08	Li X	1128	Macpherson H.
3	11	Li-Qiong Wang	0.06	Li Y	1066	Vickers A.
4	10	Tian-Qi Wang	0.06	Lin L	988	Foster N.
5	10	Fan Wu	0.06	Chen S	985	Witt C.
6	10	Jing-Wen Yang	0.06	Chen X	979	Linde K.
7	9	Li-xing Lao	0.05	Liu J	979	Sherman K.
8	9	Lu-Lu Lin	0.05	Li J	718	Maschino A.
9	9	Xue-Yong Shen	0.05	Li B	641	Cronin A.
10	9	Ling Zhao	0.05	Wu F	275	Kong J.

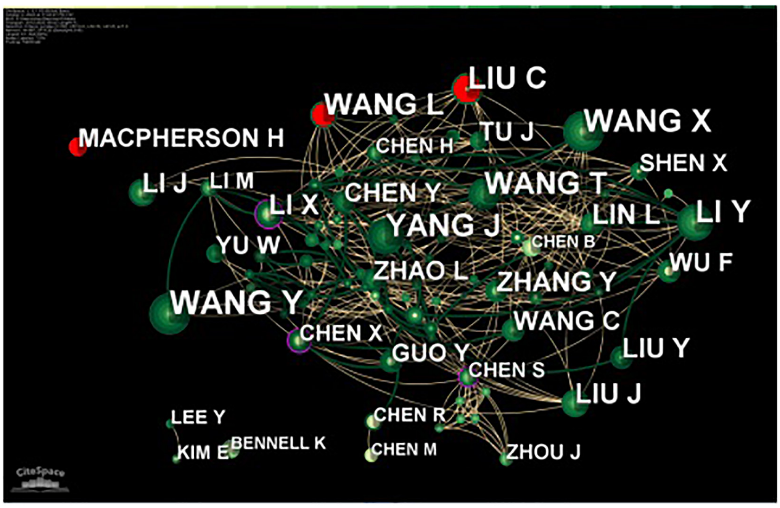

FIGURE 4
The collaboration map of Authors related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

in Medicine (0.08). The top three journals in terms of number of publications were *Evidence-Based Complementary* and *Alternative Medicine* (Wang et al., 2016), *Medicine* (Choi et al., 2017), and *Trials* (Vickers et al., 2012; **Table 6**). Journals with purple outer rings indicate high between centrality, publish important literature and were key hubs for the entire network. Journals marked in red indicate a high highlighting frequency during a given time period. For example, *clinical Journal of Pain*, *Journal of Pain Research*, and *Medicine* were the journals that have been highlighted most frequently in the last 3 years (**Figure 5**).

Reference analysis

We screened the most representative literature about traditional Chinese non-pharmacological therapies in the treatment of KOA from 2012 to 2022. The yellow line represents literature from 2012 to 2015, and the representative cluster labels were "alternative therapy," "group acupuncture" and "exercise prescription," and the green line represents the literature from 2016 to 2022 with the representative cluster labels of "knee osteoarthritis," "massage analgesia," "warm acupuncture," and "non-specific efficacy" (**Figure 6**). We found that the most frequently cited literature was the 2014 guidelines issued by the International Society for Osteoarthritis Research (OARSI), which listed Tai Chi as a core treatment for KOA (McAlindon et al., 2014). In addition, the American College of Rheumatology guidelines also list Tai Chi as a recommended treatment for KOA (Hochberg et al., 2012). These two guidelines have received extensive attention from researchers, and their recommendations have been adopted in a number of studies (**Table 7**). Six of the first 10 cited articles discussed the clinical effects of acupuncture on KOA, and the use of which has received a lot attention from researchers, particularly the placebo effect of acupuncture. A randomized controlled clinical trial published by Hinman RS in JAMA showed that acupuncture was no more beneficial than sham acupuncture in treating chronic knee pain (Hinman et al., 2014).

Keyword analysis

We analyzed literature related to traditional Chinese non-pharmacological therapies on KOA in the past decade and summarized the keywords with the highest co-occurrence frequency and centrality (**Table 8**). The co-occurrence frequency indicates the frequency of the keywords, and the centrality represents the degree to which keywords are noticed. A node with a centrality greater than 0.1 indicates that the node has greater influence in the study. "Knee osteoarthritis" had the highest co-occurrence frequency (211), "adjunctive therapy" (172) and "pain" (160) were three keywords with the highest co-occurrence. The top three keywords in centrality were acupuncture (0.25), chronic pain (0.19), and alternative medicine (0.18). **Figure 7** shows highlighted keywords with red nodes, representing great changes in co-occurrence frequency in a certain period of time and are used to find keywords that are decreasing or increasing. We found that "quality of life," "older adult," and "manual therapy" were the keywords that suddenly dominated the most during the period 2020–2022.

Figure 8 shows the keyword change and keyword clustering over time from 2012 to 2022. We found that the traditional Chinese non-pharmacological therapies such as "Tai Chi," "Qi Gong," "electro-acupuncture," and "auricular acupuncture" will always be high-frequency keywords, and the emotion, inflammation and evaluation scales of KOA patients will also have higher co-occurrence frequency. Among the first 10 keyword clusters, "chronic pain" was the largest cluster with a total of 67 members.

Analysis of therapies, acupoints, and evaluation index

We found that many traditional Chinese non-pharmacological therapies such as acupuncture and moxibustion involve the use of acupoints. In order to understand the use of acupoints in the treatment of KOA, we used VOSviewer and SCImago Graphica

TABLE 6 Top 10 co-cited journals related to Chinese non-pharmacological therapy on KOA.

Rank	Co-citation	Journal	Centrality	Journal	Publications	Journal
1	560	Osteoarthr Cartilage	0.1	Arthritis Rheum-US	40	Evid-Based Compl Alt
2	409	Pain	0.08	Arthrit Care Res	35	Medicine
3	365	Acupunct Med	0.08	Complement Ther Med	25	Trials
4	358	Evid-Based Compl Alt	0.08	J Altern Complem Med	20	Acupunct Med
5	318	ANN Rheum Dis	0.07	Clin J Pain	13	Osteoarthr Cartilage
6	313	ANN Intern Med	0.06	Lancet	13	J Tradit Chin Med
7	264	BMJ-Brit Med J	0.06	Zhen Ci Yan Jiu	11	J Pain Res
8	250	Lancet	0.06	Zhongguo Gu Shang	8	Plos One
9	214	J Alter Complem Med	0.05	Arthrit Care Res	7	BMJ Open
10	206	JAMA	0.05	Arthritis Res Ther	6	Int J Clin Exp Med

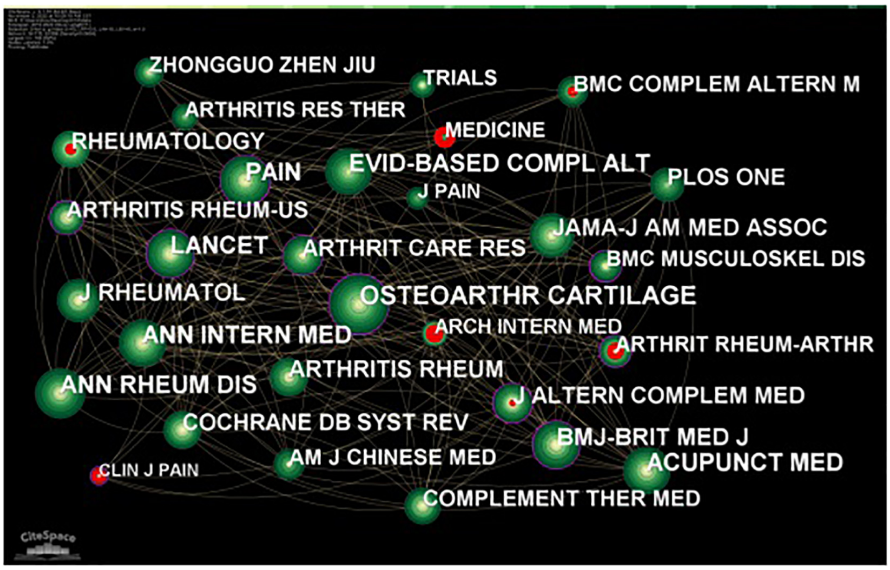

FIGURE 5
The co-cited journal related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

with co-occurrence frequency as screening condition. The most commonly used acupoints for treating KOA were analyzed. In addition, for other traditional Chinese non-pharmacological therapies, we analyzed the use frequency and corresponding evaluation indexes in the same way, hoping to provide ideas and references for researchers and clinicians.

The results showed that a total of 22 Chinese non-pharmacological interventions were used to treat KOA, and 16 interventions were co-occurring more than five times as often (Figure 9). A total of 49 acupoints have been mentioned in the article, 17 of which had a co-occurrence frequency of more than three times (Figure 10), and a total of 112 evaluation indexes were mentioned. Of these, 19 evaluation indicators had a co-occurrence frequency of more than five times (Figure 11).

The three most frequently used acupoints were ST36 (Zusanli), ST10 (Dubi), and GB34 (Yanglingquan). The three most widely used intervention methods were manual acupuncture, electro-acupuncture, and moxibustion, and the three most widely used evaluation indicators were WOMAC, VAS, and SF-36 (Table 9).

Discussion

This study aims to describe the global participation and research trends of traditional Chinese therapies in the treatment of KOA. traditional Chinese non-pharmacological therapies, the benefits of which were gradually being recognized globally, may be a potential treatment for KOA. As the birthplace of traditional Chinese medicine culture, China has a large number of researchers participating in this field. It should be noted that despite the fact that Chinese scientists published the most academic findings, academic publications had little effect, which may be related to the rapid increase in the number of literature in recent years and the lack of domestic academic cooperation. South Korea and Japan were influenced by traditional Chinese medicine (TCM) since the Tang dynasty (Yu et al., 2017). Korea Institute of Oriental Medicine and Kyung Hee University as representative research institutions have made active exploration on the treatment of KOA (Choi et al., 2017, 2021). Western developed countries were also inclined to TCM which has been

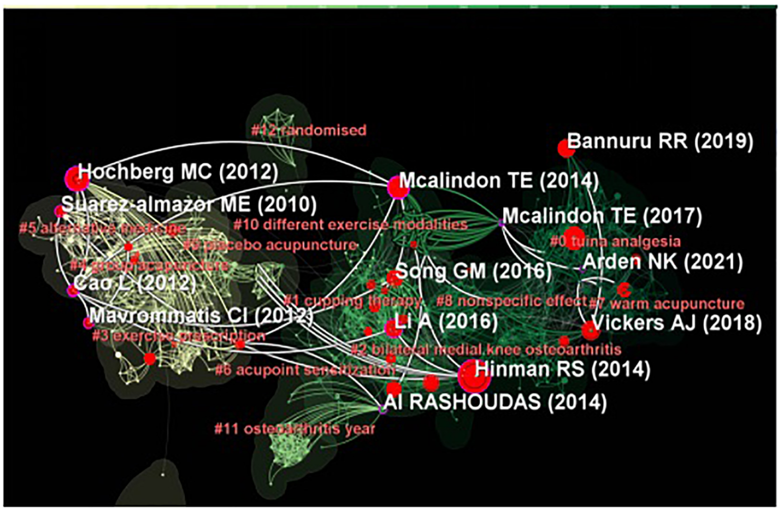

FIGURE 6
The network and cluster map of co-cited references related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

TABLE 7 Top 10 cited references related to Chinese non-pharmacological therapy on KOA.

Rank	Citations	Cited reference	Journal	Representative author (publication year)
1	1741	OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis	Osteoarthritis Cartilage	McAlindon et al. (2014)
2	641	Acupuncture for chronic pain individual patient data meta-analysis	JAMA Intern Med	Vickers et al. (2012)
3	270	Acupuncture for chronic pain: Update of an individual patient data meta-analysis	J Pain	Vickers et al. (2018)
4	146	Acupuncture for chronic knee pain a randomized clinical trial	JAMA	Hinman et al. (2014)
5	106	Evidence-based evaluation of complementary health approaches for pain management in the United States	Mayo Clin Proc	Nahin et al. (2016)
6	102	Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: Network meta-analysis	Osteoarthritis Cartilage	Corbett et al. (2013)
7	84	The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain	PAIN	MacPherson et al. (2017)
8	77	Influence of control group on effect size in trials of acupuncture for chronic pain: A secondary analysis of an individual patient data meta-analysis	PLoS One	MacPherson et al. (2014)
9	76	Pain management with acupuncture in osteoarthritis: A systematic review and meta-analysis	BMC Coplem Altern M	Manyanga et al. (2014)
10	76	Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture	PAIN	White P. et al. (2012)

incorporated into regulations in some countries (Xue et al., 2009; Luo et al., 2018). The International Society for Osteoarthritis Research (OARSI) recommends that acupuncture should be added to the treatment of knee osteoarthritis (Bannuru et al., 2019). National legislation and the introduction of international guidelines has promoted the research in western countries to some extent.

Acupuncture was the most widely used Chinese non-pharmacologic therapy, among which ST36 (Zusanli) was the most frequently used acupoint, while most other acupoints were concentrated near the knee joint, reflecting the distribution of pain sensitivity (Luo et al., 2018). A lot of studies have demonstrated that acupuncture can help relieve pain in patients with KOA, promote recovery and reduce the burden on patients and society (Wang et al., 2016; Ma et al., 2017). Traditional Chinese non-pharmacological therapies such as moxibustion and Tai Chi have also shown high credibility (Liu et al., 2017; Xiao et al., 2020; Guo et al., 2022). The International Society for Osteoarthritis (OARSI) even recommends Tai Chi for all knee osteoarthritis patients because of its satisfactory performance in relieving pain and improving proprioception of knee joints (Woods et al., 2017; Liu et al., 2019; Hu et al., 2020). For the efficacy of traditional Chinese non-pharmacological therapies, researchers generally used WOMAC to evaluate knee joint dysfunction because of its objectivity, effectiveness, and sensitivity (Wolfe, 1999; Lingard et al., 2001; Da et al., 2021). The quality of life

TABLE 8 Top 10 keywords related to Chinese non-pharmacological therapy on KOA.

Rank	Co-occurence	Keyword	Centrality	Keyword
1	211	Knee osteoarthritis	0.25	Acupuncture
2	172	Chronic pain	0.19	Chronic pain
3	160	Acupuncture	0.18	Alternative medicine
4	102	Hip	0.13	Adjunctive therapy
5	106	Osteoarthritis	0.12	Efficacy
6	89	Adjunctive therapy	0.1	Electro-acupuncture
7	85	Randomized controlled trial	0.08	Hip
8	78	Managment	0.08	Randomized controlled trial
9	58	Electro-acupuncture	0.08	Systematic review
10	43	OARIS recommendations	0.08	Older adult

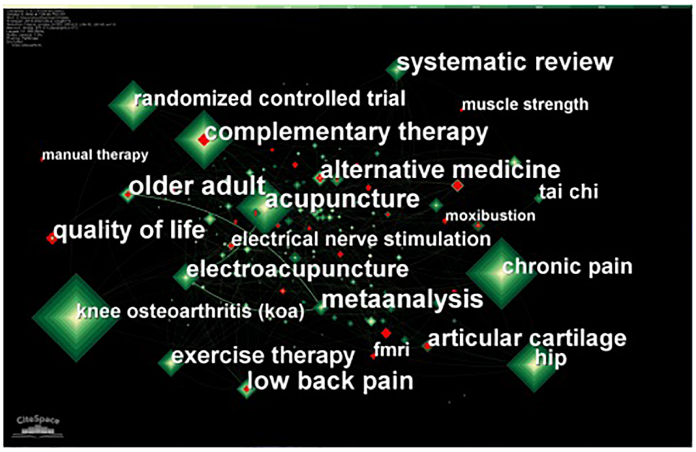

FIGURE 7
The network of co-occurrence keywords related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

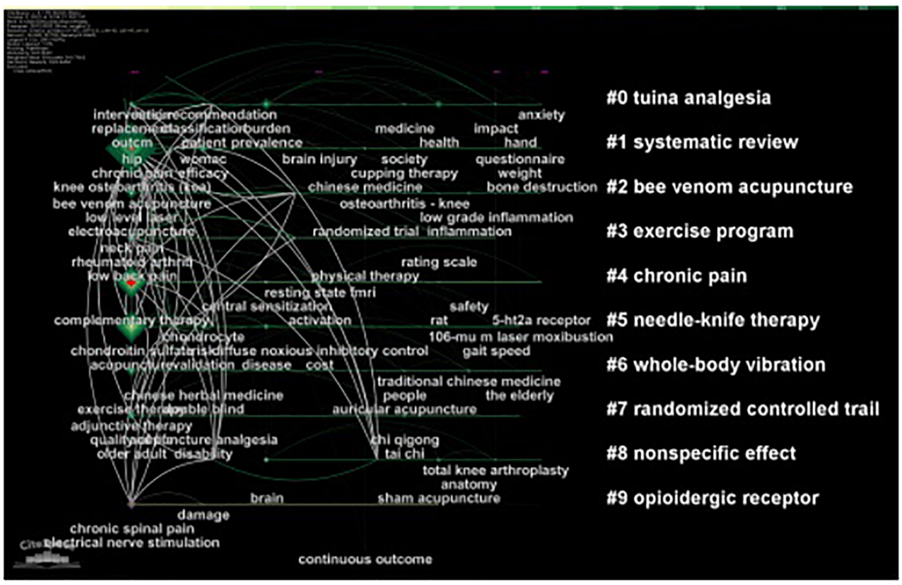

FIGURE 8
The timeline map of co-occurrence keywords related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

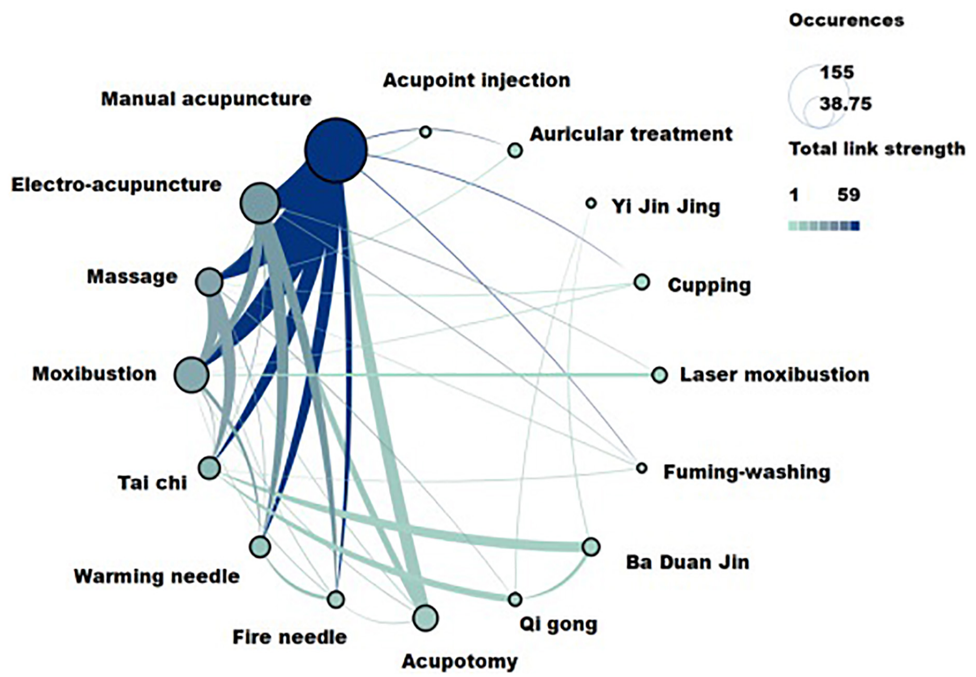

FIGURE 9
The therapies with co-occurrence frequency greater than five related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

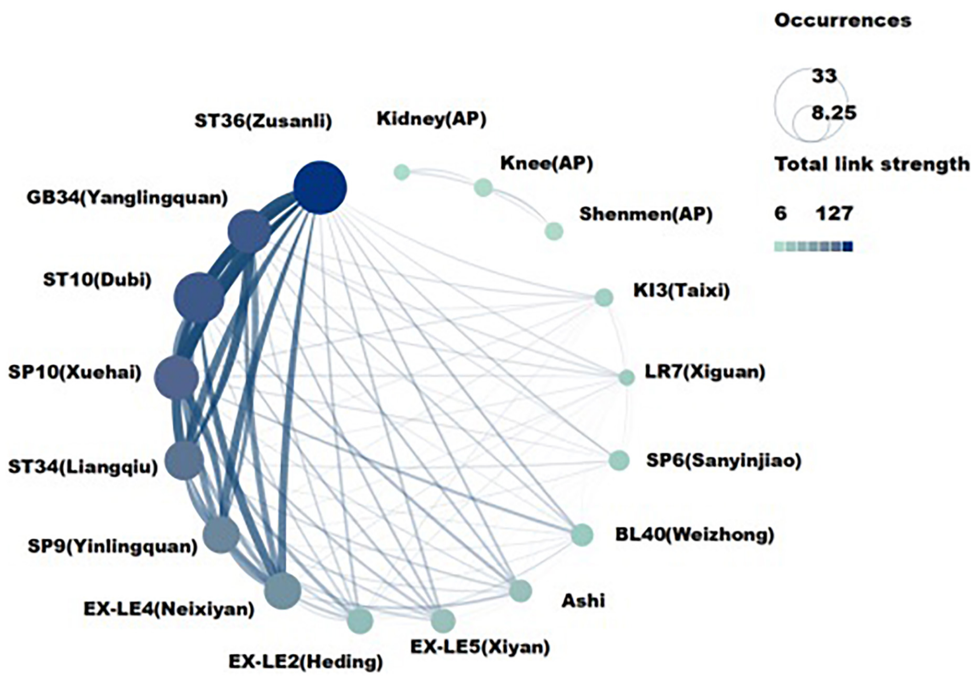

FIGURE 10
The acupoints with co-occurrence frequency greater than five related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA).

and emotion of elderly patients have been paid much more attention in recent years, and the majority of them were female, accounting for about 65% of KOA patients, with an average age of about 65 years (Li et al., 2018; Wang Q. et al., 2020; Zhao et al., 2021), which may be related to post-menopausal osteoporosis (Zhang Y. et al., 2012; Qin et al., 2013). Notably, certain randomized controlled clinical trials have revealed subpar evidence of traditional Chinese non-pharmacological therapy's efficacy against KOA (Li et al., 2017; Lam et al., 2021), and the National Institute for Health and Care Excellence (NICE)

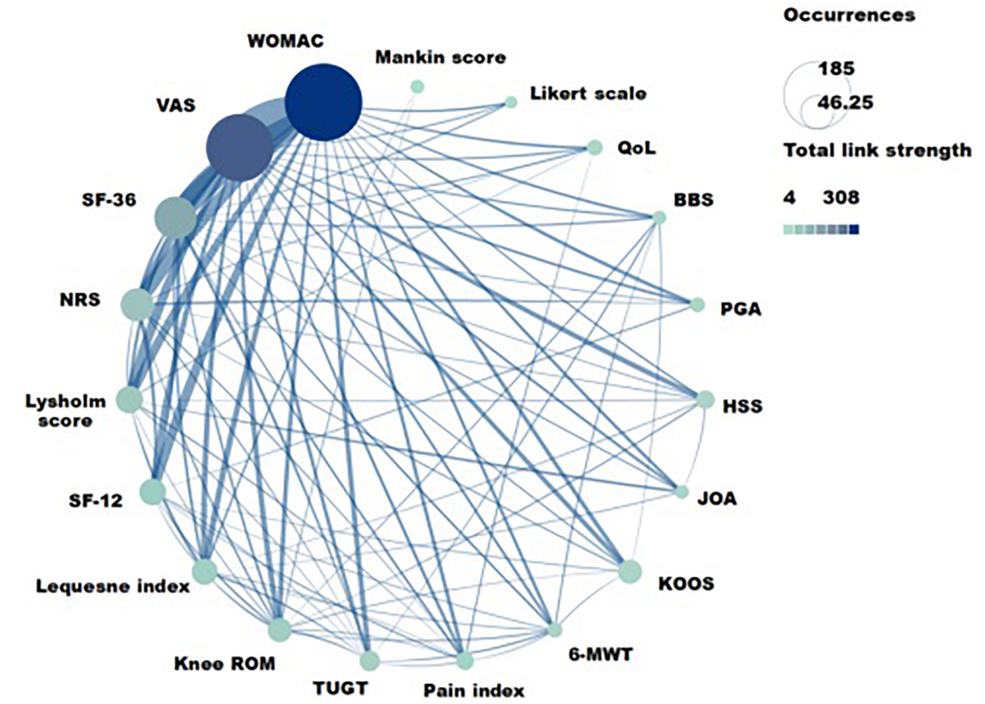

FIGURE 11
The evaluation indexes with co-occurrence frequency greater than five related to traditional Chinese non-pharmacological therapies on knee osteoarthritis (KOA). WOMAC, The western Ontario and McMaster universities osteoarthritis index; VAS, Pain visual analog scale; NRS, Numeric rating scale; Kee ROM, Knee range of motion test; TUGT, Timed up and go test; 6-MWT, 6-Minute walk test; KOOS, The knee injury and osteoarthritis score; JOA, Japanese Orthopedic Association knee score; HSS, Hospital for special surgery knee score; PGA, Patient Global Assessment; BBS, Berg balance scale; QoL, Qualiy of life.

TABLE 9 Top 10 co-occurence indexes, therapies, and acupoints related to Chinese non-pharmacological therapy on KOA.

Rank	Co-occurence	Evaluation index	Co-occurence	Therapies	Co-occurence	Acupoints
1	185	WOMAC	155	Manual acupuncture	33	ST36 (Zusanli)
2	140	VAS	61	Electro-acupuncture	30	ST10 (Dubi)
3	55	SF-36	46	Moxibustion	23	GB34 (Yanglingquan)
4	34	NRS	28	Massage	22	SP10 (Xuehai)
5	23	Lysholm score	24	Acupotomy	18	ST34 (Liangqiu)
6	22	SF-12	18	Tai Chi	16	EX-LE4 (Neixiyan)
7	21	Lequesne index	16	Warming needle	8	EX-LE2 (Heding)
8	18	Knee ROM	11	Ba Duan Jin	7	EX-LE5 (Xiyan)
9	13	TUGT	10	Fire needle	6	SP9 (Yinlingquan)
10	10	Pain index	8	Cupping	6	Ashi

recommendations even advise against the use of acupuncture for osteoarthritis (Conaghan et al., 2008). Therefore, more randomized controlled trials with strict design are needed to confirm the impact of traditional Chinese non-pharmacological therapies on KOA.

Limitations

Citespace software can not directly identify literature from PubMed database, we need to convert the PubMed data into WoS format, which may lead to identification bias of some data, we have tried our best to correct this situation, but there may still be minor deviations.

Conclusion

Chinese non-pharmacological therapies has shown certain advantages in the treatment of KOA and has received wide attention. Relieving pain and restoring quality of life of KOA patients has been a common concern of researchers all over the world. At present, the development of Chinese non-pharmacological therapies was unbalanced with acupuncture accounting for a relatively high proportion, and the application of tuina, moxibustion, and other therapies in KOA needs to be further explored. In addition, how to exclude the possible placebo effect in response to international doubts is also an urgent problem for the future.

Author contributions

XT and XZ contributed to the concept and design of the research. MZ, YL, and SJ conducted the data collection and analysis. SZ and YW wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Mawangdui-Guidance Qigong Exercise for patients with chronic non-specific low back pain: Study protocol of a randomized controlled trial

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Introduction: Worldwide, there is a high frequency of chronic non-specific low back pain (CNLBP), which is a significant public health concern. The etiology is complicated and diverse, and it includes a number of risk factors such as diminished stability and weak core muscles. Mawangdui-Guidance Qigong has been employed extensively to bolster the body in China for countless years. However, the effectiveness of treating CNLBP has not been assessed by a randomized controlled trial (RCT). In order to verify the results of the Mawangdui-Guidance Qigong Exercise and examine its biomechanical mechanism, we intend to perform a randomized controlled trial.

Methods and analysis: Over the course of 4 weeks, 84 individuals with CNLBP will be randomly assigned to receive either Mawangdui-Guidance Qigong Exercise, motor control exercise, or medication (celecoxib). Electromyographic data, including muscle activation time, iEMGs, root mean square value (RMS) and median frequency (MF), will be the main outcomes. The Japanese Orthopedic Association (JOA) Score, the Mcgill Pain Questionnaire (MPQ), beta-endorphin, and substance P are examples of secondary outcomes. At the start of treatment and 4 weeks later, all outcomes will be evaluated. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) will be used for all of the analysis.

Discussion: The prospective findings are anticipated to offer an alternative treatment for CNLBP and provide a possible explanation of the mechanism of Mawangdui-Guidance Qigong Exercise on CNLBP.

Ethics and dissemination: The Sichuan Regional Ethics Review Committee on Traditional Chinese Medicine has given the study approval (Approval No. 2020KL-067). It has also registered at the website of China Clinical Trial Center Registration. The application adheres to the Declaration of Helsinki's tenets (Version Edinburgh 2000). Peer-reviewed papers will be used to publicize the trial's findings.

Trial registration number: ClinicalTrials.gov, identifier ChiCTR2000041080.

KEYWORDS

Qigong, postural balance, paraspinal muscles, RCT, low back pain

Strengths and weaknesses of this research

1. The purpose of this study protocol is to conduct the first-ever single-blinded, randomized controlled trial to assess the effectiveness and potential mechanism of Mawangdui-Guidance Qigong Exercise for CNLBP.
2. Biological markers and EMG data are included in the primary and secondary outcomes. There has been no agreement achieved despite numerous EMG investigations that attempted to disclose the CNLBP with muscle activity sequence mechanism. Beta-endorphin levels and substance P, which are quick, safe, and effective markers to gauge pain relief will be tested.
3. Participants are limited by ages between 20 and 39 for easily identification of specific chronic LBP or CNLBP, further researches on differences of various ages are needed.
4. This is a single-center RCT with limited sample size, multi-center experiments can be conducted to get reproducible and stable results in the future.
5. The treatment duration keeps 4 weeks without longer-term observation, we plan to conduct a follow-up at the 8th and 12th weeks by phone after the trial finished.

Introduction

Pain between the costal margin and inferior gluteal fold is known as low back pain (LBP). Chronic non-specific low back pain (CNLBP) is defined as LBP for at least 12 weeks, which is not caused by a specific pathology such as a tumor, infection, fracture, structural deformity, radiculopathy, osteoporosis, inflammatory disorder, or cauda equina syndrome (Furlan et al., 2009). The literature reports a wide range of estimated prevalence rates for CNLBP, ranging from 4 to 14% (Parthan et al., 2006; van Tulder et al., 2006; Chou et al., 2007). One of the most prevalent musculoskeletal conditions in the world today is CNLBP (Maher et al., 2017). Effective therapies from drugs to surgery for CNLBP are widely used (Ma et al., 2019). NSAIDs, such as Celecoxib and other COX-2 inhibitors are frequently advised for the treatment of CNLBP (Birbara et al., 2003; Katz et al., 2003; Pallay et al., 2004; Airaksinen et al., 2006). The effectiveness of exercise therapy in CNLBP, including pilates, Tai Chi, yoga, and motor control exercise (MCE), has received greater attention in recent years (van Middelkoop et al., 2011; Holtzman and Beggs, 2013; Macedo et al., 2013; Eliks et al., 2019). For the treatment of persistent, nonspecific LBP, exercise therapy has been utilized extensively (Saragiotto et al., 2016).

Mawangdui-Guidance Qigong Exercise is an arising exercise therapy organized and created by the Fitness Qigong Management Center of the State General Administration of Sport of China (Fan, 2002). Traditional Chinese exercises, including Qigong and Tai Chi, are recommended to relieve pain intensity in patients with LBP (Zhang et al., 2019). Qigong may achieve the same efficacy as other exercise therapies in the treatment of CNLBP (Blödt et al., 2015). The pain intensity and back dysfunction are significantly regulated for people who practice Qigong (Phattharasupharerk et al., 2019), and it is safe in the treatment of musculoskeletal pain (Marks, 2019).

In order to assess internal and external postural interference in patients with LBP, the quick arm raise test and the falling ball test by surface electromyograph (sEMG) are frequently utilized (Hodges and Richardson, 1996; Tsao and Hodges, 2008; Jacobs et al., 2017; Xie and Wang, 2019; Larivière and Preuss, 2021; Yu et al., 2021). Although no consensus was established, numerous EMG studies attempted to shed light on the CNLBP with muscle activity sequence mechanism (Geisser et al., 2005; Marshall and Murphy, 2008; Falla and Hodges, 2017). The influence of adjusting posture on pain reduction and disability improvement may be observed by using EMG to examine the changes in muscle initiation time and iEMGs in patients with CNLBP (Yu et al., 2021). The management of spinal postural alignment and overall body balance are thought to depend mostly on the back muscles (Daggfeldt and Thorstensson, 2003;

Abbreviations: CNLBP, chronic non-specific low back pain; RCT, randomized controlled trial; RMS, root mean square value; MF, median frequency; JOA, Japanese Orthopedic Association; MPQ, Mcgill Pain Questionnaire; LBP, low back pain; MCE, motor control exercise; sEMG, surface electromyograph; CDUTCM, Hospital of Chengdu University of Traditional Chinese Medicine; TrA, transverse abdominis muscle; DMC, Data Monitoring Committee.

Christophy et al., 2012). The Chinese Association for the Study of Pain (Ma et al., 2019) advises sEMG y as an objective method of assessing the back muscles' functionality (Akbari et al., 2015).

There is not enough solid evidence to support the high efficacy of Qigong when compared to other various nonoperative treatments. Mawangdui-Guidance Qigong Exercise has not been subjected to a randomized controlled trial (RCT) to determine the effectiveness in treating CNLBP. We strive to confirm the critical function in treating chronic CNLBP by contrasting Mawangdui-Guidance Qigong Exercise with MCE and medication.

Methods and design

Study design

This study is a randomized, single-blinded clinical trial to investigate the effectiveness of Mawangdui-Guidance Qigong Exercise for CNLBP. This study will be conducted at the Hospital of Chengdu University of Traditional Chinese Medicine (CDUTCM). For the duration of the 4-week course of therapy, 84 participants who meet the trial criteria will be assigned at random to the Mawangdui-Guidance Qigong Exercise group, the MCE group, or the medicine group. Participants in Qigong group and MCE group will receive different types of exercise therapies under the supervision of different professional coaches. Others in the medicine group will be given celecoxib orally on a regular basis. EMG data, including muscle activation time, iEMGs, root mean square value (RMS) and median frequency (MF), will be the main outcomes. The Japanese Orthopedic Association (JOA) Score, the Mcgill Pain Questionnaire (MPQ), beta-endorphin, and substance P will be the secondary outcomes. All outcomes will be evaluated at the start of treatment and 4 weeks later. We think Mawangdui-Guidance Qigong Exercise can produce an improvement in pain and lumbar function that is equal to or greater than what the other two groups can.

The study is approved by the Sichuan Regional Ethics Review Committee on Traditional Chinese Medicine (Approval No. 2020KL-067) and registered with China Clinical Trial Center Registration (ChiCTR2000041080). The implementation follows the principles of the Declaration of Helsinki (Version Edinburgh 2000). The SPIRIT guidelines and CONSORT flow diagram will be followed in this investigation. The whole study design will be illustrated as a flow chart in **Figure 1** and the process timetable will be shown in **Table 1**.

Inclusion criteria

Eligible participants who met the following criteria will be included: (i) pain between the costal margin and inferior gluteal fold for at least 12 weeks which is not caused by a specific pathology, (ii) age between 20 and 39 years old, (iii) never received drug treatment, non-pharmacy, or surgical treatments for CNLBP during the previous 12 weeks, and (iv) agree to join the study and sign the written informed consent.

Exclusion criteria

Participants matching any of the following criteria will be excluded: (i) LBP with a specific diagnosis such as lumbar disc herniation, fracture of lumbar vertebra, spinal stenosis, severe osteoarthritis, or ankylosing spondylitis, (ii) be suffering from serious diseases of the heart, liver, kidney, or other organs, (iii) pregnant women, tumor patients, or those with serious disorders, (iv) structural deformity of the lumbar spine, (v) be suffering from other diseases that cause pain, such as migraine, angina, etc., and (vi) patients received surgery, acupuncture, massage, Tuina, spinal manipulation, and NSAIDs treatment in the past 12 weeks.

Interventions

Mawangdui-Guidance Qigong Exercise therapy

For a session of 4 weeks, participants in the experimental group will receive Mawangdui-Guidance Qigong Exercise therapy five times each week. Each exercise will continue for 30 min and be led by a particular coach who is equally skilled and experienced and has received training in how to manage a project. **Figure 2**, **Table 2**, and **Supplementary video 1** show the program of the Mawangdui-Guidance Qigong Exercise's "yinyao" movement.

Motor control exercise

The main goal of these exercises in the MCE group is to normalize the significant motor abnormalities by teaching participants to maintain stable posture while properly contracting their muscles to lessen pain and intensity. Precious study helps to set the MCE strategy (Li et al., 2021). Participants will practice five times a week for 30 min each under the guidance of a specified experienced physiotherapist. **Table 3** depicts the MCE process steps.

Drug treatment

A qualified and experienced doctor who has received the same training as the medicine group will evaluated and give oral celecoxib (Celebrex, Pfizer), 200 mg once daily, for 4 weeks to participant. The doctor will provide drug counseling throughout the duration of the experiment, as well.

To guarantee impartiality and rigor, participants with increased muscle pain after exercise and no obvious relief after rest will be treated with appropriate cryotherapy under the supervision of researchers. However, additional treatments including decoction, Chinese herbs, acupuncture, Tuina, and other painkillers will not be permitted.

Outcome measures

Primary outcomes

Primary outcomes include muscle activation sequence (Hodges, 2001; Suehiro et al., 2015), iEMG, RMS, and MF, generated from sEMG (Thomas et al., 2007; Aruin et al., 2015; Aruin, 2016). The EMG data will be gathered from the probe on the surface of deltoids, lumbar multifidus, transverse abdominis muscle (TrA), erector spinae muscle, gluteus maximus, and hamstrings. Each channel's interelectrode distance will be 10 mm.

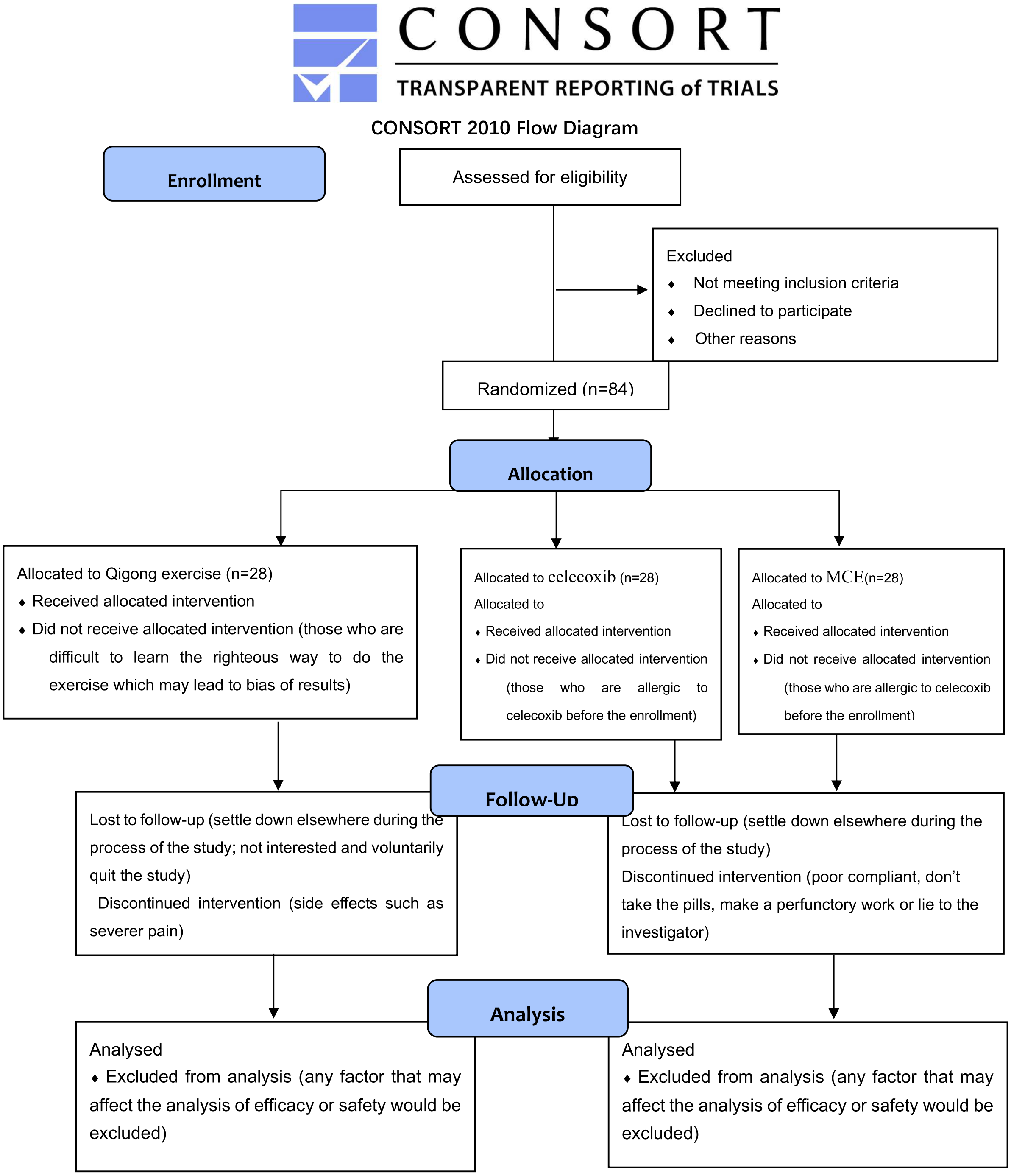

FIGURE 1
Flow chart of the whole study design.

Secondary outcomes

The JOA Score (Oshima et al., 2020) and the McGill Pain Questionnaire (MPQ) (Main, 2016) are the secondary outcomes. JOA Score takes into account bladder function, daily activity, clinical indicators and subjective complaints, with the lowest score of 6 and the highest score of 29. Better functioning conditions are indicated by higher overall scores. MPQ is made up of 15 carefully chosen words, comprising 4 emotional and 11 sensory words. Each item is given a number from 0 to 3, with a higher score denotes a severer symptom (Choi et al., 2015). Biomarkers like substance P (Bhatia, 2015) and beta-endorphin (Choi and Lee, 2019) will also be tested.

All the primary and secondary outcomes will be assessed before and 1 week after treatment.

Adverse events

Researchers will keep track of adverse events and evaluate the correlation with therapies. Once relevant severe adverse event

TABLE 1 Process timetable.

		Study period							
		Enrollment	Allocation	Post allocation			Close-out	Follow-up	
Timepoint	Week	−1	0	1	2	3	4	8	12
Enrollment									
Inclusion/exclusion criteria		√							
Informed consent		√							
Medical history		√		√	√	√	√		
Laboratory tests		√					√		
Muscle action time, EMG data		√					√		
JOA, MPQ		√					√		
Random allocation			√						
Interventions									
Mawangdui-Guidance Qigong Exercise					⟶				
MCE					⟶				
Celecoxib					⟶				
Assessments									
Laboratory tests		√					√		
Muscle action time, EMG data		√					√		
JOA, MPQ		√					√	√	√
Adverse events				√	√	√		√	√
Safety evaluation							√	√	√

occurs (major damage to the heart, liver, kidneys, or other organs), the researchers will evaluate the participant can continue this trial or not. If serious adverse reactions occur, visits will continue after safety and treatment after the patient's trial is suspended.

Sample size

By utilizing a two-sided 0.05 level *t*-test with >95% power and assuming a 10% dropout rate, the sample size was estimated to demonstrate the influence of the target muscles on MF (Zhou, 2018). To detect a target effect size of 0.44 (GPower 3.1) with 28 participants in each group, a sample size of 84 participants is needed.

Participants recruitment

Chronic non-specific low back pain is an exclusionary diagnosis. Patients with chronic LBP who do not have particular illnesses will be given this diagnosis (Koes et al., 2006). Eligible patients will be recruited from the Department of Orthopedics of Chengdu University of Traditional Chinese Medicine (CDUTCM). To ensure that recruitment messages are easily received by patients interested in the trial, recruitment posters and leaflets are placed in hospital lobbies and orthopedic clinics. Patients can also contact the staff through WeChat and the hospital website to sign up for the trial. In order to improve compliance, participants will be fully informed before signing informed consent. Researchers will keep track of participants' compliance, including monitoring drug use and exercise on a regular basis. The participant recruiting process started on 23 October 2022, is still running, and it should be finished by 31 December 2022.

Allocation

Eligible patients will be randomly assigned to the Qigong group (n = 28), the MCE group (n = 28), or the medication group (n = 28) according to the inclusion and exclusion criteria with a ratio of 1:1:1. Prior to intervention, each patient will receive a random number in a sealed envelope. An automated random number generator created this random number, which is specific to each row in the table. A randomizer will assign patients to the experimental or control groups. An assessor who is unrelated to the study will maintain absolute confidentiality regarding the allocation list.

Blinding

In this study, a single blind approach will be used to execute the Mawangdui-Guidance Qigong Exercise. It is impossible to blind participants and researchers to the group assignment. The same unbiased, skilled evaluators who are blind to the allocation will measure each result.

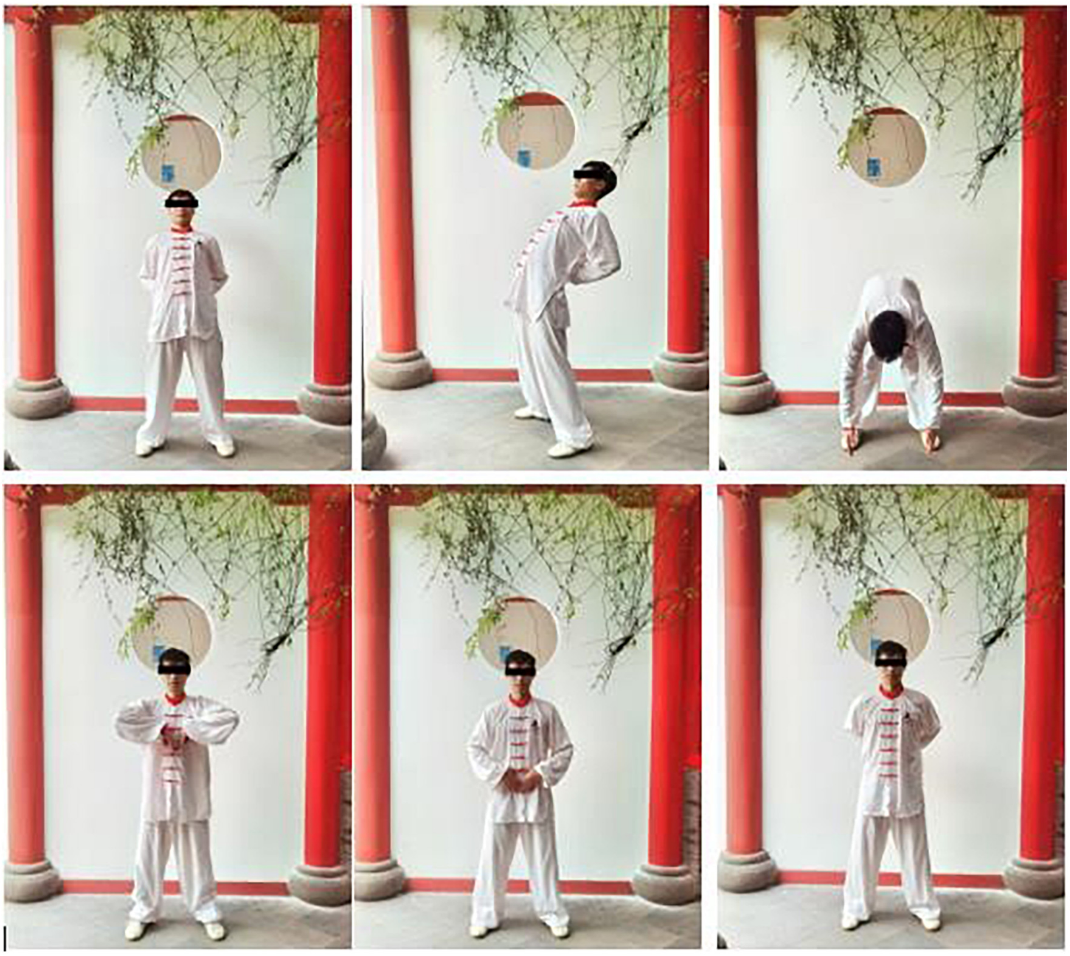

FIGURE 2
The action of the Mawangdui-Guidance Qigong Exercise's "yinyao" movement.

Data collecting and monitoring

The Data Monitoring Committee (DMC) for Medical Data in this project is the Chengdu University of Traditional Chinese Medicine Evidence-based Medicine Center. Designated outcome assessors will record data on paper and computerized CRFs, and the DMC will keep an eye on it. Every 3 months, monitors will audit the data. During the evaluation process, coaches and statisticians will not have access to these data.

Statistical analysis

Test-retest reliability and content consistency reliability will be used to gauge the scale's dependability (test-retest reliability). Cronbach's coefficient is the most often used measure of internal consistency reliability. The better the homogeneity, the higher the Cronbach's alpha coefficient. If the scale's consistency is greater than 0.8, it is considered to be good, and if it is greater than 0.7, it is considered to be acceptable.

SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) will be used for all of the analysis. The significance threshold will be set at 0.05, and the confidence interval will be 95%. The χ^2 will be used to analyze categorical data. For continuous variables, mean ± SD will be recorded by using ANOVA test if they were normally distributed, or the median with interquartile range will be shown with Kruskal–Wallis H test. The Bonferroni correction and Tukey *post-hoc* test (for ANOVA) will be used to handle multiple comparisons (for Kruskal–Wallis). The Chi-square test will be used to verify the classification count data. Two-tailed test will be used in this study. The difference will be regarded as statistically significant when $P < 0.05$.

To handle missing data, we will evaluate the underlying cause, employ an imputation adjustment approach, and do a last observation carried forward analysis. Following the primary analysis, a sensitivity analysis will be carried out to determine the effect of missing data on the trial outcomes by contrasting the findings from the per-protocol analysis and the intention to treat analysis. Also planned are subgroup analysis by the center.

Quality assurance

Before agreeing to participate, it will be ensured that each participant meets tight eligibility requirements. All of the researchers have received professional training to understand how to carry out a typical research protocol and the operational requirements. Particularly, there will be individuals in charge of gathering and registering test information. Periodically, the data will be audited by the DMC monitors.

Discussion

The purpose of this study is to explore the effectiveness of Mawangdui-Guidance Qigong Exercise on CNLBP, and to further discuss the potential neuroelectrophysiology mechanism. Lumbar multifidus muscle has been proved crucial to the intersegmental stability of lumbar spine (Beimborn and Morrissey, 1988). Higher level of multifidus muscle activation observed in CNLBP patients is related to muscle spasm and the Pain Adaptation Model (Sherman, 1985; Ahern et al., 1988; Ansari et al., 2018). TrA primarily contributes to the dynamic stability of the lumbar spine by contracting the abdominal muscles to regulate various pain adaption models (van Dieën et al., 2003; Allison and Morris, 2008; da Silva et al., 2017). The data of lumbar multifidus muscle and TrA (Beneck et al., 2016; Shah et al., 2020) are usually collected using sEMG in the study of postural balance in patients with LBP. The relationship between neuromuscular control mechanisms and pain, however, is yet unclear.

Neurological system moderately activates the muscles at the proper time in the event of spinal injury, according to the "spinal stability model" (Panjabi, 1992). Feed-forward, feed-back, and voluntary control makes up of the basic central motor control modes of lumbar spinal stability muscles. According to visual, auditory, postural, and proprioceptive senses as well as feed-forward and feed-back control, the nervous system regulates the lumbar stability muscles to maintain lumbar stability or unconsciously protect the spine. The probable mechanism of Qigong may involve stretching and strengthening the core muscles in the waist. In patients with CNLBP, Mawangdui-Guidance Qigong Exercise, according to our hypothesis, preserves postural stability by altering the order of muscle activation.

Since the pathophysiology of CNLBP is unknown, LBP is frequently included in discussions about CNLBP illness management (Maher et al., 2017). Inflammation may continue throughout the entire course of LBP (Vucetic and Svensson, 1996; Vroomen et al., 2002) and is a key component of both pain and spinal degenerative processes (Wuertz and Haglund, 2013; Risbud and Shapiro, 2014). Beta-endorphin and substance P are also advised as alternatives to inflammatory markers as indicators of how well a treatment is working for patients with LBP (Bhatia, 2015; Choi and Lee, 2019). We believe that Mawangdui-Guidance Qigong Exercise can achieve the same or even more improvement in pain and lumbar function than the other two groups.

Prescription of Mawangdui-Guidance Qigong Exercise revolve limb opening and closing, rotation flexion and extension, stretching, and bone stretching, based on meridian guidance. It is a popular kind of Traditional Chinese Medicine (TCM) rehabilitation exercise therapy recently for cardiovascular, metabolic, and musculoskeletal system diseases (Wang et al., 2014; Sun and Wang, 2015; Chen, 2016; Ding et al., 2019). Though it is beneficial to the changes in the cellular level of elderly women (Wang et al., 2016), generally speaking, application of guidance still focuses on the observation of the overall effect on the body. The current research should focus on the therapeutic impact mechanism of Mawangdui guidance.

Compared with younger people, people over the age of 40 have a higher incidence of degenerative diseases such as lumbar disc herniation (Brinjikji et al., 2015). It is difficult to prove that LBP in patients over 40 years old is not caused by the above-mentioned specific causes. The specificity and non-specificity of LBP can be easily identified in younger people. That is why we designed this RCT with participants limited by ages between 20 and 39. As a result, the current study could not clearly explain the differentiation between various ages, and future researches on the effectiveness of multiple ages are needed. Secondly, since the single-center design with limited sample size may restrict the credibility of this trial, multi-center experiments in the future may help in enhancing the reproducibility and stability of the research. In addition, the treatment duration keeps 4 weeks without longer-term observation, we plan to conduct a follow-up at the 8th and 12th weeks by phone after the trial finished.

By contrasting the efficacy and safety of Mawangdui-Guidance Qigong Exercise in CNLBP treatment with MCE and oral medication, the prospective findings are anticipated to offer an alternative treatment for CNLBP and provide a possible

TABLE 2 The steps of the Mawangdui-Guidance Qigong Exercise's "yinyao" movement training.

i	Relaxed standing, both hands staying at palm, move both palms from abdomen to waist along Belt Vessel with hands sticking to it; palms brace against waist and push it ahead to the body leaned forward.
ii	Both palms move downward to hip and turn body bended, keep moving palms along the back of thighs and shins to heel and moving palms from heel to forward, hanging the arms and palms upon the tiptoes, rise head and look straight ahead.
iii	With the last posture referred in (ii), rotate the waist and lift the left shoulder and palm at the same time, meanwhile, turn the head backward and look to left rear.
iv	Rotate the waist and droop the left shoulder, meanwhile, turn back the head and look to infra-anterior.
v	Lift the body upright as well as the palms lift to the chest with it rotating interior and back of the palms being against to each other along the anterior median line, and look straight ahead.
vi	Move both palms to belly, and move them from abdomen to waist along Belt Vessel with hands sticking to it; palms brace against waist and push it ahead to the body leaned forward.

The main movement is the same as ii–v, except for the rotation of head, waist, and shoulder turns to right. Both palms fall at both sides until the second movement terminated and look straight forward.

TABLE 3 The steps of motor control exercise.

i	In the first step, the participants' ability to control the joint neutral position in the four-point kneeling position will be retrained. The participants learned how to find their postural balance in the basic training.
ii	In the second step, the participants will learn how to control movements in their lumbar spine with minimal effort while moving their arms and legs. Participants will be asked to lift one limb to a horizontal position for 5 s during four-point kneeling. Each limb will be repeated thrice with a break of 15 s.
iii	In the third step, the participants will lift one arm and the contralateral leg to a horizontal position for 5 s. This action will also be repeated three times with a break of 15 s.

explanation of the mechanism of Mawangdui-Guidance Qigong Exercise on CNLBP.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GZ, LG, YS, ZZ, and YH participated in the conception and design of this trial. GZ, DZ, and HL were responsible for planning the draft and revising the manuscript. GZ was monitor of this study. All authors contributed to this work, read the manuscript, and approved the publication of this protocol.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1090138/full#supplementary-material

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Traditional Chinese Manual Therapy (Tuina) reshape the function of default mode network in patients with lumbar disc herniation

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Purpose: Investigating the changes of regional homogeneity (ReHo) values and both static and dynamic functional connectivity (FC) before and after Traditional Chinese Manual Therapy (Tuina) in patients with lumbar disk herniation (LDH) through resting-state functional magnetic resonance imaging (RS-fMRI). Based on this, we observe the effect of Tuina on the above abnormal changes.

Methods: Patients with LDH (n = 27) and healthy controls (HCs) (n = 28) were recruited. The functional magnetic resonance imaging (fMRI) scanning was performed two times in LDH patients, before Tuina (time point 1, LDH-pre) and after the sixth Tuina (time point 2, LDH-pos). And for one time in HCs which received no intervention. The ReHo values were compared between LDH-pre and HCs. The significant clusters detected by ReHo analysis were selected as seeds to calculate static functional connectivity (sFC). We also applied the sliding-window to perform dynamic functional connectivity (dFC). To evaluate the Tuina effect, the mean ReHo and FC values (both static and dynamic) were extracted from significant clusters and compared between LDH and HCs.

Results: In comparison to HCs, LDH patients displayed decreased ReHo in the left orbital part middle frontal gyrus (LO-MFG). For sFC analysis, no significant difference was found. However, we found decreased dFC variance between LO-MFG and the left Fusiform, and increased dFC variance in the left orbital inferior frontal gyrus and left precuneus. Both ReHo and dFC values revealed after Tuina, the brain activities in LDH patients were similar to HCs.

Conclusion: The present study characterized the altered patterns of regional homogeneity in spontaneous brain activity and those of functional connectivity in patients with LDH. Tuina can reshape the function of the default mode network (DMN) in LDH patients, which may contribute to the analgesic effect of Tuina in LDH patients.

KEYWORDS

lumbar disc herniation, resting-state fMRI, regional homogeneity, functional connectivity, Tuina

Introduction

Lumbar disc herniation (LDH), defined as the displacement of lumbar disc material beyond the limits of the disc space, is one of the most common spinal disorders and significantly affects the quality of life of patients and the social security system (Al Qaraghli and De Jesus, 2022). Surgery or conservative treatment is used to treat this disease. Most patients with LDH prefer conservative treatment because it is non-invasive and effective (Gadjradj et al., 2017; Wan et al., 2022).

One of the most commonly used conservative treatment methods is Traditional Chinese Manual Therapy (Tuina). The performer rolls, pinches, and squeezes the skin and paravertebral muscles of the patient's lumbar vertebrae to relax the muscles and intervertebral joints around the lumbar vertebrae and pulls diagonally to correct dysfunctional joints and promote recovery of protruding discs. A systematic review found that spinal massage can significantly improve pain and dyskinesia in patients with low back pain, making it an indispensable method in non-surgical therapy (Paige et al., 2017; Rubinstein et al., 2019; de Zoete et al., 2021). Studies have proven that Tuina improves biomechanics (correction of bone dislocation, relief of nerve root compression caused by protrusions, relief of muscle contracture of paravertebral tissues) and promotes the absorption of endogenous inflammatory substances (Rong et al., 2017; Ke et al., 2021).

In recent years, the application of resting-state functional magnetic resonance imaging (RS-fMRI) has made it possible to study neural activity in a living brain without causing injury. According to studies, patients with LDH have abnormal brain activity. Zhou et al. found that patients with LDH had increased Amplitude of Low-Frequency Fluctuations (ALFF) abnormalities in the pain matrix and information processing areas and decreased ALFF in the default mode network (DMN) (Zhou et al., 2018). According to Zhang et al., LDH-related chronic sciatic syndromes can cause regional brain changes involving self-referential, emotional responses, and pain regulation functions (Zhang et al., 2022). However, there is still no unified conclusion on the changes in brain activity caused by LDH. On the other hand, existing studies mainly focus on changes in brain function in the LDH disease state and do not examine whether normal brain activity can be restored after effective treatment. Therefore, further elucidation of the characteristics of brain activity changes under LDH status and verification of the reversibility of abnormal brain activity changes have important guiding importance for clinical practice.

Our previous research has shown that the lingual gyri and left cerebellum of LDH patients have abnormally high Crus1 ALFF and fractional ALFF (fALFF) in the slow-4 and conventional bands. By comparing the changes in abnormal brain activity before and after spinal manipulation, the increase of ALFF and fALFF in abnormal brain activity decreased to normal levels after Tuina (Wen et al., 2022). In this study, we focused on the intensity of spontaneous activity in local brain regions but paid no attention to the coherence of spontaneous activity in local brain regions or the correlation between brain activities in different areas.

An indicator of spontaneous brain activity is called regional homogeneity (ReHo), which assesses the degree of local synchronization between the closest neighboring voxels (e.g., 7,9,27 voxels). The modification of the temporal coherence of the local neuronal activity is indicated by an increase or decrease in the ReHo value (Zang et al., 2004). ReHo has been shown to be highly reproducible, sensitive, and reliable for identifying local functional activities (Zuo and Xing, 2014; Jiang and Zuo, 2016). Researchers found that abnormal ReHo in specific brain regions may be related to pain processing in patients with this condition (Zhang S. S. et al., 2014) and that impaired ReHo was related to pain severity (Zhou et al., 2019). ReHo can successfully reveal pain-related pathological mechanisms, according to evidence from these studies. To determine the functional connections between brain regions, functional connectivity (FC) calculates the correlation coefficient of the blood oxygen level-dependent (BOLD) time series between a specific starting point and all other voxels or brain regions of interest (ROIs) (Shahhosseini and Miranda, 2022). Growing evidence suggests that the brain is a dynamic system that quickly switches discrete models (Hutchison et al., 2013; Vidaurre et al., 2017). Thus dynamic indices based on sliding-window shifts can better reflect the brain's information processing efficiency and is more insightful than the static index (Lindquist et al., 2014).Our understanding of the intricate process by which spinal massage controls brain activity may be enhanced by RS-fMRI research on static functional connectivity (sFC) and dynamic functional connectivity (dFC).

In this study, we first identified the different brain regions by calculating Reho and used the different brain regions as seeds to study the static and dynamic functional connectivity between different groups. Our research may reveal whether the brain activity changes of LDH patients are reversible, and whether effective Tuina can correct the brain activity of LDH disorders.

Materials and methods

Participants

In our study, 30 LDH patients and 30 healthy controls (HCs) were recruited from the First Clinical Medical College of Zhejiang Traditional Chinese Medical University from 24th November 2020, to 17th August, 2021. Both groups were matched with age, years of education and gender. All the patients were required to complete two clinical assessments, Visual Analogue Scale (VAS) (Hawker et al., 2011), and the Chinese Short Form Oswestry Disability Index Questionnaire (C-SFODI) (Smeets et al., 2011), to evaluate the degree of pain and daily functional activities of participants.

The criteria for inclusion of patients with LDH were as follows: (1) right-handed; (2) aged between 20 to 60 years; (3) evidence of compression of the spinal canal on a lumbar MRI; (4) radiating pain from the lumbar region to the buttocks and lower limb; (5) positive in straight leg-raising test and augmentation test; knee and Achilles jerk reflexes weakened or missing; (6) VAS score $\geq$ 3/10; (7) C-SFODI score $\geq$ 20%; (8) not taking pain therapy for at least 1 month before the enrollment.The criteria for inclusion of HCs were as follows: (1) right-handed; (2) aged between 20 to 60 years; (3) no history of LDH; (4) no history of pain caused by any disease and haven't accepted any pain-related treatment at least 1 month before enrollment.

The criteria for exclusion of all participants were as follows: (1) a history of spinal surgery or severe spinal trauma; (2) bone tuberculosis, tumor, severe osteoporosis, and other orthopaedics diseases; (3) combined with serious medical or psychiatric diseases, such as cardiovascular and cerebrovascular diseases, and those occur in the blood system and digestive system; (4) pregnancy or breastfeeding; (5) having autoimmune diseases, allergic diseases, acute and chronic infectious diseases; (6) having contraindications to functional magnetic resonance imaging (fMRI), such as metal implants, claustrophobia or devices in the body; (7) fMRI examination showing free nucleus pulposus and cauda equina syndrome; (8) vision loss and vestibular dysfunction;(9) acute or chronic pain caused by other diseases.

This study was approved by the Medical Research Ethics Committee and the Institutional Review Board of the First Clinical Medical College of the Zhejiang Traditional Chinese Medical University (No.2017-k-237-01) and was registered in Clinical Trial Registry (No. NCT03475095). We obtained written informed consents from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Tuina interventions

We performed Tuina interventions using traditional Chinese Tuina which includes multiple manipulations (Lee et al., 2017). In

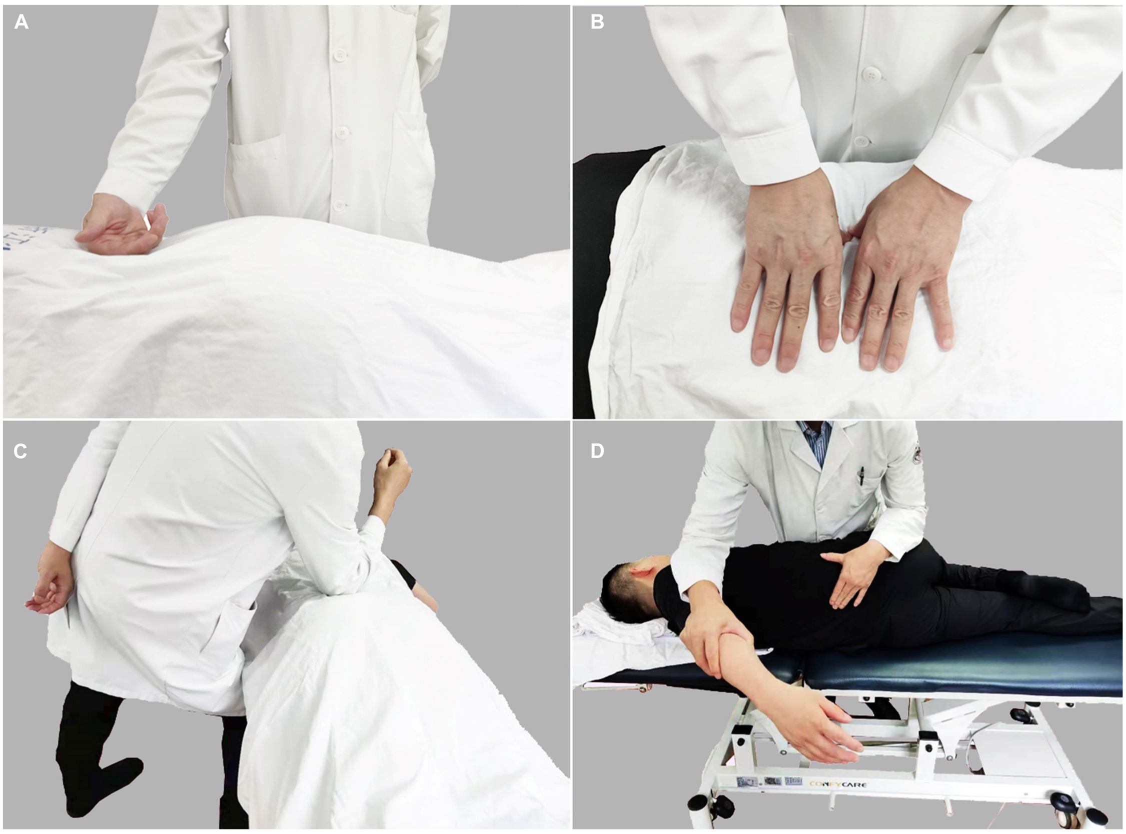

FIGURE 1
Tuina performed by rolling **(A)**, kneading **(B)**, pushing **(C)**, and the pulling and rotating **(D)** to relax the muscles in the lower back area for the purpose of alleviating pain and improving lumbar function.

the present study, the Tuina interventions were conducted to relax the lumbar muscles by rolling (Figure 1A), kneading (Figure 1B), pushing (Figure 1C) and the pulling and rotating manipulations (Figure 1D) were utilized to correct disordered spinal joints, to relieve pain and to improve lumbar function. Each Tuina session lasted approximately 25 min. All patients received a total of six Tuina sessions, and three times of Tuina proceeded in one week.

Quality control of Tuina

Requirements for physician: Tuina was operated by the same physician who has more than 5 years of massage clinical practice experience. Moreover, the physician has received the standardized requirements of this specialty massage training and holds a physician's certificate. Before conducting treatment for patients with LDH, the physician had to standardize the specific Tuina operation according to the operation essentials to maintain stability in strength, shape and frequency.

Requirements for Tuina environment and equipment: Multi-functional massage beds were used, along with proper adjustment of angle and height which were set to keep patients comfortable. Meanwhile, standard treatment towels and disposable bed sheets provided by Zhejiang Provincial Hospital of Chinese Medicine were used. In our study, all patients enrolled completed six Tuina sessions, and had no complications from Tuina sessions.

MRI data acquisition

All participants underwent a 3T Siemens scanner (Verio, Siemens AG, Erlangen, Germany) with a 12-channel head coil. HCs group underwent one fMRI scan, while the LDH group needed to be scanned twice, before Tuina and after the sixth Tuina. The functional images were obtained using a gradient echo-planar imaging sequence. The scanning parameters were as follows: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, 43 interleaved axial slices, matrix size = 64 × 64, field of view (FOV) = 220 mm × 220 mm, flip angle (FA) = 90°, slice thickness = 3.2 mm, gap = 0 (voxel size 3.4 × 3.4 × 3.2), number of volumes = 230. The structural images were obtained by a sagittal T1-weighted 3D sequence with magnetization prepared rapid gradient echo (MPRAGE). The scanning parameters were as follows: TR/TE = 8100/3.1 ms, sagittal slices, slice number = 176, matrix size = 256 × 256, FOV = 256 mm × 256mm, FA = 8°, slice thickness = 1 mm, gap = 0 (isotropic voxel size = 1 × 1 × 1). During rs-fMRI scanning, all participants were asked to keep their eyes closed, not to think about anything and not to fall asleep.

Data preprocessing

The data preprocessing were performed using RESTplus V1.25 software (Jia et al., 2019) and included the following steps: (1) removing the first 10 volumes; (2) slice-time correction; (3) realignment; (4) normalization was performed using T1 image new segment; (5) removing the linear trend; (6) nuisance regression, including the white matter, the cerebrospinal fluid and Friston-24 head motion parameters (Friston et al., 1996); (7) filtering in the frequency range between 0.01 and 0.08 Hz; (8) spatial smoothing with a 6-mm full width at half maximum Gaussian smooth kernel (only for static and dynamic functional connectivity analysis).

Regional homogeneity analysis

The Kendall's coefficient of concordance (KCC) was used to measure the local synchronization of the time series of neighboring voxels as follows (Zang et al., 2004):

$$W = \frac{\sum (R_i)^2 - n(\overline{R})^2}{\frac{1}{12}K^2(n^3 - n)}$$

where W is the KCC among given voxels, ranging from 0 to 1; R_i is the sum rank of the ith time point; $\overline{R}$ (n+1) K)/2 is the mean of the R_i; K is the number of time series within a measured cluster (K = 7, 19, and 27, respectively. K = 27 is used in the current study); n is the number of ranks. The ReHo value of each voxel was then divided by the global mean ReHo of each participant for standardization purposes. Noted that the spatial smoothing with a 6-mm isotropic full width at half maximum (FWHM) Gaussian kernel was performed after ReHo calculation.

Static functional connectivity analysis

The significant clusters detected by ReHo analysis between LDH-pre patients and HCs were selected as seed regions of interest (ROIs) to calculate static functional connectivity. Briefly, for each participant, the mean time course of each ROI was correlated with the time courses of each voxel using Pearson correlation. The Fisher's z-transform was applied to convert FC maps into Z maps to acquire optimum normality.

Dynamic functional connectivity analysis

The significant clusters detected by ReHo analysis between LDH-pre patients and HCs were selected as seed regions of interest (ROIs) to calculate dynamic functional connectivity (dFC). The sliding window approach was applied to obtain the dFC maps for each participant by DynamicBC (V2.2)[1] (Liao et al., 2014). We selected a window length of 50 TRs (100 s) and a window overlap of 98% (step size by 1 TRs) to compute the dFC of each participant (Li et al., 2018, Ma et al., 2021). The FC map for each participant were computed within each window, generating a series of FC maps. Subsequently, the coefficient of variance (CV) of dFC maps across time was calculated to measure the temporal variability of intrinsic brain activity. Finally, the dFC variability of all participants were then transformed into standardized z scores by subtracting the mean and dividing by the SD across each voxel to enhance data normality.

1 http://restfmri.net/forum/DynamicBC

TABLE 1 Demographic characteristics of the LDH patients and HC groups.

	LDH	HCs	*P*-value
Participants	27	28	–
Gender (male\female)	(17\10)	(17\11)	0.8638[a]
Age (year)	32.2 ± 9.5	31.8 ± 8.1	0.8552[b]
Years of education (year)	16.04 ± 1.93	16.36 ± 2.20	0.5691[b]
VAS scores (LDH-pre\pos)	(5.6 ± 2.1\1.7 ± 1.1)	-	< 0.0001[c]
C-SFODI scores (LDH-pre\pos)	(26.9 ± 8.1\18.7 ± 5.4)	-	< 0.0001[c]

[a] χ2 test; [b] Two sample *t*-test; [c] Paired *t*-test between LDH patients before and after Tuina treatment. LDH, lumbar disc herniation; HCs, healthy controls; VAS, visual analogue scale; C-SFODI: the Chinese Short Form Oswestry Disability Index Questionnaire.

Statistical analysis

The demographics and clinical variables were analyzed by the Statistical Package for the Social Sciences (SPSS) 22.0. The differences between the LDH patients and the HCs in age, years of education and clinical scores were tested with Student's *t*-test. The gender difference was tested using the Pearson Chi-Square test.

For the ReHo analysis, we performed the two-sample *t*-tests to compare LDH-pre and HCs. Gaussian Random Field (GRF) was applied in multiple comparison corrections (voxel-level $p < 0.05$, cluster-level $p < 0.05$). The significant whole clusters obtained from ReHo analysis were defined as ROIs. For the static FC and dFC analysis, two-sample *t*-tests was also applied to compare LDH-pre patients and HCs. GRF was applied in multiple comparison corrections (voxel-level $p < 0.05$, cluster-level $p < 0.05$).

To evaluate the Tuina effect, the abnormal brain regions identified by group comparisons (LDH-pre vs. HCs) were created as brain masks separately. The mean ReHo and FC values (both static and dynamic) were extracted within the brain masks. Two-sample *t*-tests were performed to compare these values between LDH-pre and HCs, and those between LDH patients after Tuina interventions (LDH-pos) and HCs ($p < 0.05$). Paired *t*-test was used to compare mean ReHo values between LDH-pos and LDH-pre ($p < 0.05$). GraphPad Prism 8 was used to assess the changes of ReHo/FC values.

Results

Demographic and clinical characteristics

In total, 3 LDH patients and 2 HCs who had maximum head movement exceeding 3 mm or 3°were excluded from the subsequent statistical analysis. we ultimately included 27 LDH patients (17 males, age: 32.2 ± 9.5) and 28 HCs (17 males, age: 31.8 ± 8.1). The two groups had no significant differences in age ($p = 0.8552$), years of education ($p = 0.5691$) and gender ($p = 0.8638$). Compared with the LDH-pre patients, the LDH-pos patients had significantly lower VAS scores ($p < 0.0001$) and C-SFODI scores ($p < 0.0001$) (Details are shown in Table 1).

TABLE 2 Significantly different regions in ReHo between LDH-pre patients and HCs.

Brain area	Voxel size	Peak (MNI,x,y,z)	Peak *T* value	*P* value
LO-MFG	727	−30 48 −6	−4.0725	0.0002

ReHo, regional homogeneity; LDH-pre, lumbar disc herniation patients before Tuina treatment; HCs, healthy controls; LO-MFG, the left orbital part middle frontal gyrus; MNI, Montreal Neurological Institute.

Differences in regional homogeneity between LDH-pre and HCs

The result of ReHo analysis showed that LDH-pre patients had decreased ReHo values in the left orbital part middle frontal gyrus (LO-MFG, Montreal Neurological Institute (MNI) coordinate: −30 48 −6) (Table 2 and Figure 2).

Differences in static FC analysis between LDH-pre and HCs

LO-MFG was selected as a seed to compare the FC between LDH-pre and HCs. We didn't find any significant difference regions between LDH-pre patients and HCs after GRF multiple comparisons correction.

Differences in variability of dFC analysis between LDH-pre and HCs

LO-MFG was selected as a seed to compare the dFC variance between LDH-pre and HCs. Two-sample *t*-test revealed LDH-pre patients shown decreased dFC variance in left Fusiform, increased dFC variance located in left orbital inferior frontal gyrus and left precuneus, compared to the HCs (Table 3 and Figure 3).

Assessment of Tuina intervention

We extracted mReHo values within LO-MFG mask from LDH-pre, LDH-pos and HCs separately. LDH-pos patients had increased ReHo compared with LDH-pre patients ($p = 0.029908$). Meanwhile, both the LDH-pre and LDH-pos patients showed significantly decreased ReHo compared with the HCs ($p < 0.0001$ and $p < 0.001$) (Table 4 and Figure 2).

We extracted mean dFC variance values within left Fusiform, left orbital inferior frontal gyrus and left precuneus mask from LDH-pre, LDH-pos and HCs separately. In left Fusiform, LDH-pos patients had increased dFC variance compared with LDH-pre patients ($p = 0.009$), no significant difference compared with HCs ($p = 0.9796$). Meanwhile, LDH-pre showed significantly decreased dFC variance compared with the HCs ($p = 0.0004$). In left orbital inferior frontal gyrus, LDH-pre patients had increased dFC variance compared with HCs ($p < 0.0001$), no significant difference compared with LDH-pos and HCs ($p = 0.0827$ and $p = 0.1891$). In left precuneus, LDH-pre patients had increased dFC variance compared with HCs ($p = 0.0002$), no significant difference

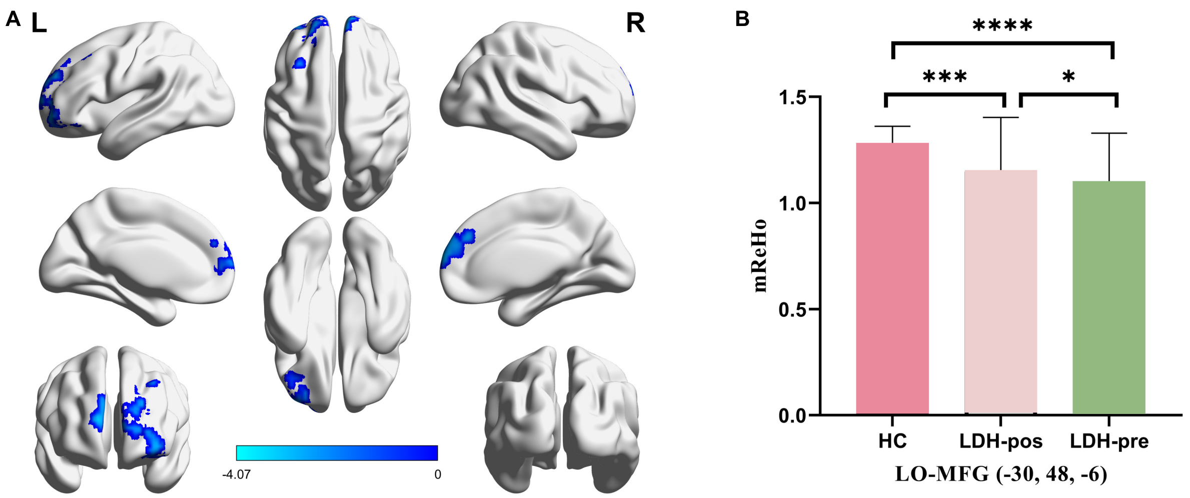

FIGURE 2
(A) Significantly different regions in ReHo between LDH-pre patients and HCs. **(B)** The bar graphs represent the mean ReHo extracted from abnormal clusters. The LDH patients and HCs were compared using two-sample *t*-tests, and LDH patients before and after Tuina were compared by paired *t*-tests. * indicated significance level at $p < 0.05$ (two-tailed), *** indicated significance level at $p < 0.001$ (two -tailed), **** indicated significance level at $p < 0.0001$ (two -tailed). HC, healthy controls; LDH-pos, LDH patients after Tuina; LDH-pre, LDH patients before Tuina; LO-MFG, left orbital part middle frontal gyrus.

TABLE 3 Significantly different regions in dFC variance between LDH-pre patients and HCs.

Seed region	Connected regions	Voxel size	Peak (MNI,x,y,z)	Peak *T*-value	*P*- value
LO-MFG (−30 48 −6)	Fusiform_L	10	−36, −72, −15	−2.5631	0.0132
	Frontal_Inf_Orb_L	37	−39, 33, −3	3.3115	0.0017
	Precuneus_L	10	0, −60, 54	2.833	0.0065

LDH-pre, lumbar disc herniation patients before Tuina treatment; HCs, healthy controls; LO-MFG, left orbital part middle frontal gyrus; Fusiform_L, left Fusiform; Frontal_Inf_Orb_L, left orbital inferior frontal gyrus; Precuneus_L, left Precuneus; MNI, Montreal Neurological Institute.

compared with LDH-pos and HCs (p = 0.1279 and p = 0.0529) (Table 5 and Figure 3).

Discussion

Main results of this study

In this study, rs-fMRI was used in combination with ReHo and seed-based FC analysis to examine the coherence of local neural activity and whole brain connectivity in LDH patients. Next, using this information as a basis, we evaluated the effective of Tuina intervention. Compared with HCs, patients with LDH had reduced ReHo in LO-MFG and anomalous variance of dFC between LO-MFG and three brain regions, including the central brain region of the default mode network (the left precuneus), the medial prefrontal cortex (mPFC) (the left orbital inferior frontal gyrus), and the left fusiform cortex. After Tuina treatment, the coherence of LO-MFG neural activity of LDH patients increased and their dFC variability was also improved.

LDH patients may have default mode network dysfunction

We finded that he ReHo in the LO-MFG, located in the mPFC, was lower in LDH patients,agreeing with the result from Zhou et al. (Zhou et al., 2019). The reduced ReHo in LO-MFG could indicate that this gene is involved in the pathology of LDH and that its ability to regulate emotion is deteriorating (Zhao et al., 2019). The decreased activity of the LO-MFG may result in a weakened impact on mood regulation, an increase in anxiety and depression, and a reduced ability to use emotion adjustment techniques to alter the amygdala's response to harmful stimuli (Rolls, 2019).

The mPFC form a hub (or core) node of the DMN, and disrupted connectivity of the DMN in chronic low back pain (Huang et al., 2019; Ng et al., 2021). We selected the LO-MFG seed to calculate static and dynamic functional connectivity.The dFC variance of left orbital inferior frontal gyrus and left precuneus were larger in LDH patients compared to HC. The left fusiform dFC variance was lower in LDH patients than in HCs. The fusiform, a portion of the temporal and occipital lobes, is known to be engaged in several neuronal pathways that are involved in recognition (Jonas et al., 2015; Beelen et al., 2022), memory (Liu et al., 2021; Yan et al., 2022), and emotion (Liu et al., 2021; Yan et al., 2022), despite the fact that its role is not entirely understood. The orbital inferior frontal gyrus and the precuneus are both a member of the standard mode network. When the brain is at rest, the standard network serves as the main hub of functional connections across brain regions, monitoring both internal and external environments, episodic memory, and ongoing cognitive and emotional activity (Brewer et al., 2011). Numerous studies have shown that individuals with chronic low back pain have aberrant brain areas and functional connections associated to miswiring (Zhang S. et al., 2014; Ng et al., 2021). Additionally, Zhang and colleagues demonstrated that patients with cLBP had increased

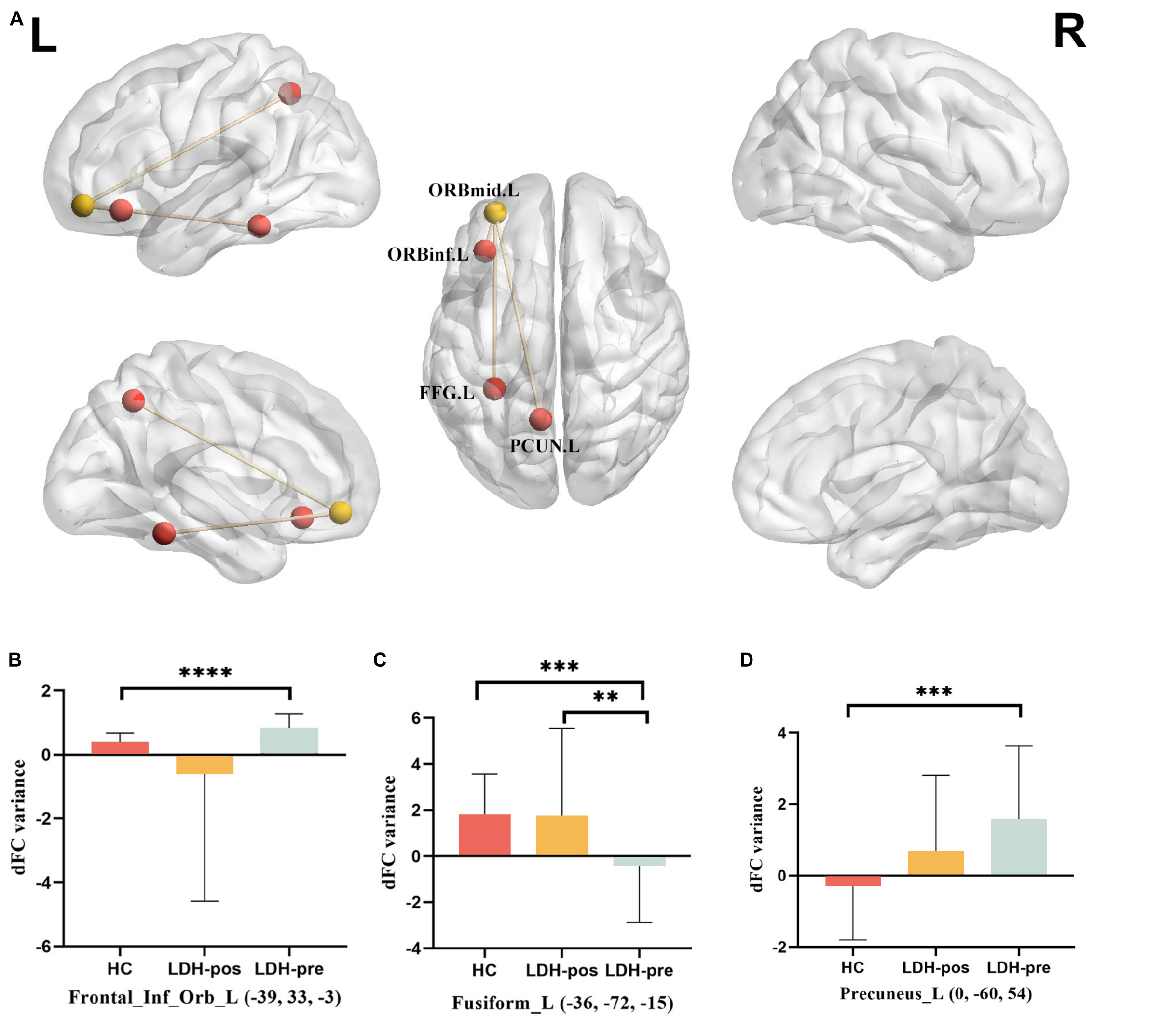

FIGURE 3
(A) Brain regions showing group differences between LDH_pre and HCs in dynamic FC variance with the LO-MFG as seed. **(B)** DFC variance located in Frontal_Inf_Orb_L (compare each group with every other group). **(C)** DFC variance located in Frontal_Inf_Orb_L (compare each group with every other group). **(D)** DFC variance located in Precuneus_L (compare each group with every other group). The LDH patients and HCs were compared using two-sample *t*-tests, and LDH patients before and after Tuina were compared by paired *t*-tests. ** indicated significance level at $p < 0.01$ (two -tailed), *** indicated significance level at $p < 0.001$ (two -tailed), **** indicated significance level at $p < 0.0001$ (two -tailed). HC, healthy controls; LDH-pos, LDH patients after Tuina; LDH-pre, LDH patients before Tuina; LO-MFG, left orbital part middle frontal gyrus. Frontal_Inf_Orb_L, left orbital inferior frontal gyrus; Fusiform_L, left Fusiform; Precuneus_L, left Precuneus.

ALFF in the hippocampal/parahippocampal gyrus but a decrease in ALFF values in the remaining gyrus DMN regions when their spontaneous low back pain increased after the pain amelioration maneuver (Zhang et al., 2019). In comparison to healthy controls, individuals with discogenic leg pain had decreased ALFF values in DMN areas, according to Zhou and colleagues (Zhou et al., 2018). This means that a DMN problem may also be the root of the cognitive and behavioral issues identified in LDH.

The disordered default mode network can be functionally reversed by Tuina

Tuina has a strong analgesic response when used to treat chronic LDH (Kong et al., 2012). Previous research on the mechanism of analgesia has mainly concentrated on the biomechanical effect, which is hypothesized to be the main therapeutic mechanism. For example, Du et al. investigated the effect of lumbar manipulations with finite element technique, showing the relative displacement between the intervertebral disc and adjacent nerve roots and the internal stress change of the lumbar intervertebral disc (Du et al., 2016). But for pain relief, the central nervous system must be mediated (Ng et al., 2021). The default mode network is part of the triple network model which explains the whole range of pain related co-morbidities (De Ridder et al., 2022). To clear the effect of Tuina on the default mode network in LDH patients is of great importance to understand the central mechanism of Tuina for pain relief.

In the past, the resting magnetic resonance studies on the effect of Tuina mainly focused on changes in spontaneous brain activity

TABLE 4 Group differences in mean ReHo values.

Coordinates	Brain region	Contrast	*P*-value	*T*-value
−30 48 −6	LO-MFG	LDH-pre vs. HCs	<0.0001	−7.56100
		LDH-pos vs. LDH-pre	0.0299	2.297216
		LDH-pos vs. HCs	0.0009	−3.53306

LO-MFG, the left orbital part middle frontal gyrus; LDH-pre, lumbar disc herniation patients before Tuina treatment; HCs, healthy controls; LDH-pos, lumbar disc herniation patients after Tuina treatment.

TABLE 5 Group differences in mean dFC variance values.

Seed region	Connected regions	Coordinates	Contrast	*P*-value	*T*-value
LO-MFG (-30 48 -6)	Fusiform_L	−36, −72, −15	LDH-pre vs. HCs	0.0004	−3.8158
			LDH-pos vs. LDH-pre	0.0090	2.8234
			LDH-pos vs. HCs	0.9796	0.0257
	Frontal_Inf_Orb_L	−39, 33, −-3	LDH-pre vs. HCs	< 0.0001	4.6484
			LDH-pos vs. LDH-pre	0.0827	−1.8049
			LDH-pos vs. HCs	0.1891	−1.3303
	Precuneus_L	0, −60, 54	LDH-pre vs. HCs	0.0002	3.9325
			LDH-pos vs. LDH-pre	0.1279	−1.5722
			LDH-pos vs. HCs	0.0529	1.9802

LDH-pre, lumbar disc herniation patients before Tuina treatment; LDH-pos, lumbar disc herniation patients after Tuina treatment; HCs, healthy controls; LO-MFG, left orbital part middle frontal gyrus; Fusiform_L, left Fusiform; Frontal_Inf_Orb_L, left orbital inferior frontal gyrus; Precuneus_L, left Precuneus.

or functional connectivity, but not on whether Tuina can restore abnormal brain activity or functional connectivity to a normal level. Actually, to prove that Tuina can reverse the brain function damaged by disease, is of great significance to reveal the remodeling of nervous functions mechanism of Tuina effect. We finded that after effective Tuina intervention, the ReHo value of the LO-MFG decrease in LDH patients increased. The dFC variability of the default mode network anomalies in LDH patients also improved at the same time. Our results lend credence to the notion that the DMN activity is the neural correlate of LDH and that the control of dFC in important DMN brain areas may help to explain the analgesic effect of Tuina and the brain response of LDH patients to pain management after Tuina.

Limitations

Our study has several drawbacks as well. First, because we applied tight inclusion and exclusion criteria, our sample size was small. Future studies should examine local synchronous activity anomalies in LDH patients using a larger sample size. Second, since there was no intervention in HCs, we assumed that the fMRI data has no change within two weeks of the study period, but this may not be the case. In future research,a group of HCs receiving manipulation of intervention can be added. Last,following the sixth TMS, we did not obtain any follow-up information from patients with LDH. Future studies might involve lengthier follow-ups to obtain data on the duration of pain relief after Tuina.

Conclusion

In comparison to HCs, LDH patients have decreased regional homogeneity of major brain regions of the default mode network and disorder functional connectivity. Our research indicated that Tuina can reshape the function of the default mode network (DMN) in LDH patients, which may contribute to the analgesic effect of Tuina in LDH patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Research Ethics Committee of the First Clinical Medical College of the Zhejiang Chinese Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

H-GD and ZJ designed the study. YW collected the data. X-MC analyzed the data. X-MC and YW wrote the first version. SC, CL, WW, and NK revised the manuscript. X-MC, YW, XJ, D-YL, QH, J-EC, X-LZ, JL, M-SX, ZJ, and H-GD added their comments. All authors approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and safety of Tuina (Chinese Therapeutic Massage) for knee osteoarthritis: A randomized, controlled, and crossover design clinical trial

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Background: Knee osteoarthritis (KOA) is a highly prevalent joint disease among the middle-aged and elderly population that can lead to pain, functional impairment, decreased quality of life, and a large number of medical expenses. Physical therapy is one of the main treatment methods for KOA. In China, Tuina has been widely used in the treatment of KOA, but up to now, there is no high-quality medical evidence to support its effectiveness and safety. The purpose of this study was to objectively evaluate the efficacy and safety of Tuina in the treatment of KOA.

Methods: A crossover design clinical trial was performed on 96 patients. The test group and the control group in the trial were allocated randomly in a ratio of 1:1. The test group received Tuina treatment for 4 weeks first and then received health education intervention for another 4 weeks. The control group received health education intervention for 4 weeks first and then received Tuina treatment for another 4 weeks. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score was chosen as the primary outcome. The WOMAC pain score, WOMAC stiffness, WOMAC daily activity score, and visual analog scale (VAS) score were the secondary outcomes. Adverse events during the intervention were collected in both groups.

Results: Compared with the baseline, the WOMAC total score, WOMAC pain score, WOMAC stiffness, WOMAC daily activity, and VAS score of patients in both groups were improved significantly at weeks 4 and 8 ($p < 0.001$). All patients who received Tuina treatment were significantly superior to those who received health education intervention in the WOMAC total score (194.96, 95% CI = 164.94–224.97, $P < 0.001$), WOMAC pain score (45.96, 95% CI = 35.82–56.09, $P < 0.001$), WOMAC stiffness (31.42, 95% CI = 26.37–36.46, $P < 0.001$), WOMAC daily activity (117.58, 95% CI = 97.56–137.61, $P < 0.001$), and VAS score (1.07, 95% CI = 0.83–1.32, $P < 0.001$). Both groups had no serious adverse events during the treatment.

Conclusion: This trial demonstrated that Tuina can reduce joint pain in patients with KOA and improve the physical functions of the knee joint effectively and safely.

Clinical trial registration: This trial was registered in the Chinese Clinical Trial Registry (No. ChiCTR-TTRCC-13003157). http://www.chictr.org.cn/showproj.aspx?proj=6402.

KEYWORDS

Tuina, knee osteoarthritis, clinical trial, crossover design, WOMAC

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Introduction

Knee osteoarthritis (KOA) is a highly prevalent joint disease among middle-aged and elderly people, and it is a leading cause of pain, impaired function, reduction of life quality, and astonishing medical costs for treatment (1, 2). At the age of 60 years and older, approximately 10% of men and 13% of women have KOA (3). With an aging population and obesity epidemic, the incidence of KOA has been increasing year by year (4). A survey in 2018 found that the overall incidence rate of KOA in China was 18%, 11% in men, and 19% in women (5). American College of Rheumatology (ACR) launched a pyramid scheme of KOA treatment, which was based on measures of education, exercise, and weight reduction, supplementing externally used non-steroidal anti-inflammatory drugs (NSAIDs) if necessary, adding the use of acetaminophen and NSAIDs orally under the ineffective situation, and performing intra-articular corticosteroid injections during acute attack (6). At the same time, definite adverse reactions of NSAIDs have been reported, and the risk of the surgery itself and the high medical cost limited the wide range of clinical applications of the aforementioned therapies. In China, Tuina is one of the main non-surgical treatments for KOA and is included in relevant diagnosis and treatment guidelines (7). Tuina is a manual therapy under the guidance of the meridian theory in traditional Chinese Medicine. It stimulates specific acupuncture points along the pathways of meridians and performs regular passive movements on the patient's joints to alleviate the patient's symptoms. Tuina requires lasting, powerful, uniform, deep, and soft when implemented in clinical treatments. It can be implemented in several ways even at the same point, notably by pressing, pushing, and kneading. Different Tuina treatments should be used for different diseases which have been widely applied in clinical treatments because of their significant efficacy in symptomatic improvement and reduction of pain (8). Many years of clinical practice have shown that Tuina is safe and effective for KOA. Some researchers have also carried out research on its action mechanism on KOA and found that Tuina manipulation and passive movement can regulate the muscle activation mode, repair the function of ligament cartilage, improve the mechanical balance of the knee, improve the inflammatory status, reduce joint pain, and achieve a good therapeutic effect for KOA (9, 10). However, up to now, there has been no high-quality medical evidence to support the effectiveness of Tuina in the treatment of KOA. Although relevant clinical studies have been carried out previously, there are obvious defects in their study design, selection of efficacy indicators, control of treatment confounding factors, quality assurance of clinical trials, etc. Therefore, it is necessary to carry out well-designed and high-quality clinical trials.

Materials and methods

Trial design

Considering that KOA is a chronic disease, the symptoms can easily recur, patients with mild knee osteoarthritis ($700 \leq$ WOMAC total score $\leq 1,200$) were included in this study, and the short-term absence of proven effective intervention will not bring obvious risks to patients. To minimize the impact of different patients on the curative effect, this study adopts a randomized, controlled, and crossover design.

Patients were randomly allocated into the test group and the control group. The test group first received Tuina treatment for 4 weeks and then received health education intervention for another 4 weeks. The control group first received health education intervention for 4 weeks and then received Tuina treatment for another 4 weeks. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was chosen to evaluate the primary efficacy of the treatment. Referring to the osteoarthritis (OA) treatment cycle and related international clinical trials (CLASS and VIGOR trials), the course of this clinical trial was set for 4 weeks (11, 12). The protocol was approved by the Ethical Review Committee of Chinese Registered Clinical Trials on 15 April 2013 (No. ChiECRCT-2013010) and registered in the Chinese Clinical Trial Registry (No. ChiCTR-TTRCC-13003157). The diagram of the trial design is presented in Figure 1.

Subjects

A total of 122 patients with KOA were recruited from the osteoarthritis specialist clinic, Shuguang Hospital affiliated with Shanghai University of Traditional Chinese Medicine between July 2013 and August 2016, and 96 patients meeting the criteria were screened into this study.

Diagnostic criteria

The 2001 American College of Rheumatology (ACR) diagnostic criteria for KOA state that patients who have knee joint pain can be diagnosed with KOA with three of the following seven conditions:

(1) Age $\geq$ 50 years old.
(2) Morning stiffness $<$ 30 min.
(3) Having bone noises during joint movement.
(4) Examination of the knee shows osseous hypertrophy.
(5) Tenderness and pain of bone.
(6) No obvious temperature rising of synovial membrane.
(7) Radiology shows osteophyte formation.

The inclusion criteria were as follows: subjects who signed written informed consent; age range from 50 to 80 years old (including boundary values); male or female; meeting the diagnostic criteria of KOA; X-ray imaging score of the knee joint; KL classification $\leq$ 3; the severity of KOA; $700 \leq$ WOMAC total score $\leq 1,200$; and clinical diagnosis of unilateral knee osteoarthritis.

The exclusion criteria were as follows: subjects with acute fracture damage of the meniscus or surrounding ligament; rheumatic or rheumatoid arthritis; tumor around the knee joint; tuberculosis; idiopathic osteonecrosis of the knee joint; women who are breastfeeding or pregnant; having severe diseases such as cardiovascular, pulmonary, hepatic, renal, and hematopoietic systems, hemophilia, and other hemorrhagic

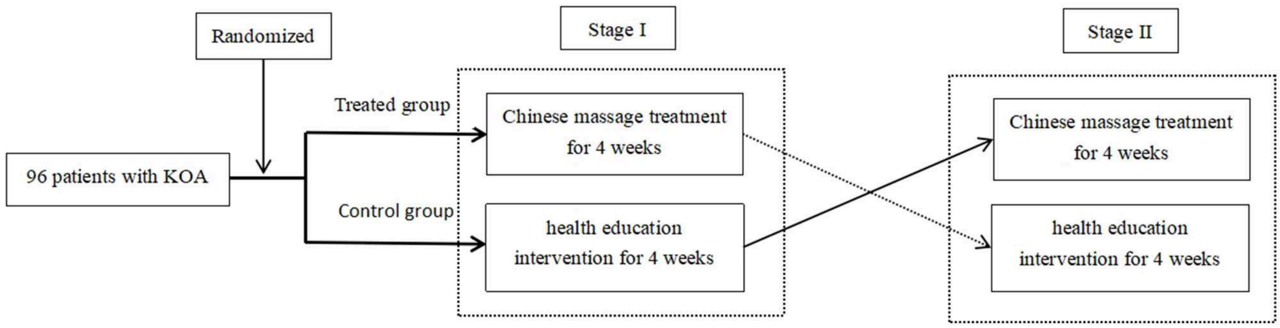

FIGURE 1
Trial design.

diseases, and mental disease; use of a cardiac pacemaker; received intra-articular injection within 6 months prior to the trial; used disease-improving drugs and cartilage protectors within 6 months prior to the trial; treated with corticosteroids, acupuncture, or physical therapy 1 week before the treatment; the skin of patients on the treatment sites being damaged; long-term use of other drugs that affect the efficacy and safety judgment and have comprehensive treatment; and participated in other studies within 3 months before the trial. The researchers considered these patients inappropriate to be included.

Sample size calculation

According to the literature reports, the effective rate of Tuina in the treatment of knee osteoarthritis within 4 weeks varies from 75 to 98%. However, we found that the effective rate of Tuina for KOA was far lower than that reported in the literature in clinical practice. Therefore, according to the early clinical practice data, we set the effective rate of Tuina in the treatment of KOA as 55%. It has been reported that ∼20% of patients with KOA experienced self-relief within 4 weeks, and the sample size of this study was calculated based on this situation.

Due to the comparison of two sample rates, the sample size was calculated as $n = (u_\alpha+u_\beta)^2/[2(\sin^{-1}\sqrt{p_1}\text{-}/\sin^{-1}\sqrt{p_2})]^2$, where $\alpha = 0.05$, $u_{0.05/2} = 1.960$, $\beta = 0.10$, $u_{0.01} = 1.282$, $p_1 = 0.55$, and $p_2 = 0.2$. According to the aforementioned formula, $n = 40.22 \approx 40$ cases can be obtained. Considering a 20% shedding rate, the sample size of each group is $N = 48$. A total of 96 patients in two groups with KOA were observed.

Randomization

A total of 96 subjects were selected from those who met the inclusion criteria after screening and randomly allocated into the test group and the control group in a 1:1 ratio.

Intervention

For the test group, the intervention protocol of Tuina for KOA was formulated according to College Textbooks ***Tuina (Chinese Therapeutic Massage)*** (5th edition). The treatment time was ∼15 min, and the frequency was twice a week. To ensure the standardization of the manual treatment scheme, assurance measures have been formulated (see the Quality control section for details). The Tuina treatment protocol for KOA is as Table 1.

For the control group, patients were given health education in the prescribed research period, including knowledge publicity and education related to KOA for patients, teaching patients to correct unhealthy living habits, keeping knee joints warm, and avoiding sports that would aggravate injury of the knee joint. At the same time, patients were told not to receive other treatments of KOA during the observation period. To ensure the quality of health education, patients were told to visit the hospital clinic at least once a week. During the study, the subjects can consult the research doctor about relevant health problems by telephone at any time.

Combined treatment and medication regulations: during the period of trial, except for the regulated intervention methods, no other Chinese or Western drugs for osteoarthritis and no other treatment methods are allowed. The medical case should be recorded as ineffective if analgesic drugs are used for KOA. The name and dosage of the drug used should be recorded clearly.

Outcome measurements

Primary outcome—WOMAC total score

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is mainly used to evaluate patients' overall evaluation of their disease in the past 48 h. The specific content of the scale includes 24 questions from three aspects of pain, stiffness, and difficulty of daily activities (the maximum score of each question is 100, and the total score is 2,400):

- **Pain score :** It contains five questions—the degree of pain when walking on a flat road, the degree of pain when going

TABLE 1 Tuina treatment protocol for KOA.

Treatment position:	The patient lies on their back with relaxed lower limbs. The doctor stands on the affected side.
Step 1: relaxation manipulation	① ***Kneading:*** Use the left or right palm root or the major thenar eminence to perform a rhythmic spiral movement on the quadriceps femoris from top to bottom. Repeat the manipulation 3–5 times. Do not use too much force. ② ***Grasping:*** The doctor should exert force between the thumb of both hands and the palmar surface of the other four fingers, pinch and lifts the quadriceps femoris and gastrocnemius up and down, and then slowly relax. Repeat the manipulation from the proximal end to the distal end 3–5 times. The strength is based on the patient's tolerance. Do not use too much force. ③ ***Rolling:*** The doctor's right hand should exert force on the dorsal ulnar side, stick it to the quadriceps femoris, and roll back and forth through continuous movement of wrist flexion and extension and forearm pronation and supination. The frequency is about 120 times/min. Repeat the manipulation from top to bottom 3–5 times.
Step 2: Point tapping manipulation	Using their thumb or index finger, the doctor should press the Liangqiu (ST34), Xuehai (SP10), EX-LE2, Dubi (ST35), Yanglingquan (GB34), Zusanli (ST36), and Ashi points around the knee joint slowly for 5–10 s and hook the Weizhong (BL40) and Chengshan (BL 57) with the middle finger or index finger for 5–10 s, taking the patient's feeling of soreness, distension, and pain as the degree of tolerance. Do not exert too much force.
Step 3: Patellar management manipulation	① ***Patella lifting:*** Grasp the patella with one hand and five fingers and fix it with the other hand. Lift the patella upward to the maximum extent to make it leave the articular surface of the femoral condyle and repeat the manipulation 3–5 times. ② ***Patella kneading:*** The doctor should press the patella with the palm to perform clockwise or counterclockwise circular kneading and repeat the manipulation 5–10 times.
Step 4: Tendon adjustment manipulation	① ***Tendon splitting:*** Press the nail part of the thumb claw against the iliotibial tract, medial collateral ligament, and lateral collateral ligament around the knee joint, and scrape along the fiber direction 3–5 times. ② ***Tendon pulling:*** Place the middle finger pulp of both hands at the inner and outer head of the gastrocnemius muscle and popliteal muscle, respectively, and perform horizontal back and forth pulling 3–5 times.
Step 5: Active joint manipulation	① ***Flexion, extension, stretching, and shaking of knee joint:*** The doctor should hold the patient's ankle with one hand and the knee joint with the other hand, flexing and extending the knee joint to the maximum extent 2–3 times, and then quickly pull and shak the knee joint. ② ***Stretching method:*** The doctor should hold the patient's foot with one hand to extend the ankle back and presses the knee with a steady force to the maximum extent that the patient can endure. This should be kept up for 5–10 s.
Step 6: Ending manipulation	***Kneading:*** Use the palm root of the left or right hand or thenar part to exert force, and perform rhythmic spiral movement from top to bottom on the quadriceps femoris and tibialis anterior muscle of the patient. Repeat the manipulation 3–5 times. Do not exert too much force.

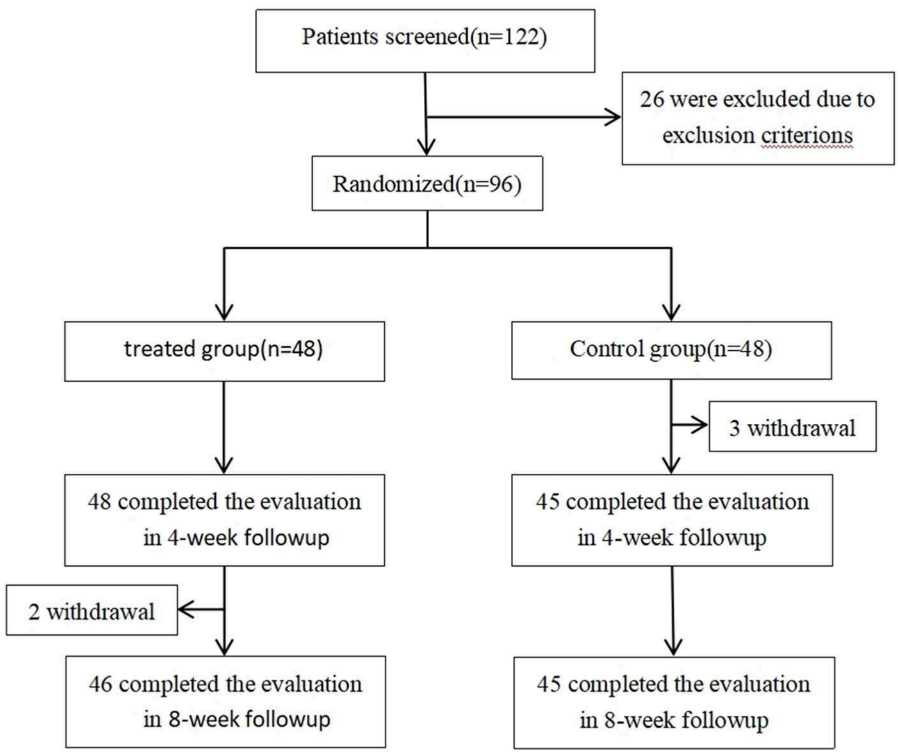

FIGURE 2
Flow diagram of participant screening and randomization.

TABLE 2 Comparison of baseline data between the two groups (M ± SD).

Observation index	Test group ($N = 48$)	Control group ($N = 48$)	p
Gender (n, %)	Female (30, 62.5%)	Female (28, 58.3%)	0.676
diseased knee joint (n, %)	Right (37, 77.1%)	Right (33, 68.8%)	0.358
X-ray KL	I18/II25/III5	I21/II24/III3	0.687
Age, year	60.33 ± 3.44	59.56 ± 3.57	0.394
BMI	25.20 ± 2.83	25.77 ± 2.34	0.284
WOMAC-total score	791.02 ± 146.14	773.44 ± 82.34	0.750
WOMAC-pain score	188.71 ± 33.68	183.92 ± 18.52	0.803
WOMAC-stiffness score	97.29 ± 15.90	94.60 ± 13.33	0.372
WOMAC-daily activity score	505.02 ± 111.17	494.92 ± 66.05	0.585
VAS-score	4.94 ± 1.08	4.79 ± 1.05	0.579

M ± SD, mean ± standard deviation; X-ray KL, X-ray Kellgren-Lawrence; BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Arthritis Index; VAS, visual analog scale.

upstairs or downstairs, the influence of knee joint pain on nocturnal sleep, the degree of pain when sitting or lying down, and the degree of pain when standing upright (the maximum score of each question is 100, and the total pain score is 500).

- **Stiffness:** It contains two questions. How severe is your stiffness when you just wake up in the morning? How severe is your stiffness after sitting, lying, or resting? (the maximum score of each question is 100, and the total stiffness score is 200).
- **Difficulty in daily activities:** It contains 17 questions. Going downstairs; going upstairs; standing up from sitting; standing; walking on a flat ground; getting on and off the car or bus; going shopping; wearing ones socks or stockings; standing up from bed; drawing off ones socks or stockings; lying on the bed; getting out of the bathtub; sitting; sitting on, or standing up from toilet; doing heavy homework; and doing easy homework (the maximum score of each question is 100, and the total score of daily activities is 1,700).

Secondary outcome—Visual analog scale score

The visual analog scale (VAS) score is a national general pain evaluation index, and this method uses a 10 cm line or ruler. There are 0 and 10 at each end; 0 means painless, and 10 means the most severe pain. The patient was told to mark the corresponding position of their pain on a straight line or ruler.

Safety

Adverse events during the intervention were collected in both groups.

Statistical analysis

The statistical software was SPSS21.0. The chi-square test was used to compare and analyze differences between count data. For numerical data subject to a normal distribution, an independent sample t-test was used to assess the inter-group difference, and paired sample t-test was used to assess the intra-group difference. For numerical data not subject to the normal distribution, the Mann–Whitney U-test was used to assess the inter-group difference, and the Wilcoxon signed rank-sum test was used to assess the intra-group difference. The ANOVA test for two-stage crossover design was used to analyze the differences in efficacy by different intervention factors, stage, and individual differences.

All numerical data were expressed by mean ± standard deviation (M ± SD). All statistical tests used a two-sided test, and a P-value of <0.05 is considered statistically significant. Patients who took other drugs for osteoarthritis were regarded as having no efficacy. Intention-to-treat analysis (ITT) was used to evaluate the efficacy. For the estimation of the missing value of the main efficacy outcome, the results of the latest observation were carried forward to the missing part of the trial data.

Quality control

(1) Overall quality control measures. The overall quality of this clinical study was implemented with reference to good clinical practice (GCP), and the protection of subjects followed the Declaration of Helsinki. The research group hired a full-time monitor for quality supervision. (2) Quality control measures for consistency of Tuina manipulation. Qualification requirements were as follows: having practiced manual therapy for at least 5 years. Access requirements were as follows: key parameters of manual operation should be formulated. Before the formal start, the research group shall carry out manipulation training for all research doctors. Relevant training, examination videos, and written records should be well-kept. Process quality control: a standardized spot check should be regularly and irregularly conducted on manipulative doctors during the process. (3) Efficacy index quality control. Since the blind method cannot be implemented in this study, to ensure the reliability of the research results, an independent efficacy evaluation and safety event judgment researcher were set up for this study. The researcher does

TABLE 3 ANOVA test for two-stage crossover effects.

Observation index	Source of variance	*F*	*P*-value
WOMAC-total score	Intervention effect	132.539	<0.001
	Stage effect	24.034	<0.001
	Individual difference	0.614	0.991
WOMAC-pain score	Intervention effect	60.421	<0.001
	Stage effect	46.009	<0.001
	Individual difference	0.505	0.999
WOMAC-stiffness score	Intervention effect	121.713	<0.001
	Stage effect	8.099	0.005
	Individual difference	0.606	0.992
WOMAC-daily activity score	Intervention effect	112.264	<0.001
	Stage effect	9.841	0.002
	Individual difference	0.678	0.970
VAS-score	Intervention effect	67.794	<0.001
	Stage effect	17.950	<0.001
	Individual difference	0.902	0.691

WOMAC, Western Ontario and McMaster Universities Arthritis Index; VAS, visual analog scale.

not participate in the subject intervention and does not know what kind of intervention the subject has received.

Results

A total of 96 patients were randomized into a test group and a control group, 48 patients in each group. Two patients in the test group withdrew in the 2nd week of the second stage, and three patients in the control group, respectively, withdrew in the 2nd, 3rd, and 4th week of the first stage (Figure 2; flow diagram of participant screening and randomization for details). Two groups are comparable in age, gender, BMI, X-ray image classification, WOMAC total score, WOMAC pain score, WOMAC stiffness score, WOMAC daily activity score, and VAS score (detailed baseline data of 96 patients are shown in Table 2).

The analysis of variance (ANOVA) test for two-stage crossover designs was used to analyze the differences among intervention effects, stage effects, and individual differences. The results have shown that both the intervention effect and the stage effect contributed to the difference in the WOMAC total score, WOMAC pain score, WOMAC stiffness score, WOMAC daily activity score, and VAS score ($p < 0.05$). Detailed results are shown in Table 3. However, as shown in Table 4, the change value of the second stage is smaller than that of the first stage, so the stage effect reduces the difference between the two treatments. In this case, the difference between the two treatments is still statistically significant, indicating that the conclusion is still reliable.

Compared with the baseline, the WOMAC total score, WOMAC pain score, WOMAC stiffness, WOMAC daily activity, and VAS score of patients in both groups improved significantly at

TABLE 4 Outcome comparison between the two groups.

Observing index	group	*N*	0 W (M ± SD)	4 W (M ± SD)	8 W (M ± SD)	d1 (M ± SD) (95% CI)	d2 (M ± SD) (95% CI)	*P*-value*
WOMAC-total score	Test group	48	791.02 ± 146.14	423.52 ± 192.62	334.00 ± 207.78	367.5 ± 120.92 (−402.61 to −332.39)‡	89.52 ± 88.58 (−115.24 to −63.80)	<0.001
	Control Group	48	773.44 ± 82.34	588.35 ± 129.56	291.33 ± 76.08	185.08 ± 85.9 (−210.03 to −160.14)	297.02 ± 120.83 (−332.11 to −261.93)	<0.001
WOMAC-pain score	Test group	48	188.71 ± 33.68	83.69 ± 46.09	64.73 ± 50.15	105.02 ± 33.65 (−114.79 to 95.25)‡	18.96 ± 29.32 (−27.47 to −10.45)	<0.001
	Control Group	48	183.92 ± 18.52	124.13 ± 39.71	58.48 ± 28.67	59.79 ± 35.49 (−70.10 to −49.49)	65.65 ± 42.63 (−78.02 to −53.27)	<0.001
WOMAC-stiffness score	Test group	48	97.29 ± 15.90	47.63 ± 21.24	37.48 ± 22.01	49.67 ± 17.52 (−54.75 to 44.58)‡	10.15 ± 15.69 (−14.70 to −5.59)	<0.001
	Control Group	48	94.60 ± 13.33	76.08 ± 21.89	34.25 ± 15.63	18.52 ± 17.46 (−23.59 to −13.45)	41.83 ± 19.93 (−47.62 to −36.05)	<0.001
WOMAC-daily activity score	Test group	48	505.02 ± 111.17	292.21 ± 132.41	231.79 ± 143.29	212.81 ± 84.72 (−237.41 to −188.21)‡	60.42 ± 57.22 (−77.03 to −43.80)	<0.001
	Control Group	48	494.92 ± 66.05	388.15 ± 83.19	198.60 ± 46.62	106.77 ± 55.98 (−123.02 to −90.52)	189.54 ± 78.75 (−212.41 to −166.67)	<0.001
VAS-score	Test group	48	4.94 ± 1.08	2.56 ± 1.20	1.81 ± 1.28	2.38 ± 0.98 (−2.66 to −2.09)‡	0.75 ± 0.70 (−0.95 to −0.55)	<0.001
	Control Group	48	4.79 ± 1.05	3.17 ± 1.06	1.02 ± 0.67	1.63 ± 0.61 (−1.80 to −1.45)	2.15 ± 1.09 (−2.46 to −1.83)	<0.001

d1, difference between 0 and 4 w (95% CI).
d2, Difference between 4 and 8 w (95% CI).
*Significant difference from 4-week group vs. baseline and 8-week group vs. 4 weeks.
‡Significant difference from the control group.
M ± SD, mean ± standard deviation; WOMAC, Western Ontario and McMaster Universities Arthritis Index; VAS, visual analog scale.

TABLE 5 Comparison of change in different intervention factors.

Observing index	N^*	Tuina treatment‡	Health education†	Estimated difference (95% CI)	t	P-value
WOMAC-total score	96	332.26 ± 125.35	137.30 ± 99.19	194.96 (164.94–224.97)	11.95	<0.001
WOMAC-pain score	96	85.33 ± 43.02	39.38 ± 38.34	45.96 (35.82–56.09)	7.81	<0.001
WOMAC-stiffness	96	45.75 ± 19.08	14.33 ± 17.04	31.42 (26.37–36.46)	12.04	<0.001
WOMAC-daily activity	96	201.18 ± 82.19	83.59 ± 60.93	117.58 (97.56–137.61)	11.26	<0.001
VAS-score	96	2.26 ± 1.04	1.19 ± 0.79	1.07 (0.83–1.32)	8.07	<0.001

*The total number of patients receiving the same treatment.
‡The change value of efficacy indexes of all patients receiving Tuina treatment in both groups.
†The change value of efficacy indexes of all patients receiving health education in both groups.
WOMAC, Western Ontario and McMaster Universities Arthritis Index; VAS, visual analog scale.

weeks 4 and 8 ($p < 0.001$). However, at week 4, the test group was superior to the control group in the WOMAC total score, WOMAC pain score, WOMAC stiffness, WOMAC daily activity, and VAS score ($p < 0.001$). Detailed results are shown in Table 4.

At the same time, an independent sample t-test was used to compare and analyze differences between different intervention effects (Tuina and health education). The results showed that the mean difference between the efficacy of the Tuina treatment and health education was significant in the WOMAC total score (194.96, 95% CI = 164.94–224.97, $P < 0.001$), WOMAC pain score (45.96, 95% CI = 35.82–56.09, $P < 0.001$), WOMAC stiffness (31.42, 95% CI = 26.37–36.46, $P < 0.001$), WOMAC daily activity (117.58, 95% CI = 97.56–137.61, $P < 0.001$), and VAS score (1.07, 95% CI = 0.83–1.32, $P < 0.001$). Tuina therapy was superior to health education in improving the WOMAC total score, WOMAC pain score, WOMAC stiffness, WOMAC daily activity, and VAS score ($p < 0.001$). Detailed results are shown in Tables 4, 5 and Figure 3.

Safety

Both groups had no serious adverse events during the treatment. A total of two female patients in the test group had local skin pain around the knee joint after Tuina therapy, which was caused by the stimulation of manipulation, and completed all treatments without special treatment. One patient in the control group withdrew because the pain in the knee joint increased during health education. A total of two patients in the control group took celecoxib (0.2 g, qd, po) because of increased pain during health education.

Discussion

Tuina is a manual therapy under the guidance of the meridian theory of traditional Chinese Medicine. It stimulates specific acupuncture points along the pathways of meridians and performs regular passive movements on patients' joints to alleviate patients' symptoms. As for studies on its action mechanism for knee osteoarthritis, Salter (13, 14) confirmed that continuous passive exercise during an early period can help repair and regenerate cartilage through long-term research. It is believed that repeated joint flexion and extension exercise can stimulate the transformation of undifferentiated interstitial cells in cartilage tissue into cartilage cells and accelerate the repair of cartilage tissue. When applied to the affected site of patients with KOA, mechanical receptors on the surface of articular cartilage cells can transform mechanical signal into a chemical signal, thus regulating the proliferation and differentiation of articular cartilage cells, accelerating the repair of articular cartilage, and relieving articular cartilage degeneration (15). The study of Chen et al. (16) has shown that Tuina can relieve the degeneration of knee cartilage in patients with KOA. However, animal experiments (17) confirmed that Tuina can help to prevent KOA; however, it cannot completely stop the process of articular cartilage degeneration. In addition, its effect was different from that of the sodium hyaluronate group. The experiment results of Dai et al. (18) showed that the content of 8-hydroxydeoxyguanosine in the Tuina group was lower than that in the control group. It might suggest that the Tuina treatment had certain efficacy in reducing damage to the DNA of cartilage cells by oxygen-free radicals. In terms of hemodynamics, previous studies (19, 20) have shown that its action mechanism might be related to the passive activity of the joint, which can promote the infiltration and diffusion of synovia to articular cartilage, improve nutritional metabolism of tissue, benefit blood circulation around the joint, reduce intraosseous pressure, and accelerate self-repair of tissue around the joint. In morphology, Tang and Du (21) applied kneading manipulation to both sides of the patella, knee joint, and the posterior fossa of the knee joint to modeled Wister rats, followed by bending and stretching the knee joint. The results were that the degenerative changes of articular cartilage in the manipulation group and the sodium hyaluronate group, such as vacuolar degeneration of cytoplasm, decreased quantity, and degraded function of articular chondrocytes, nucleus pyknosis, and necrosis even disintegration of cells, were lesser than that in the group without treatment.

This study shows that Tuina has significant efficacy on stiffness and activities of daily living. The action mechanism may be related to its functions in regulating muscle balance and improving the abnormal biomechanical state of the knee joint. Limitation range of motion of the knee joint in patients with KOA is closely associated with fatigue of the quadriceps femoris (22). Tuina manipulation helps to stretch muscle fibers, improve muscle tension, endurance, and elasticity, and correct biomechanical disorder of the knee joint. Therefore, it can speed up the recovery of knee muscle strength and improve its stability (23). Gong et al. (24) treated patients with KOA with Tuina and found that quadriceps femoris peak torque

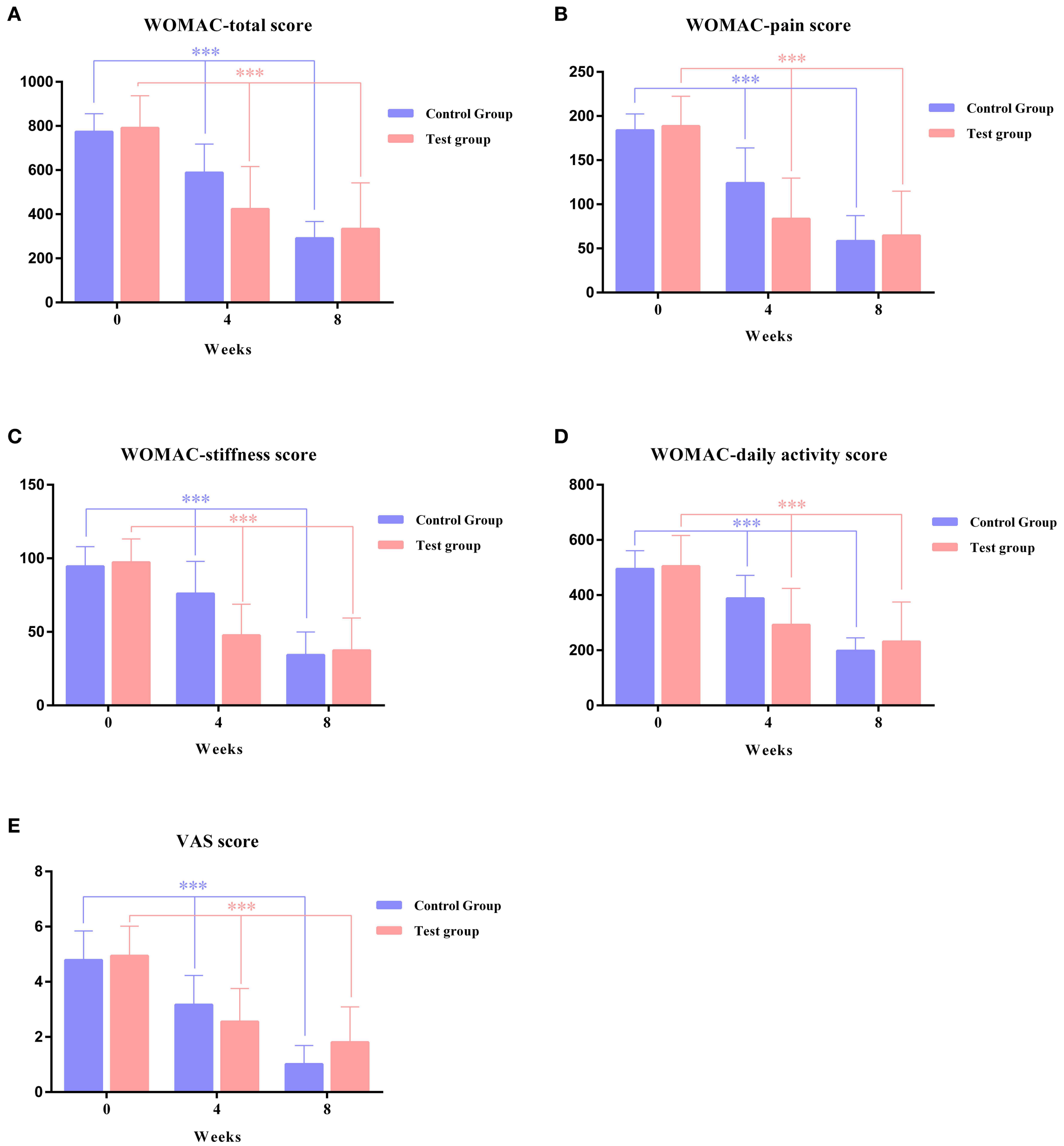

FIGURE 3
Changes in primary outcomes over an 8-week study period between the test group and control group. **(A)** WOMAC total score, **(B)** WOMAC pain score, **(C)** WOMAC stiffness score, **(D)** WOMAC daily activity score, and **(E)** VAS score. ***Significant difference from 4-week group vs. baseline and 8-week group vs. 4 weeks.

(PT), single total work (TW), and average power (AP) were all significantly increased by the isokinetic muscle strength test. The Lequene and Mery severity index and the JOA score were also improved significantly.

A 4-week Tuina therapy can significantly improve clinical symptoms in patients with KOA. This study also confirms that Tuina can reduce pain in patients with KOA effectively. The mechanism may be related to its functions in improving local blood circulation and reducing levels of inflammatory cytokines. Repeated rubbing stimulation to the affected knee can increase the temperature in the deep tissue, dilate blood vessels, accelerate the blood flow rate of the knee joint, improve local microcirculation, and thus promote absorption of inflammatory substances. Meanwhile, it can also promote synovial fluid secretion and improve cartilage nutrition. Best et al. (25) believed that absorption may increase tissue revascularization by upregulating VEGF. Previous studies (26–29) have shown that absorption can regulate synovial blood flow of the knee joint in patients with KOA, inhibit the release of PGE2, reduce levels of IL-1, IL-6, TNF-α, MMP-3, relieve pain, protect the knee joint, increase levels of serum osteoprotegerin (OPG) and osteocalcin (BGP), and promote osteogenesis.

Meanwhile, there are limitations of this study, such as the follow-up time being too short to objectively evaluate the long-term efficacy of Tuina for KOA. At the same time, the blind method cannot be realized due to the large differences in intervention measures, and the primary and secondary outcomes were non-objective indicators, bringing great challenges to research quality assurance. However, to maximize the reliability of the result, our study group took some measures in the process. For example, we hired a full-time monitor for quality supervision, developed quality control measures for consistency of Tuina manipulation, and set up an independent efficacy evaluation and safety event judgment researcher in the study.

Conclusion

This is a crossover, randomized, and controlled clinical trial to provide evidence that Tuina therapy is safe and effective for patients with KOA. It demonstrated that a 4-week Tuina therapy period can effectively and safely increase physical functions of the knee joint, reduce joint pain, and improve the quality of life in patients with KOA compared with health education.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Chinese Ethics Committee of Registering Clinical Trials. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WY designed this trial, led this trial quality assurance, and revised the manuscript. KL and YZhan drafted and revised this manuscript. HL contributed to data statistical analysis. YZhang, YZhao, and YC performed data interpretation. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Identification of necroptosis-related genes in Parkinson's disease by integrated bioinformatics analysis and experimental validation

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Background: Parkinson's disease (PD) is the second most common neurodegeneration disease worldwide. Necroptosis, which is a new form of programmed cell death with high relationship with inflammation, plays a vital role in the progression of PD. However, the key necroptosis related genes in PD are not fully elucidated.

Purpose: Identification of key necroptosis-related genes in PD.

Method: The PD associated datasets and necroptosis related genes were downloaded from the GEO Database and GeneCards platform, respectively. The DEGs associated with necroptosis in PD were obtained by gap analysis, and followed by cluster analysis, enrichment analysis and WGCNA analysis. Moreover, the key necroptosis related genes were generated by PPI network analysis and their relationship by spearman correlation analysis. Immune infiltration analysis was used for explore the immune state of PD brain accompanied with the expression levels of these genes in various types of immune cells. Finally, the gene expression levels of these key necroptosis related genes were validated by an external dataset, blood samples from PD patients and toxin-induced PD cell model using real-time PCR analysis.

Result: Twelve key necroptosis-related genes including ASGR2, CCNA1, FGF10, FGF19, HJURP, NTF3, OIP5, RRM2, SLC22A1, SLC28A3, WNT1 and WNT10B were identified by integrated bioinformatics analysis of PD related dataset GSE7621. According to the correlation analysis of these genes, RRM2 and WNT1 were positively and negatively correlated with SLC22A1 respectively, while WNT10B was positively correlated with both OIF5 and FGF19. As the results from immune infiltration analysis, M2 macrophage was the highest population of immune cell in analyzed PD brain samples. Moreover, we found that 3 genes (CCNA1, OIP5 and WNT10B) and 9 genes (ASGR2, FGF10, FGF19, HJURP, NTF3, RRM2, SLC22A1, SLC28A3 and WNT1) were down- and up- regulated in an external dataset GSE20141, respectively. All the mRNA expression levels of these 12 genes were obviously upregulated in 6-OHDA-induced SH-SY5Y cell PD model while CCNA1 and OIP5 were up- and down- regulated, respectively, in peripheral blood lymphocytes of PD patients.

Conclusion: Necroptosis and its associated inflammation play fundamental roles in the progression of PD and these identified 12 key genes might be served as new diagnostic markers and therapeutic targets for PD.

KEYWORDS

parkinson's disease, programmed cell death, necroptosis, inflammation, integrated bioinformatics analysis, immune infiltration, macrophage

1. Introduction

Parkinson's disease (PD) is a common degenerative disease of the central nervous system along with multisystem disorder in middle-aged and elderly people (Chong et al., 2013; Costa et al., 2023) and is the second most common neurodegenerative disease after Alzheimer's disease (AD) in the world (Mansour et al., 2023). PD's main clinical manifestations include static tremors, rigidity, bradykinesia and parkinsonian gait and so on (Marino et al., 2020). According to the epidemiological studies, the prevalence of PD increases with the rise of aging populations. The incidence of PD is 1.5–2% among people over 60 years old and up to 4% in people over 80 years old (Marino et al., 2020), and the global PD patients has increased from 2.5 to 6.1 million since the 1990s (Rajan and Kaas, 2022). In China, the prevalence of PD was 1.37% in people over 60 years old, and the number of people suffering from the disease has exceeded 3.62 million indicated by a community-based study (Qi et al., 2021). Recent studies have found that dyssomnia, sleep disorder, mental disorder, cognitive disorder, and somatoform autonomic dysfunction are commonly exist in PD patients and occur among different stages of motor symptoms, affecting the life quality of patients (Suzuki et al., 2022). Due to the high rate of disability and a long therapeutic procedure, PD brings heavy burden and troubles to patients and their families (Zhang et al., 2005; Kumar et al., 2010; Seol, 2010; Rajan and Kaas, 2022). Therefore, it is extremely important to study the etiology and pathogenesis of PD nowadays.

The main pathological characteristic of PD is the degeneration and necrosis of dopaminergic neurons in the substantia nigra (Mollenhauer and von Arnim, 2022), which results in the decrease of neurotransmitter dopamine (DA) synthesis as well as its amount in the synaptic cleft (Tysnes and Storstein, 2017; Marino et al., 2020). But the specific underlying mechanisms that cause the necrosis of dopaminergic neurons are not yet fully known. Necroptosis, which is a type of cellular necrosis initiated by death receptor ligands, has been discovered that might be co-related with the progression of PD (Kim et al., 2023). Moreover, necroptosis is a unique caspase-independent programed cell death with distinctive morphological features of necrosis, which is regulated by receptor interaction proteins (RIP) including RIP1 and RIP3 and their downstream signaling molecules mixed-lineage kinase domain-like protein (MLKL), and specifically blocked by the small molecule compound, necrostatin-1 (Nec-1) (Zhang and Liu, 2013; Fayaz et al., 2014; Zhang et al., 2022; Kim et al., 2023). Inflammation and immune dysregulation are fundamental pathophysiological features of PD and contribute to its progression (Tansey et al., 2022). However, the pathological role of necroptosis in the etiology of PD still needs to be clarified.

In the current study, we downloaded PD related datasets from the GEO database and analyzed the associate of necroptosis-related genes between PD and control brain samples by gap analysis, cluster analysis, enrichment analysis, weighted gene co-expression network analysis (WGCNA), protein–protein interaction (PPI) networks analysis and correlation analysis according to previous studies (Zhou et al., 2020a,b; Zhao et al., 2021). Finally, several key necroptosis-related differentially expression genes (DEGs) are identified, and their interaction with immune cells was also analyzed. In addition, the mRNA expression of these key genes were verified by external dataset and real-time PCR analysis both in blood samples from control and PD patients and toxin-induced neuroblast cell PD model. The current research strategy is referred as Figure 1, and this study might provide a meaningful basis for exploring the molecular pathogenesis, diagnostic markers and drug development of PD.

2. Materials and methods

2.1. Source of data

The gene expression data were extracted from the GEO Database via the GEO query package (Davis and Meltzer, 2007). We downloaded the Parkinson's disease-related datasets GSE7621 (Lesnick et al., 2007) and GSE20141 (Zheng et al., 2010), which are all from *Home sapiens* and generated from GPL570 data platform. GSE7621 contains 25 samples with 9 and 16 samples in the control and PD groups, respectively. GSE20141 contains 18 samples with 8 and 10 samples in the control and PD groups, respectively. All samples were employed in the current study, and we normalized and standardized the data by limma package (Ritchie et al., 2015). In addition, necroptosis-related gene sets were obtained from the GeneCards database.[1]

2.2. Gap analysis

Gap analysis of genes in different groups was performed using the limma R package (Ritchie et al., 2015). This research set $|\log FC| > 1$ and p value <0.05 as the threshold for DEGs, where DEGs were upregulated in the disease group with logFC >0 and DEGs were downregulated in the disease group with logFC <0. The results of the

1 https://www.genecards.org/

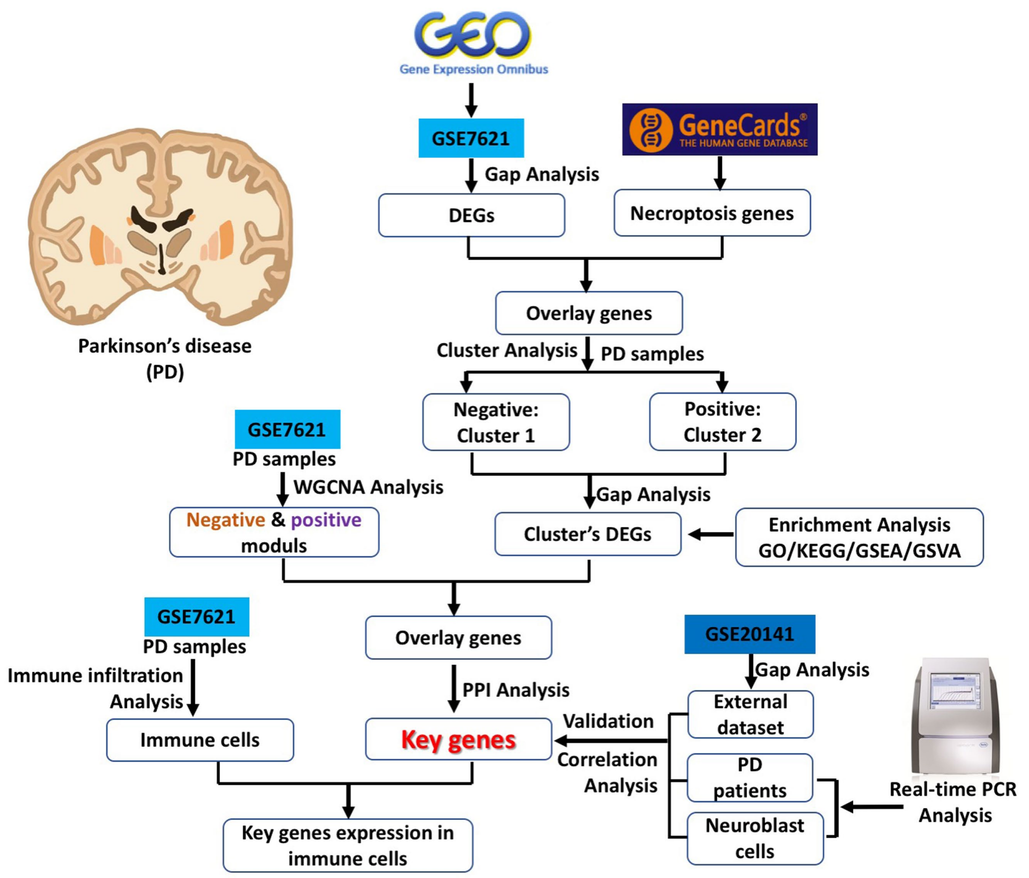

FIGURE 1
Research strategy of the current study.

gap analysis were presented by the heatmaps and volcano plots drawn by gglot2 in R package (Li et al., 2022).

2.3. Cluster analysis

Consensus Clustering is a method for determining the number and membership of possible clusters in a dataset (microarray gene expression). We used the "Consensus Cluster Plus" R package (Wilkerson and Hayes, 2010) to perform consensus clustering on samples from the disease group of PD in the GSE7621 dataset using differentially expressed necroptosis-related genes to facilitate better differentiation between different subtypes of PD. In this process, the number of clusters was set between 2 to 9, and 80% of the total samples were drawn in 1000 replicates, clusterAlg = "pam," distance = "euclidean." The *t*-Distributed Stochastic Neighbor Embedding (tSNE) technique was used for visualized and analyzed efficiently (Pezzotti et al., 2017).

2.4. Enrichment analysis (GO/KEGG/GSEA/GSVA)

Gene Ontology (GO) analysis is a common method for conducting large-scale functional enrichment studies, including biological process (BP), molecular function (MF) and cellular component (CC). Kyoto Encyclopedia of Genes and Genomes (KEGG) is a widely used database for storing information about genomes, biological pathways, diseases and drugs (Kanehisa and Goto, 2000). GO annotation analysis and enrichment analysis of the KEGG pathway of DEGs were performed by using the Database for Annotation, Visualization and Integrated Discovery (DAVID),[2] with a critical value of the false discovery rate (FDR) <0.05 considered to be statistically significant (Sherman et al., 2022). The results of the enrichment analysis were visualized by using the ggplot2 in R package.

To investigate the differences in biological processes between different groups, we performed a gene set enrichment analysis (GSEA) (Subramanian et al., 2005) based on datasets of gene expression profiling from PD samples in the GSE7621 dataset. GSEA is a computational method for analyzing whether a particular gene set is statistically different between two biological states and is commonly used to estimate changes in the pathway and biological process activity in samples of expression data sets. The "c2.cp.kegg.v6.2.-symbols" gene set was downloaded from the MSigDB (Liberzon et al., 2015) for GSEA, and FDR < 0.25 was considered significantly enriched.

2 https://david.ncifcrf.gov/

In addition, we use the R package to perform gene set variation analysis (GSVA) (Hänzelmann et al., 2013). The single sample gene set enrichment analysis (ssGSEA) method was used to calculate the scores of the relevant pathways based on the gene expression matrix of each sample separately, and we performed differential screening on the enrichment functions (or pathways) by using the limma package (Ritchie et al., 2015).

2.5. WGCNA analysis

Weighted Gene Correlation Network Analysis (WGCNA) is used for identifying correlative gene modules, exploring the relationship between gene networks and phenotypes, and studying the core genes in the network (Langfelder and Horvath, 2008). A soft threshold is calculated by the pick Soft Treshold function, with 5 being the best soft threshold, followed by the construction of a scale-free network based on the soft threshold and the construction of a topological matrix, and finally the hierarchical clustering. Eigengenes were calculated by dynamically cutting the identified gene modules with the minimum number of genes 50 in the module. Inter-module correlations were constructed based on module eigengenes, and hierarchical clustering was performed to merge modules with correlations above 0.4 (Zhao et al., 2015). The generation of modules and correlations between modules and clinical features were known through spearman correlation analysis (Wang et al., 2020).

2.6. PPI network construction

The STRING database[3] is a database for searching known proteins and predicted protein–protein interactions for 2031 species, containing 9.6 million proteins and 138 million protein–protein interactions (Szklarczyk et al., 2017). It contains results obtained from experimental data, text mining of PubMed abstracts, and other database data as well as results predicted by using bioinformatics methods. We constructed a protein–protein interaction (PPI) network of differentially expressed necroptosis-related genes using the STRING database with the parameter of a factor = 0.4 by default software execution. And spearman correlation analysis was employed for the relation between identified key necroptosis related genes (Wang et al., 2020).

2.7. Immune infiltration analysis

CIBERSORT is based on the principle of linear support vector regression to deconvolute the transcriptome expression matrix to estimate the composition and abundance of immune cells in a mixture of cells (Chen et al., 2018). We uploaded the gene expression matrix data to CIBERSORT and combined it with the LM22 eigengene matrix to screen samples with the criteria of $p < 0.05$, and finally generated the immune cell infiltration matrix. The R programming ggplot2 package was used to plot bar graphs to show the distribution of the 22 kinds of immune cells infiltrating in each sample.

3 https://string-db.org/

2.8. Quantitative real-time PCR analysis

Twelve venous blood samples from clinical PD patients ($n = 6$) and healthy adults ($n = 6$) were collected. Peripheral blood lymphocytes were separated from a lymphocyte separation medium cushion (Ficoll-Paquplus, GE). Besides, toxin-induced cell model was employed for gene expression verification. The neuroblast SH-SY5Y cells (ATCC) were treated with or without 200 μM 6-Hydroxydopamine (6-OHDA) (Sigma) for 24 h, then the cells were harvested for further analysis. Total RNA was extracted using TRIZOL (Roche). The RNA concentration was determined by a UV-spectrophotometer (M200, Tecan). Reverse transcription was performed following the reverse transcript kit (Transcriptor First Strand cDNA Synthesis Kit, Roche). Quantitative PCR was performed using SYBR Green (LightCycler 480 SYBR Green I Master, Roche) based on the LightCycle 96 platform (Roche). The PCR conditions were as follows: 95°C for 30 s, followed by 45 cycles of 95°C for 5 s, 60°C for 10 s and 72°C for 60s according to our previous study (Zhou et al., 2020a, 2023). GAPDH was used as an internal reference and gene expression changes were counted by the $2^{-\Delta\Delta Ct}$ method. The specific primer sequences of interest genes are shown in Table 1.

2.9. Statistical analysis

All data calculations and statistical analyses were performed by using R programming[4] (version 4.1.2). For the comparison of two groups of continuous variables, the statistical significance of normally distributed variables was estimated by independent Student *t* tests, and differences between non-normally distributed variables were analyzed by the Mann–Whitney U test (i.e., Wilcoxon rank sum test). Correlation analysis was performed on the two data sets by using Spearman's rank correlation test. All statistical *p*-values were two-sided, with $p < 0.05$ considered statistically significance.

3. Results

3.1. Identification of DEGs and necroptosis-related genes by gap analysis

A total of 290 DEGs were obtained from the bioinformatic analysis of Parkinson's disease-related dataset GSE7621 with the criterias of $|\log FC| > 1$ and p value <0.05, in which 151 genes were up-regulated and 139 genes were down-regulated in PD group (Figure 2A). These up- and down- regulated genes were visualized by a heatmap (Figure 2B) and a volcano plot (Figure 2D). Moreover, 614 necroptosis-related gene sets were obtained from the GeneCards database, in which 4 genes, including ubiquitin like with PHD and ring finger domains 1 (UHRF1), 1,4-alpha-glucan branching enzyme 1 (GBE1), transient receptor potential cation channel subfamily C member 6 (TRPC6) and TNFAIP3 interacting protein 3 (TNIP3), overlayed with above DEGs (Figure 2C). And these 4 necroptosis-related genes were also marked with arrows in the volcano plot (Figure 2D).

4 https://www.r-project.org/

TABLE 1 Sequences of the required primers in real-time PCR analysis.

Gene	Forward primer	Reverse primer
HJURP	5'-GTCCTGGGAGCCGATTCAAA-3'	5'-CAAAGGGCTTTGAGGCACTG –3'
ASGR2	5'-TGCTCCATGGTCTGCTTCAG-3'	5'-TCACACAGATGACCACCAGC-3'
CCNA1	5'-GATAACGACGGGAAGAGCGG-3'	5'-CGGTCTCCATCCCAAGTGAC-3'
FGF10	5'-TTGTAGAAGTGGCTCGCAGG-3'	5'-GGTGGGGAATAGGGGGAGAT-3'
FGF19	5'-GAACTGACTGGAGCAGGCAT-3'	5'-GACACCGGGACAGCAAGTTA-3'
NTF3	5'-TGCCAGAGCCTGCTCTTAAC-3'	5'-GATGCCACGGAGATAAGCGA-3'
OIP5	5'-CGCCCTTCCTAGTTGGCATT-3'	5'-CGGGAATCCCACAAGAACCA-3'
RRM2	5'-GCGCGGGAGATTTAAAGGC-3'	5'-ACACGGAGGGAGAGCATAGT-3'
SLC22A1	5'-CATTTTGTTTGCGGTGTTGGG-3'	5'-TTTCTCCCAAGGTTCTCGGC-3'
SLC28A3	5'-AAACGGAGTCTCCACTGCTG-3'	5'-CAAGTGGGAGGATGGAACCC-3'
WNT1	5'-TACCTCCAGTCACACTCCCC-3'	5'-TTGAGGAGTCCCCAGGTAGG-3'
WNT10B	5'-GGGTGGCTGTAACCATGACA-3'	5'-TTGTGGATTCGCATTCGTGC-3'
GAPDH	5'-CACCATCTTCCAGGAGCGAG-3'	5'-GACTCCACGACGTACTCAGC-3'

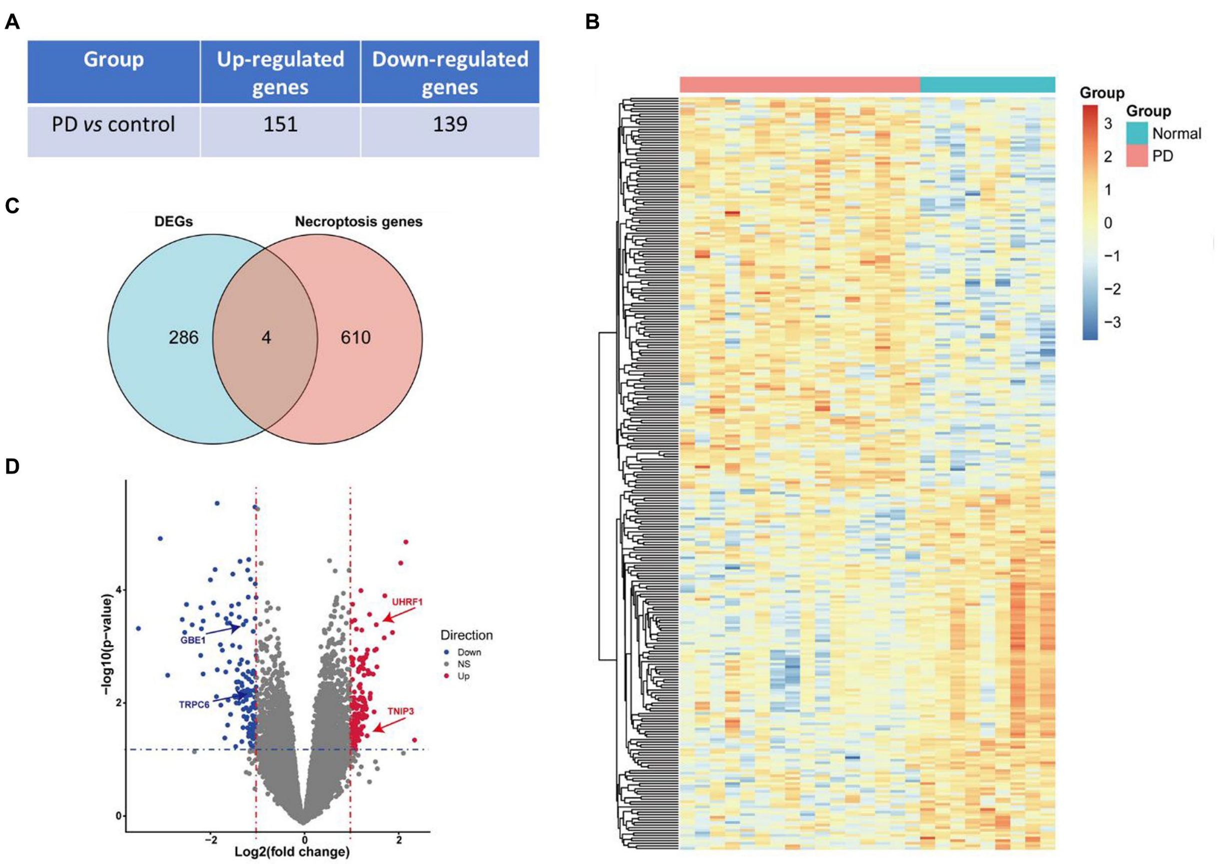

FIGURE 2
Identification of DEGs and necroptosis-related genes. **(A)** The number of up- and down- regulated genes in PD vs. control groups. **(B)** The heatmap of differentially expressed genes (DEGs) in PD vs. control groups. **(C)** Venn diagram presented 4 overlayed differentially expressed necroptosis-related genes. **(D)** Volcano plot of differentially expressed genes, in which red means up-regulated genes in the PD vs. control group while blue means down-regulated and grey means non-differentially expressed genes. The blue horizontal dotted line represents the threshold of *p* value <0.05 and the red vertical dotted line represents the threshold of |fold change|>1. Four differentially expressed necroptosis genes, including UHRF1, GBE1, TRPC6 and TNIP3, were marked with arrows.

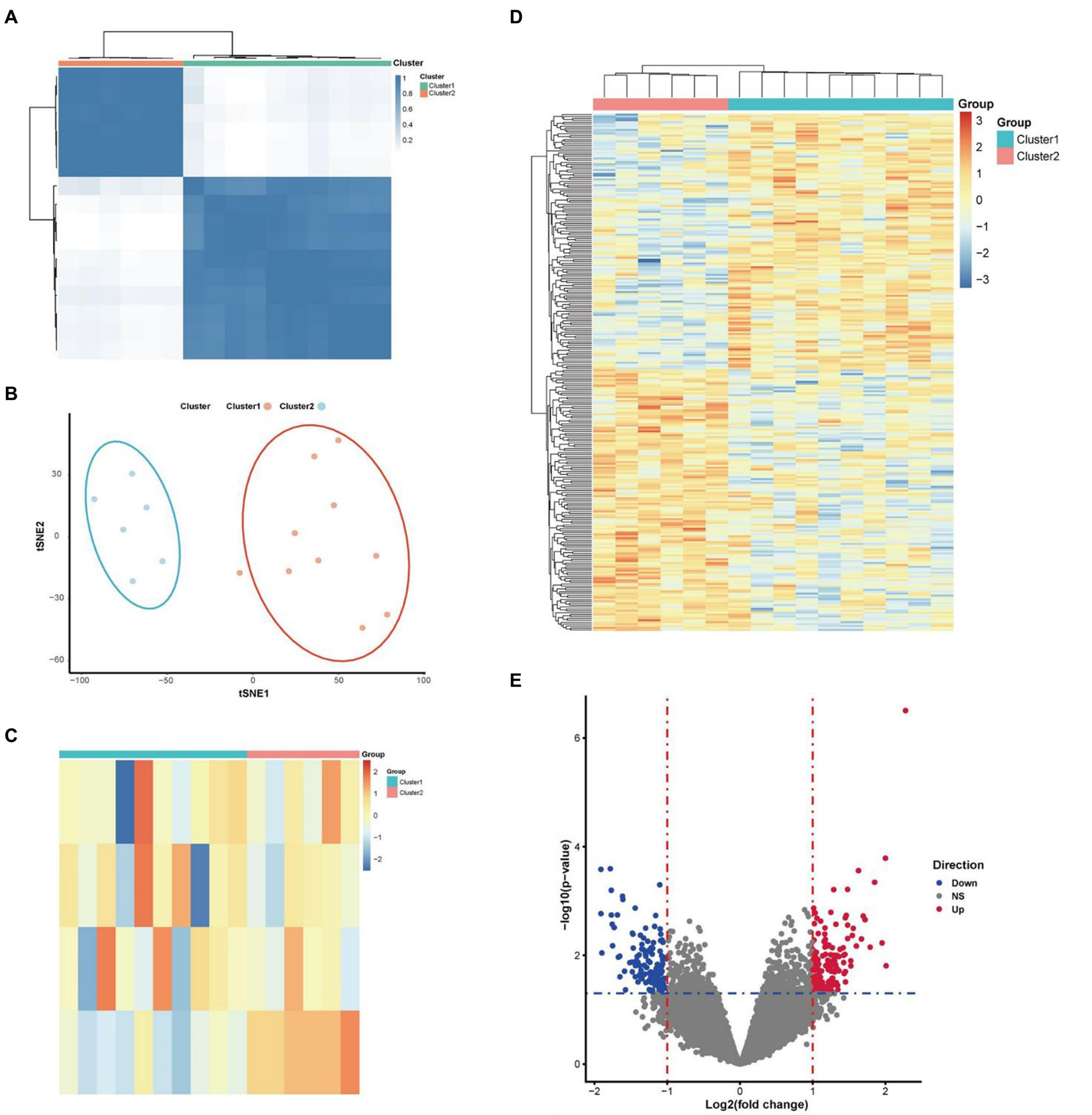

FIGURE 3
Molecular classification of PD samples and DEGs based on 4 identified differentially expressed necroptosis-related genes. **(A)** According to the guidance of four above differentially expressed necroptosis-related genes in molecular classification, Parkinson's patients can be significantly divided into two categories. **(B)** The tSNE plot shown a clear separation of low and high necroptosis types of patients. **(C)** The heatmap shown that the patients presented low and high necroptosis phenotypes in cluster1 and cluster 2, respectively. **(E)** The volcano map shown the expression levels and connections of DEGs in these two types of Parkinson's patients. **(D)** The heatmap shown the DEGs and their connections in these two phenotypes of Parkinson's patients.

3.2. Molecular classification of PD samples and DEGs based on necroptosis-related genes by cluster analysis

Concordance clustering of expressed genes in 16 PD samples was performed using above 4 differentially expressed necroptosis-related genes by the Consensus Cluster Plus package. The expressed genes were re-divided into two categories of cluster 1 and cluster 2 according to the necroptosis phenotype (Figure 3A). The tSNE plot shows that the two classes of PD samples can be significantly distinguished (Figure 3B). Visualization of differentially expressed necroptosis related genes in both patient groups revealed that patients in cluster 1 presented low necroptosis phenotype and in cluster 2 presented high necroptosis phenotype (Figure 3C). Further gap analysis was performed for these two types of PD samples with the criterias of $|logFC| > 1$ and p value <0.05. A total of 271 DEGs associated with the necroptosis phenotype were obtained and visualized using a heatmap (Figure 3D) and a volcano plot (Figure 3E).

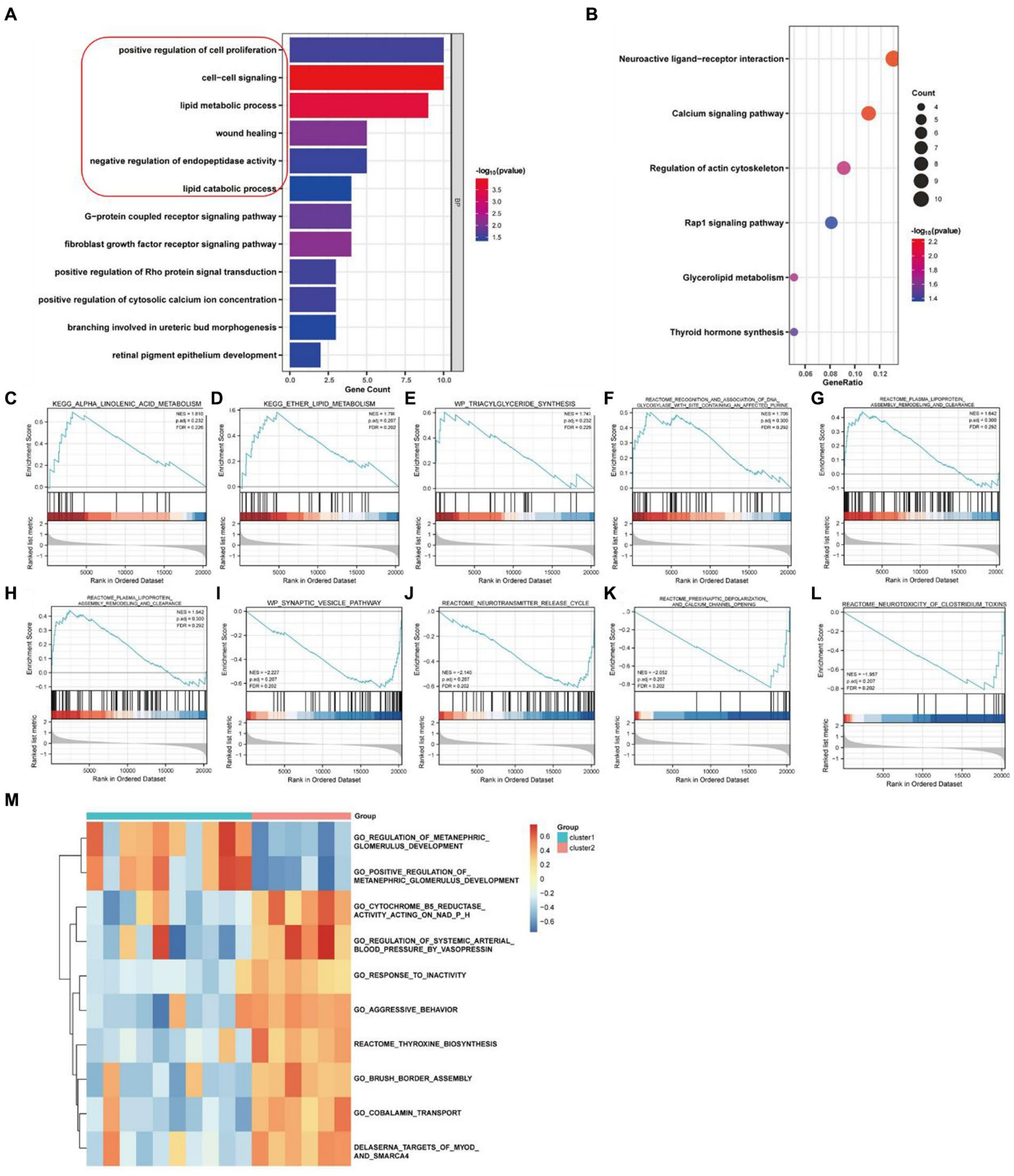

FIGURE 4
Enrichment analysis of necroptosis-related genes in PD samples. **(A)** GO enrichment analysis. **(B)** KEGG enrichment analysis. **(C–G)** Five up-regulated pathways were significantly enriched in cluster2 vs. cluster1. **(H–L)** Five down-regulated pathways were significantly enriched in cluster2 vs. cluster1 by GSEA enrichment analysis. **(M)** Pathway entries were significantly enriched in cluster1 and cluster2 by GSVA enrichment analysis.

3.3. Identification of both function and pathway of necroptosis-related genes in PD samples by GO, KEGG, GSEA, and GSVA enrichment analysis

We performed an enrichment analysis of DEGs in these two clusters of PD samples to elucidate functional differences by GO and KEGG analysis. According to GO analysis, the related biological processes are significantly enriched in entries such as positive regulation of cell proliferation, cell–cell signaling, lipid metabolic process, wound healing and negative regulation of endopeptidase activity (Figure 4A; Supplementary Table S1), while the results of KEGG analysis suggested that neuroactive ligand-receptor interaction, calcium signaling pathway, regulation of actin cytoskeleton, Rap1 signaling pathway and glycerolipid

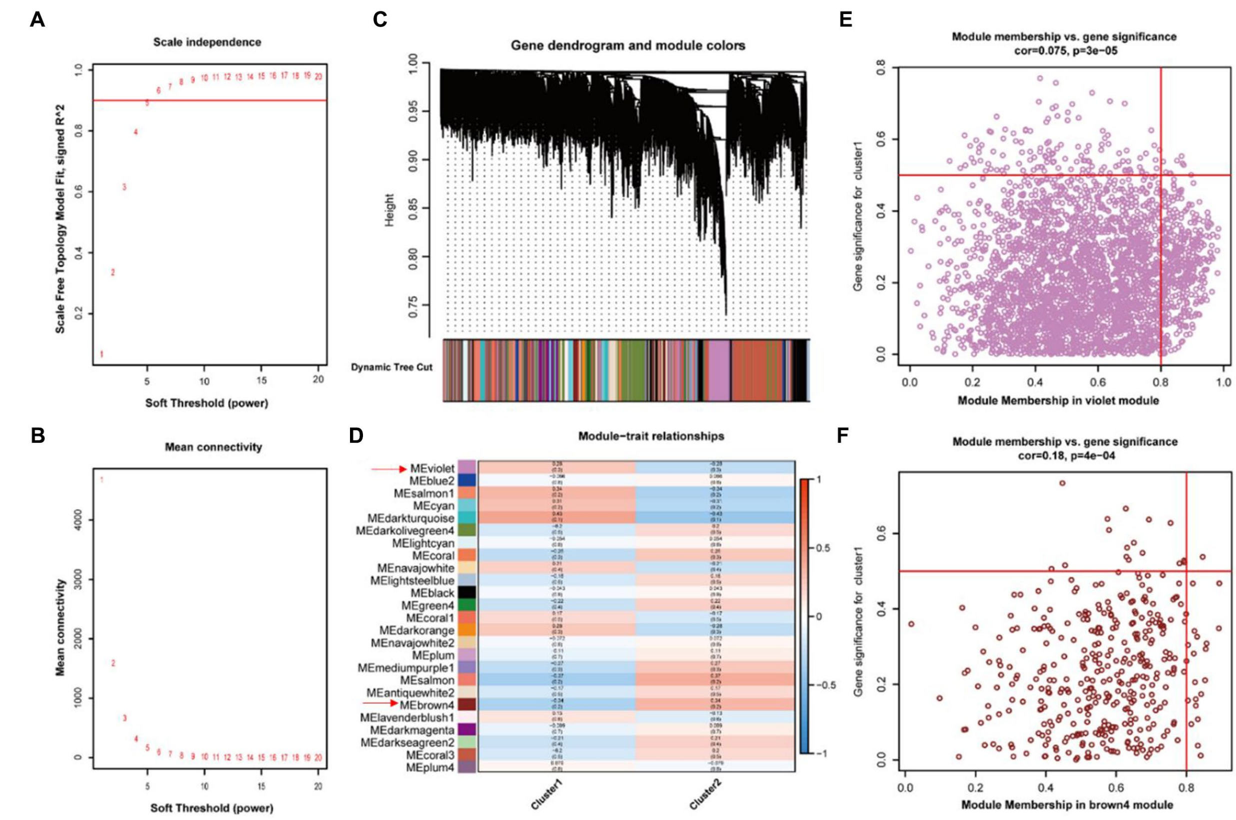

FIGURE 5
Generation of positive and negative modules involved in necroptosis by WGCNA Analysis. **(A,B)** Soft threshold screening. **(C)** Identification of gene modules by dynamic shearing tree. **(D)** Correlation analysis between modules and phenotypes. **(E)** Scatterplot of violet modules. **(F)** Scatterplot of brown4 modules.

metabolism were close association (Figure 4B; Supplementary Table S2). In addition, as the result from GSEA enrichment analysis of these DEGs, five up-regulated pathways were significantly enriched in high necroptosis phenotype cluster 2 (Figures 4C–G) and five pathways were down-regulation (Figures 4H–J) respectively (Supplementary Table S3). As the results from GSVA analysis, ten selected pathways significantly enriched in both cluster 1 and cluster 2 (Figure 4M; Supplementary Table S4).

3.4. Generation of positive and negative modules involved in necroptosis by WGCNA analysis

In order to further identification of genes significantly associated with the necroptosis-related phenotype, we performed WGCNA with the criteria of 5 as the optimal soft threshold (Figures 5A,B). We performed hierarchical clustering after constructing scale-free networks and topological matrices and finally obtained 25 modules as well as correlations between modules and clinical features (Figures 5C,D). We obtained 3,091 genes in the violet module (Figure 5E), which positively regulated necroptosis, and 383 genes in the brown4 module (Figure 5F), which negatively regulated necroptosis, consequently identification of a total of 3,474 genes which were significantly associated with necroptosis.

3.5. Identification of 12 key necroptosis related genes in PD and their correlation analysis

The DEGs between cluster 1 and cluster 2 were intersected with the relevant module genes in WGCNA, and we obtained 53 differentially expressed necroptosis-related genes that may contribute to the different phenotypes of these two clusters of PD samples (Figure 6A). The PPI network was construct based on these 53 overlayed genes using STRING database with the criteria of coefficient = 0.4, and finally we obtained three subnetworks which contained a total of 12 key upregulated genes (Figure 6B) including asialoglycoprotein receptor 2 (ASGR2), cyclin A1 (CCNA1), fibroblast growth factor 10 (FGF10), fibroblast growth factor 19 (FGF19), holliday junction recognition protein (HJURP), neurotrophin 3 (NTF3), opa interacting protein 5 (OIP5), ribonucleotide reductase regulatory subunit M2 (RRM2), solute carrier family 22 member 1 (SLC22A1), solute carrier family 28 member 3 (SLC28A3), wnt family member 1 (WNT1) and wnt family member 10B (WNT10B). As the results from correlation analysis of these 12 key necroptosis related genes in Figures 6C–G, we found that RRM2 and WNT1 were dramatically positively and negatively correlated with SLC22A1, while WNT10B was positively correlation with both OIF5 and FGF19.

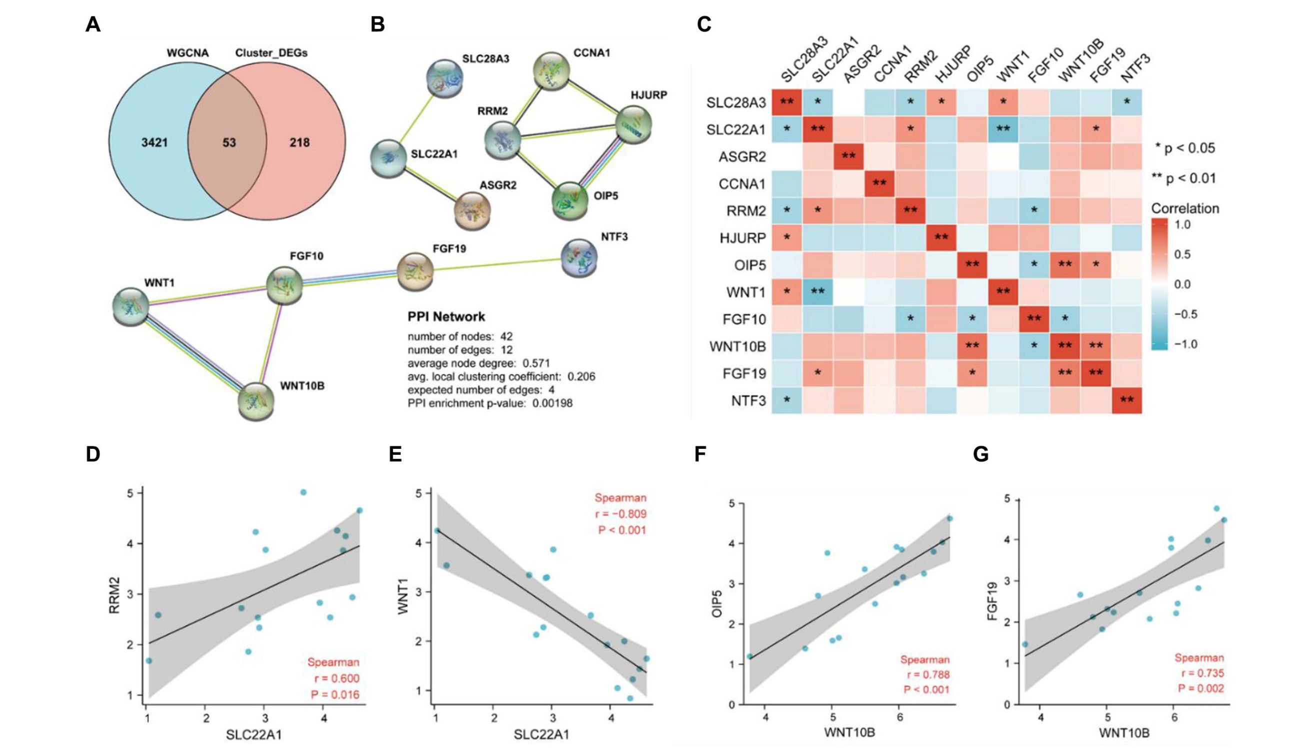

FIGURE 6
Identification of key genes by PPI network analysis and their correlation Analysis. **(A)** The 53 overlay genes between WGCNA analysis and differentially expressed necroptosis-related genes in cluster 2 were presented by Venn diagram. **(B)** Twelve key necroptosis-related genes were identified by a PPI network analysis of the 53 overlayed genes. **(C)** The heat map indicated the correlation between 12 genes by spearman correlation analysis. **(D)** Correlation analysis between SLC22A1 and RRM2. **(E)** Correlation analysis between SLC22A1 and WNT1. **(F)** Correlation analysis between WNT10B and OIP5. **(G)** Correlation analysis between WNT10B and FGF19.

3.6. The M2 macrophage was the highest population among immune cells by the immuno-infiltration analysis

We conducted an immuno-infiltration analysis using the expression matrix of PD samples in the GSE7621 dataset. The correlation between different species of immune cells and the proportion of different immune cells in all samples were presented in Figures 7A,B, respectively. These results suggested that the proportion of M2 macrophages was the highest. Besides, we further analyzed the correlations between the 12 above key necroptosis related genes in various types of immune cells, and the correlation coefficients and *p*-values were presented in the form of lollipop plots (Figures 7C–N). We could find that the expression of 9 genes (ASGR2, CCNA1, FGF19, NTF3, OIP5, RRM2, SLC22A1, WNT1, and WNT10B) were positively co-related to the function of M2 macrophage while 3 genes (FGF10, HJURP and SLC28A3) were negatively co-related to the function of M2 macrophage.

3.7. Validation the expression levels of 12 key necroptosis related genes by external dataset, toxin-induced injury of neuroblast model, and peripheral blood lymphocytes of PD patients

As the gap analysis results from the external dataset GSE20141, the expression of ASGR2, FGF10, FGF19, HJURP, NTF3, RRM2, SLC22A1, SLC28A3 and WNT1 genes were significantly increased in PD samples, whereas the genes CCNA1, OIP5, and WNT10B were significantly decreased (Figure 8A). All these 12 genes were significantly upregulated in 6-OHDA treated SH-SY5Y cells (Figure 8B). However, CCNA1 was upregulated and OIP5 was downregulated in peripheral blood lymphocytes of PD patients (Figure 8C). All the above results were summarized in Table 2.

4. Discussion

Parkinson's disease (PD) has a widespread and significant negative impact on the motor function and life quality of patients. The current treatment methods significantly ameliorate its symptoms, but they cannot prevent its deterioration (Brocker et al., 2017). Although there are many studies focused on PD in recent decades, its pathogenesis is still not fully understood, which limited the development of its specific drugs. Necroptosis, which is a new form of regulated cell death and also exists in dopaminergic neurons, has been proved that it contributed to the pathological progression of PD (Liu et al., 2014). Conventionally, necrosis and apoptosis are two well-known forms of programmed death in injured neuronal cells. Recently, many researchers found that necroptosis is also a typical mode of neuronal cell death with the feathers of morphological changes in necrotic cells, activation of autophagy and energy-depleting (Imre, 2020). In addition, necroptosis is not the same as the traditional sense of necrosis

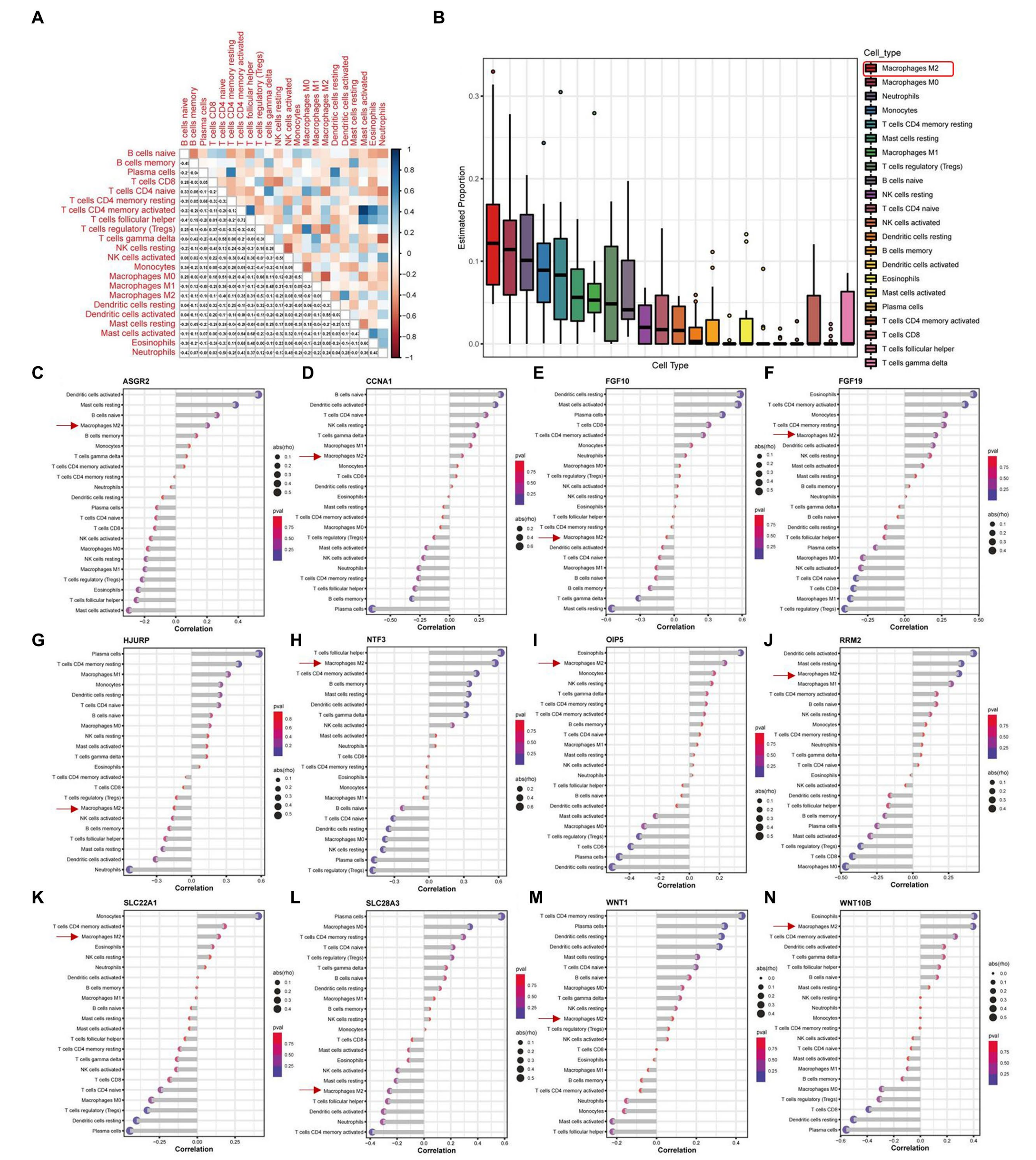

FIGURE 7
Immune infiltration analysis of PD samples and the expression of 12 key necroptosis related genes in various kinds of immune cells. **(A)** Correlation analysis between different species of immune cells. **(B)** The proportion of different immune cells in all samples. **(C–N)** The Correlation analysis between 12 key necroptosis related genes, including ASGR2, CCNA1, FGF10,FGF19, HJURP, NTF3, OIP5, RRM2, SLC22A1, SLC28A3, WNT1, and WNT10B, and various types of immune cells. Red square and arrows indicated the M2 macrophage.

(Carnevale et al., 2012). In the current study, we designed a comprehensive bioinformatic analysis and experimental validation strategy for identification of key necroptosis related genes in PD (Figure 1).

DEGs were extracted by gap analysis of dataset GSE7621, and followed by overlay of necroptosis genes (Figure 2). Consequently, 4 genes (UHRF1, GBE1, TRPC6 and TNIP3) were obtained and used for the guidance of cluster analysis (Figure 3) and enrichment analysis (Figure 4; Supplementary Tables S1–S4). In terms of molecular mechanisms, this study identified relevant molecular interactions through GO and KEGG enrichment analysis. GO enrichment analysis showed that positive regulation of cell proliferation, cell–cell signaling, lipid metabolic process, and wound healing are obvious in the biological participation processes (Figure 4A; Supplementary Table S1).

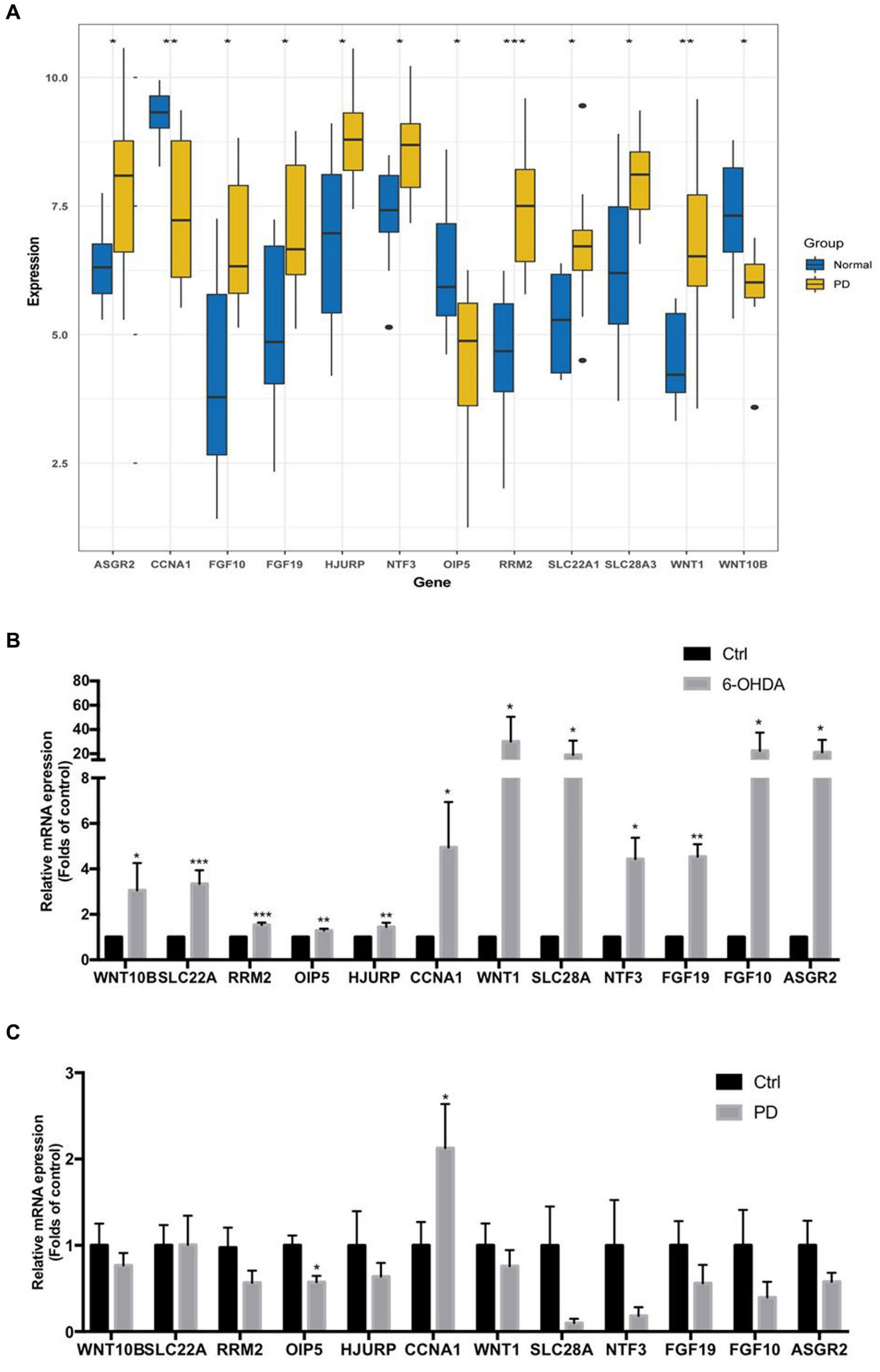

FIGURE 8
The mRNA expression levels of 12 key necroptosis related genes in external dataset, toxin-induced injury of neuroblast and peripheral blood lymphocytes of PD patients. **(A)** The expression matrix presented the expression of 12 key necroptosis related genes (ASGR2, CCNA1, FGF10, FGF19, HJURP, NTF3OIP5, RRM2, SLC22A1, SLC28A3, WNT1 and WNT10B) in both the control and PD groups from the dataset GSE20141. **(B)** The mRNA expression levels of above 12 key necroptosis related genes in toxin 6-OHDA-induced injury of neuroblast SH-SY5Y cell model. **(C)** The mRNA expression levels of above 12 key necroptosis related genes in peripheral blood lymphocytes of PD patients and health adults. *p<0.05 vs. control group; **p<0.01 vs. control group; ***p<0.001 vs. control group.

KEGG enrichment analysis showed that neuroactive ligand-receptor interaction, calcium signaling pathway, and regulation of actin cytoskeleton are obvious (Figure 4B; Supplementary Table S2). Various related signaling pathways were also identified by both GSEA and GSAV enrichment analysis (Figures 4C-M; Supplementary Tables S3, S4). According to WGCNA analysis (Figure 5) and PPI network construction analysis (Figures 6A,B), 12 key necroptosis-related genes were identified, for example FGF10 and FGF19 which are the members of the FGFs family. FGF is a cell family signaling proteins closely related to neurodegenerative diseases. FGF and its receptor FGFR, which dramatically enhance the survival of dopaminergic neurons, play important roles in the development and

TABLE 2 Expression levels of 12 key necroptosis related genes in multiple models.

Genes	The full name of genes	GSE20141 dataset	Peripheral blood lymphocytes of PD patients	6-OHDA treated SH-SY5Y cell model
ASGR2	Asialoglycoprotein Receptor 2	+	n.s.	+
CCNA1	Cyclin A1	−	+	+
FGF10	Fibroblast Growth Factor 10	+	n.s.	+
FGF19	Fibroblast Growth Factor 19	+	n.s.	+
HJURP	Holliday Junction Recognition Protein	+	n.s.	+
NTF3	Neurotrophin 3	+	n.s.	+
OIP5	Opa Interacting Protein 5	−	−	+
RRM2	Ribonucleotide Reductase Regulatory Subunit M2	+	n.s.	+
SLC22A1	Solute Carrier Family 22 Member 1	+	n.s.	+
SLC28A3	Solute Carrier Family 28 Member 3	+	n.s.	+
WNT1	Wnt Family Member 1	+	n.s.	+
WNT10B	Wnt Family Member 10B	−	n.s.	+

Remark: +, significantly upregulation vs. control group; −, significantly downregulation vs. control group; n.s., no significant difference vs. control group.

maintenance of the heath nervous system as well as neuroinflammation (Chen et al., 2020). In cellular models of PD, FGF provides effective protection against the loss of dopaminergic neurons, promotes the development and survival of the nervous system, relieves neurological symptoms, and exerts neurotrophic activity in DA neurons (Liu et al., 2021). Despite to all these 12 key necroptosis related genes are positively related with the progression of PD, their internal relationship is not well known. We found that RRM2 and WNT1 were positively and negatively correlated with SLC22A1, while WNT10B presented positively correlation with both OIF5 and FGF19 (Figures 6C–G). These results indicated that these 12 necroptosis related genes are vital in the death of neurons and progression of PD, and the regulation network of these 12 key necroptosis genes are also complicate. Furthermore, the immune state in the brain of PD patient, such as neuroinflammation, also affects the neurodegeneration. Consistently, we also found the immune-inflammation changes in PD brain samples. As the results from immune infiltration analysis, many kinds of immune cells were active in PD samples in which M2 macrophage was the highest population of immune cell (Figures 7A,B). Moreover, the expression of 9 genes were positively correlated with differentiation and function of M2 macrophage while 3 genes were negative in these 12 key necroptosis genes (Figures 7C–N). M2 macrophage is a kind of anti-inflammatory phenotype in cardiovascular disease (Ma et al., 2020) while it promotes progression of cancer (Liu et al., 2019). Whether M2 macrophage enhanced the neurodegeneration in PD is not well elucidated. Thus, the immune state is really disrupted in the brain of PD patients and the immune cells, such as M2 macrophage, might also affect the expression of these 12 key necroptosis genes, resulting in the progression of neuron death.

In order to further verify the data, the mRNA expression levels of these 12 identified key necroptosis related genes were verified in both PD patients and 6-OHDA treated SH-SY5Y neuroblast model as well as another dataset GSE20141. Finally, we found that 3 genes were downregulated while 9 genes were upregulated in PD samples according to the DEGs analysis of dataset GSE20141 (Figure 8A). The mRNA expression of all these 12 genes were upregulated in 6-OHDA-treated SH-SY5Y cell model (Figure 8B), which was consistent with our current analysis. Although we conducted the immune infiltration analysis of PD brain samples which contributed to explore the immune state and expression of these 12 key necroptosis related genes in the brain of PD patients, the mRNA expression of these key necroptosis related genes in immune cells from peripheral blood were not known as well as their correlation. Thus, we collected the peripheral blood lymphocytes from both PD patients and control people, and detected the mRNA expression levels of these genes, which might be benefit for the clinical translation of our study. However, we only found that the mRNA expression level of CCNA1 was upregulated while OIP5 was downregulated in peripheral blood lymphocytes of PD patients (Figure 8C). As the summary of these genes expression listed in Table 2, the variability of gene expression results from peripheral blood lymphocytes of PD patients and the consistent of these genes expression in PD neuroblast cells indicated that neuron cell might mainly determine the genes expression levels of these 12 key necroptosis related genes in the brain. In addition, the total number of peripheral blood lymphocyte samples (6 PD + 6 control) might also limit the obtain of accurate result. Our study still needs further investigation in animal model, particularly the internal relationship of all these identified key necroptosis related genes.

Taken together, we could conclude that necroptosis and its associated inflammation play fundamental roles in the progression of PD and these identified 12 key genes might be served as new diagnostic markers and therapeutic targets for PD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Longhua Hospital, Shanghai

University of Traditional Chinese Medicine. The patients/ participants provided their written informed consent to participate in this study.

Author contributions

CL and ZZ are jointly and comprehensively responsible for project design, experiment division, data analysis, manuscript preparation and submission. ZJ, SW, and QL complete experimental operation and data recording. YJ and HH gives technical guidance and consultation. YQ and ZZ participates in project design and provides funding support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1097293/full#supplementary-material

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Tongue acupuncture for the treatment of post-stroke dysphagia: a meta-analysis of randomized controlled trials

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Objectives: Post-stroke dysphagia is the most common neurological impairment after stroke. The swallowing process is controlled by a network made up of the cerebral cortex, subcortical area, and brainstem structure. The disruption of the swallowing network after stroke leads to dysphagia. The affected swallowing muscles after stroke mainly include the laryngeal muscles (suprahyoid muscle and thyrohyoid muscle) and infrahyoid muscle. These muscles experience kinematic effects and muscle strength weakens, resulting in reduced movement in the swallowing process. Acupuncture can change the excitability of cerebral cortical nerve cells, promote the recovery of neurological function, and enhance neuromuscular excitability, ultimately improving the control of swallowing-related nerves and muscles and promoting swallowing functional recovery. In this meta-analysis, we systematically evaluate the clinical efficacy of acupuncture in the treatment of post-stroke dysphagia.

Methods: Randomized controlled trials of tongue acupuncture therapy for post-stroke dysphagia were searched and selected from seven electronic databases (PubMed, CBM, Cochrane, Embase, CNKI, VPCS, and Wan fang). The Cochrane Collaboration tool was used to conduct methodological quality assessment. Rev. Man 5.4 software was utilized to perform data analysis.

Results: A total of 15 studies with 1,094 patients were included. Meta-analysis Showed that WST score WST score (MD=−0.56, 95% CI (−1.23, 0.12), Z=1.62, p<0.00001), SSA score (MD=−1.65, 95% CI (−2.02, −1.28), Z=8.77, p<0.00001). These results suggested that the treatment group (tongue acupuncture or tongue acupuncture combined with other therapies) was superior to the control group in reducing WST scores and SSA scores. The clinical efficacy of the tongue acupuncture group was better compared with the control group (MD=3.83, 95% CI (2.61, 5.62), Z=6.88, p<0.00001).

Conclusion: The meta-analysis showed that the total effective rate of patients with dysphagia after stroke in the treatment group (acupuncture, tongue acupuncture, and acupuncture combined with other therapy) was higher than that in the control group. These results indicated that acupuncture, tongue acupuncture, and acupuncture combined with other therapy can improve post-stroke dysphagia.

KEYWORDS

tongue acupuncture, acupuncture therapy, apoplexy, dysphagia after stroke, systematic review, meta analysis

1. Introduction

Stroke is an acute cerebrovascular disease defined as ischemia or hemorrhage, of which ischemic stroke accounts for 76% (Virani et al., 2021), and leads to a variety of neurological defects. Statistics show that there are 2.4 million new stroke patients in China every year, about 1.1 million deaths, and 11 million stroke patients, most of which are ischemic stroke, and these statistics show an upward and younger trend year by year. China has become the country with the heaviest burden of stroke in the world (Zhou et al., 2019). Data show that 29–78% of stroke patients have dysphagia (Qiao et al., 2022), and the mean incidence of the disease is 50% (Du et al., 2021). 91% of patients with post-stroke dysphagia are mild (Umay et al., 2013; Cohen et al., 2016). Although the survival rate of stroke patients has been significantly improved because of the improvement of medical skills such as first aid and thrombolysis, most survivors of stroke are affected by sequelae such as dysphagia and speech, motor, and memory impairments (Barthels and Das, 2020). Stroke is the most common neurological cause of dysphagia (Cui et al., 2020). Dysphagia is a process in which food cannot be transported safely and efficiently to the stomach because of the damaged structure and function of organs, such as the jaw, the Soft Palate, the lips, the tongue, the throat, the esophagus, etc. Swallowing muscles mainly include the laryngeal muscles (suprahyoid muscle and thyrohyoid muscle) and the subglottis. These muscles experience kinematic effects and muscle strength weakens, resulting in reduced movement in the swallowing process (Jung et al., 2020). Swallowing is one of the most complex somatic reflexes. It is controlled by the cerebral cortex, cortical medulla oblongata pathway, brainstem, the swallowing center, and pairs 3rd, 4th, 5th, 6th, and 7th of the cerebral nerves and C1, C2, and C3 of the spinal nerves (Jean, 2001; Michou and Hamdy, 2009). Stroke disrupts the swallowing network and can lead to dysphagia. According to the location of food passing through, swallowing can be divided into four stages: pre-oral stage, oral stage, pharyngeal stage, and esophageal stage (Chinese Expert Consensus Group for Rehabilitation Evaluation and Treatment of Dysphagia, 2017). The majority of post-stroke dysphagia occurs in the delivery of food and fluid from the oral cavity to the stomach, and their dysfunction occurs primarily in the oral and pharyngeal phases. It often manifests as saliva or food coming out of the mouth, holding food in the mouth for a long time without swallowing, food or water coming out of the nose (nasal reflux), food sticking to the mouth or throat, and bucking when eating or drinking. Moreover, dysphagia can lead to bucking, aspiration pneumonia, malnutrition, etc. Severe cases endanger life due to asphyxia. Thus, post-stroke dysphagia seriously affects patients' quality of life and increases family and social burdens, and it is necessary to find an effective strategy for promoting the functional recovery of patients with post-stroke dysphagia.

The European Stroke Organization and the European Society for Dysphagia have jointly developed the 2021 European guidelines for the diagnosis and treatment of dysphagia after Stroke (Dziewas et al., 2021). The guidelines recommended that the treatment for post-stroke dysphagia include dietary interventions, nutritional interventions, behavioral interventions (swallowing training), oral health, medication (Capsaicin receptor 1 agonist and dopaminergic drugs), and peripheral or central nervous regulation (repetitive trans cranial magnetic stimulation, trans cranial electrical stimulation, trans cranial direct current stimulation, and pharyngeal electrical stimulation) (Ye et al., 2022). However, so far there is no specific and effective therapeutic schedule for the treatment of post-stroke dysphagia. In China and some East Asian countries, acupuncture has been widely used in the treatment of stroke and achieved a good curative effect. Tongue acupuncture is a special micro-acupuncture therapy. Clinical practice has proved that tongue acupuncture is an effective treatment for dysphagia after a stroke. Tongue acupuncture is a kind of swift pricking blood therapy; the acupuncture therapy has the benefits of being fast, with little pain and no side effects. It is easy to administer by acupuncturists and well-accepted by patients.

In traditional Chinese medicine, post-stroke dysphagia can be classified into the "she jian" (which means sluggish tongue impeding speech) and "yin fei (which means the tongue is paralyzed and cannot work well). Their main clinical manifestations are slow rotation of tongue, uncontrolled eating, and loss of speech. Acupuncture is an effective and internationally recognized treatment of stroke that can significantly reduce the disability rate. Acupuncture can stimulate nerve terminal receptors, help nerve sensory input, promote the recovery of the damaged cerebral cortex and subcortical nerve, improve the function of the glossopharyngeal nerves and the reflex arc, and enhance the swallowing reflex (Guan et al., 2016; Zhang, 2017).

Tongue acupuncture is a special micro-acupuncture therapy created by famous acupuncturist Guan Zhengzhai, based on the theory from Huang Di Nei Jing of the relationship between tongue and Zangfu-meridians theoretic and modern biological holography, combined with decades of clinical experience, and has become an important part of acupuncture together with ear and head acupuncture methods (Guan et al., 2021).

According to the theory of Chinese medicine, the heart may be reflected on the tongue, which is connected directly or indirectly with the Zangfu-meridians theoretic by the circulation of the meridians and the infusion of qi and blood, closely connected with the heart, spleen, and kidneys. The heart is said to govern blood and vessels as well as the spirit. The tongue is governed by the heart-mind and brain marrow. Stimulation of the tongue may promote brain function repair and improve post-stroke dysfunction through "blood-vessel-heart-spirit." Acupuncture points on the tongue stimulate the connected meridians or Zangfu-meridians theoretic in order to regulate qi and blood flow, opening and closing the orifices, and at the same time nourishing the blood channels of the tongue, smoothing the tongue meridians, and promoting tongue and pharyngeal recovery. Clinical practice shows that tongue acupuncture therapy is less painful for the patient, is easy to administer, and is more effective when combined with body acupuncture. Tongue acupuncture in the treatment of dysphagia can improve swallowing function by changing the excitability of cortical nerve cells, promoting the recovery of neurological function, enhancing neuron muscular excitability, activating related pathways or the combination of both, and improving the control of swallowing-related nerves and muscles. Thus, tongue acupuncture is an effective, safe, and reliable traditional Chinese medicine therapy with many years of clinical experience and is a potential method for the treatment of dysphagia.

This article aimed to evaluate the effectiveness of tongue acupuncture in the treatment of post-stroke dysphagia by Meta-analysis, and we hope to provide a reliable therapy for the treatment of post-stroke dysphagia and to promote its clinical application.

2. Methods

2.1. Search strategy

We aggregated all the data about tongue acupuncture treatment dysphagia after stroke from the Cochrane Library, PubMed, Embase, China Biomedical Literature Service (Sino Med), Chinese journal full-text database (CNKI), wan fang databases, Chinese Science and Technology Journal Database (VPCS), and China Biomedical Literature Database (CBM). The data aggregation time is from the establishment of the database to the present. Chinese search terms included "tongue acupuncture," "tongue triple acupuncture," "acupuncture," "stroke," "pseudo bulbar palsy," "cerebral stroke," "swallowing disorder," "systematic evaluation," "randomized controlled," "clinical study," "clinical observation," and "Meta-analysis." The English search terms included "acupuncture," "tongue acupuncture," "stroke," "pseudo bulbar paralysis," "appetite disorder," "dysphagia," "systematic review," "RCT," "clinical study," and "meta-analysis."

2.2. Eligibility criteria

2.2.1. Inclusion criteria

The inclusion criteria were As follows:

1. Study subjects met diagnostic criteria for post-stroke dysphagia.
2. The intervention method involves tongue acupuncture.
3. Published randomized controlled trials (RCT).
4. The main efficiency measurements are the sub-water test and clinical efficacy; the secondary efficiency measurement is the SSA score and VFSS score.
5. The study protocol is reasonably designed, with clear proposals for acupuncture operations, treatment procedures, etc.

2.2.2. Exclusion criteria

The exclusion criteria were As follows:

1. Repeated studies in the literature, with one article retained.
2. Clinical case reports, review articles, animal studies, conference papers, papers that do not involve control groups, and multiple studies.
3. The research design is unreasonable (such as intervention measures, random methods, etc.)
4. Studies with unclear diagnostic criteria and criteria for determining efficacy.

2.3. Literature screening

We imported the obtained literature data into Note Express software, and then the duplicate literature were removed through the automatic review and manual review function. Two reviewers (LL and KP) independently reviewed the titles and abstracts of the studies according to the eligibility criteria. If potential studies met the criteria, further full-text evaluation was required. Studies that remained controversial would be arbitrated by a third researcher (XF). We used Note Express software (Version 3.7) to manage the retrieved records.

2.4. Data extraction

Two reviewers (LL and KP) extracted the following data independently of each other: first author, year of publication, simple intervention measures, tongue acupoints, treatment time, and results criteria; the extracted data were then cross-checked.

2.5. Quality evaluation

We carefully read the literature, strictly followed the inclusion and exclusion criteria, extracted the data, and referred those elements that generated disagreement and uncertainty during the screening process to a third evaluator for the final decision. The Cochrane Risk of Bias tool was used to achieve a methodological quality assessment of the literature (Higgins Julian and Sally, 2008). There were six main components: methods of random allocation, concealment of allocation scheme, blind methods, completeness of outcome data, selective reporting, other sources of bias, and the achievement of risk judgments after subjecting their content to certainty.

2.6. Criteria for clinical efficacy

The evaluation standard of clinical curative effect was drawn up according to the improvement of clinical symptoms of patients and the results of the Kubota water drinking test:

1. Cured: The swallowing function returned to normal, the clinical symptoms disappeared, and the Kubota water drinking test reached grade 1.
2. Significantly effective: The swallowing function basically returned to normal, the symptoms basically disappeared, and the Kubota water drinking test reached level 2.

3. Effective: The swallowing function was improved, and the Kubota water drinking test improved from grade 4 or 5 to grade 3 after treatment.
4. Ineffective: After treatment, the patient's swallowing dysfunction did not improve, and the Kubota water drinking test did not improve, or even worsened.

2.7. Statistical analysis

Statistical analysis was performed by Rev. Man 5.4 software. Using C^2 and I^2 tests to assess data heterogeneity, the random effects model was selected when statistical heterogeneity was significant ($p < 0.10$ or $I^2 \geq 50\%$). When statistical heterogeneity was not significant ($p \geq 0.10$ or $I^2 \leq 50\%$), the fixed effects model was selected. The odds ratio (OR) and 95% confidence interval (CI) for dichotomous variables were used to express the statistics of the efficacy analyses. For continuous data, weighted mean differences (MD) and 95% confidence intervals (CI) were used to express efficacy analysis statistics. The potential publication bias was analyzed by using an "inverted funnel" diagram, and bias in included trials was discussed.

3. Results

3.1. Basic characteristics of search results and included literature

Through the database, 55 articles were searched. After importing them to Note Express and removing duplicates, 31 articles remained. By reading the title and abstract, and strictly applying the inclusion and exclusion criteria, 20 papers remained. After detailed reading of the full texts of each article, 15 RCTs were finally selected (Jean, 2001; Li et al., 2005; Higgins Julian and Sally, 2008; Shuai and Jianqiao, 2008; Liu et al., 2009; Michou and Hamdy, 2009; Wei, 2012; Li et al., 2013; Guan et al., 2016; Chinese Expert Consensus Group for Rehabilitation Evaluation and Treatment of Dysphagia, 2017; Zhang, 2017; Jung et al., 2020; Dziewas et al., 2021; Guan et al., 2021; Ye et al., 2022), for a total of 1,094 patients. Figure 1 shows a flow diagram of the study. The basic characteristics of the included research literature are shown in Table 1.

3.2. Risk of bias

There are relatively few clinical reports on the treatment of dysphagia after apoplexy with tongue acupuncture. The included articles have complete data without selective reporting or other bias. However, only four (Gao et al., 2014; Wang and Shen, 2019; Xiao et al., 2020; Liu and Wan, 2021) describe random methods in detail, and none of them mention allocation hiding. No follow-up data were reported for all outcome data, and no reason for loss of follow-up was mentioned. This is shown in Figures 2, 3.

4. Results of the meta-analysis

4.1. Clinical efficacy

A total of 15 cases were included in the literature, and 13 studies (Li et al., 2005, 2013; Shuai and Jianqiao, 2008; Liu et al., 2009; Wei, 2012; Gao et al., 2014; Shen et al., 2015; Shao, 2019; Wang and Shen, 2019; Xiao et al., 2020; Cui et al., 2021; Liu and Wan, 2021) evaluated

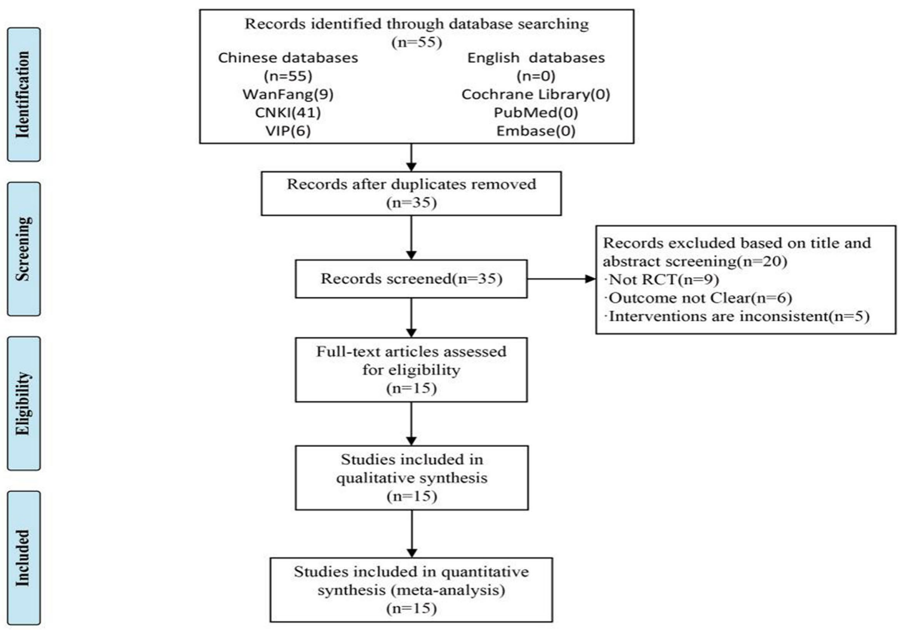

FIGURE 1
Flow chart of study selection process.

TABLE 1 Basic features of the included literature.

Study	Number	Intervention measures		Age (y)		Gender (M/F)		Days	Results
	T/C	T	C	T/C		T/C			Criteria
Li et al. (2005)	32/30	Tongue acupuncture	body acupuncture	60.5 ± 5.3	61.8 ± 6.2	20/12	18/12	24 days	③⑥⑦
Shuai and Jianqiao (2008)	39/39	Tongue acupuncture + body acupuncture	body acupuncture	68.81 ± 3.57	68.89 ± 4.11	23/16	21/18	34 days	①⑥
Liu et al. (2009)	100/100	Nape acupuncture +head acupuncture+ Tongue acupuncture+Swallowing training	Swallowing training	NA	NA	NA	NA	42 days	①⑥
Wei (2012)	31/30	Glossopharyngeal acupuncture	common acupuncture	66.8	67.2	18/13	16/14	28 days	①⑥
Li et al. (2013)	30/30	control group based +Tongue acupuncture+Electrical stimulation	Western medicine + Rehabilitation training	58.32	59.68	18/12	18/12	45 days	①⑥
Wei (2012)	40/40	Nape acupuncture +Tongue acupuncture	Nape acupuncture	63.2	61.9	26/14	25/15	28 days	①⑥
Gao et al. (2014)	52/49	Tongue acupuncture +Dysphagia therapeutic apparatus	Dysphagia therapeutic apparatus	60.25 ± 8.36	61.37 ± 7.36	31/21	27/22	29 days	①⑥⑦
Shen et al. (2015)	60/60	Tongue acupuncture	Feng chi、nei guan	NA	NA	NA	NA	28 days	④⑥
Yang and Chen (2017)	24/24	Tongue acupuncture+Catheter balloon dilatation	Catheter balloon dilatation	60 ± 8	60 ± 5	14/10	13/11	10 days	①
Liu et al. (2018)	30/30	Tongue acupuncture	Nape acupuncture	59.2 ± 6.92	59.43 ± 6.7	22/8	24/6	28 days	①
Wang and Shen (2019)	30/30	Swallowing training + head acupuncture+Tongue acupuncture	Swallowing training	55.86 ± 8.93	56.12 ± 9.04	21/9	17/13	42 days	①⑥
Shao (2019)	30/30	Rehabilitation training+head acupuncture+Tongue acupuncture	Rehabilitation training	58.45 ± 2.36	21.13 ± 2.28	18/12	17/13	28 days	①⑥
Xiao et al. (2020)	36/36	Tongue acupuncture+The seven points of the skull base acupuncture	Common acupuncture	57.11 ± 9.37	56.39 ± 10.84	22/14	25/11	14 days	①⑥
Cui et al. (2021)	40/40	Swallowing training+Tongue acupuncture	Swallowing training	NA	NA	NA	NA	14 days	⑥
Liu and Wan (2021)	30/30	Common acupuncture Tongue acupuncture +Combined exercise imagination therapy	Common acupuncture	58.36 ± 4.32	52.57 ± 3.58	17/13	16/14	28 days	①⑥

①WST score, ②SPECT, ③SSA, ④VFSS, ⑤s EMG, ⑥Total efficiency, ⑦Dysphagia score, ⑧SWAL-QOL, ⑨NIHSS.

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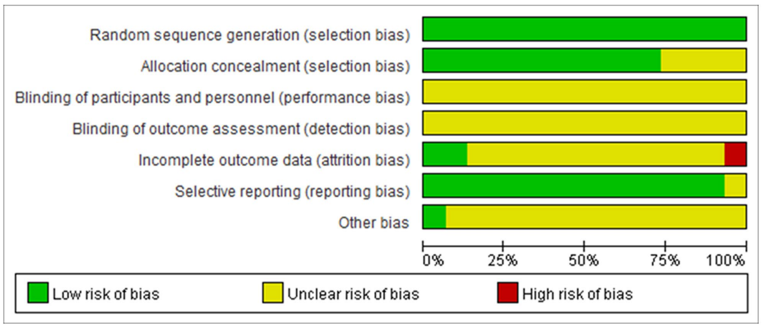

FIGURE 2
Risk of bias percentile bar graph.

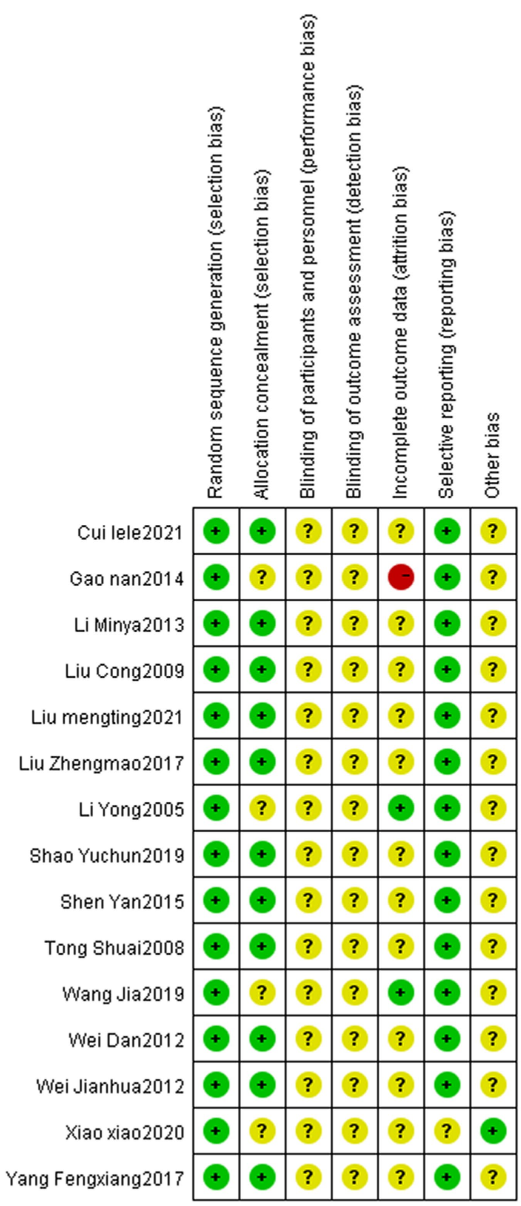

FIGURE 3
Risk of bias summary graph.

the efficiency rate with good homogeneity ($p = 0.8$, $I^2 = 0\%$) and statistically significant differences [MD = 3.83, 95% CI (2.61, 5.62), Z = 6.88, $p < 0.00001$]. It was suggested that the overall efficiency of the treatment group (tongue acupuncture or tongue acupuncture combined with other therapies) for patients with post-stroke dysphagia was higher than that of the control group. See Figure 4 for details.

4.2. WST score

In the literature included in this study, a total of 11 articles used the sub-water test as an efficacy criterion, two articles observed the grading criteria of the sub-water test, three articles did not statistically analyze the data, and six studies (Gao et al., 2014; Yang and Chen, 2017; Liu et al., 2018; Shao, 2019; Wang and Shen, 2019; Liu and Wan, 2021) used the sub-water test score and met the conditions of meta-analysis. Inter-study heterogeneity was large ($p < 0.00001$, $I^2 = 97\%$). Subgroup analysis showed that the WST scores in the treatment group (tongue acupuncture or tongue acupuncture combined with other therapies) were better than the control group [MD = −0.56, 95% CI (−1.23, 0.12), Z = 1.62, $p < 0.00001$]. See Figure 5 for details.

4.3. SSA score

In the literature included in this study, a total of three studies (Yang and Chen, 2017; Xiao et al., 2020; Liu and Wan, 2021) used the Swallowing Function Assessment Scale scores, with large inter-study heterogeneity ($p < 0.00001$, $I^2 = 96\%$), and differences between studies were statistically significant. Subgroup analysis showed that tongue acupuncture or tongue acupuncture combined with other therapies significantly improved the SSA score compared with the control group [MD = −1.65, 95% CI (−2.02, −1.28), Z = 8.77, $p < 0.00001$]. See Figure 6 for details.

4.4. Evaluation of publication bias

In this study, the funnel plot method was used to evaluate the publication bias of the main outcome indicators, sub-water test scores, and clinical efficacy.

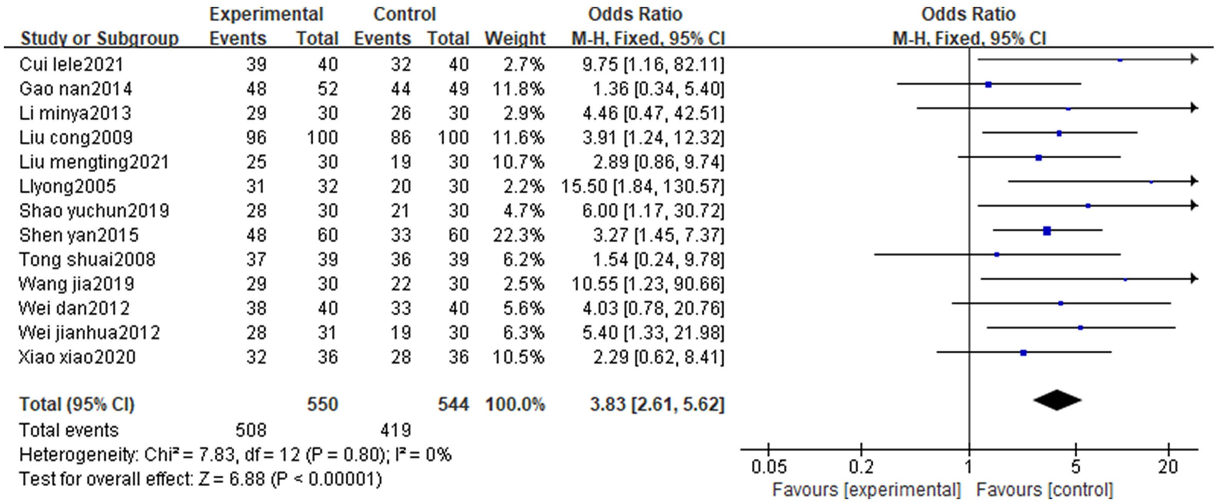

FIGURE 4
Total effective rate of tongue acupuncture for post-stroke dysphagia.

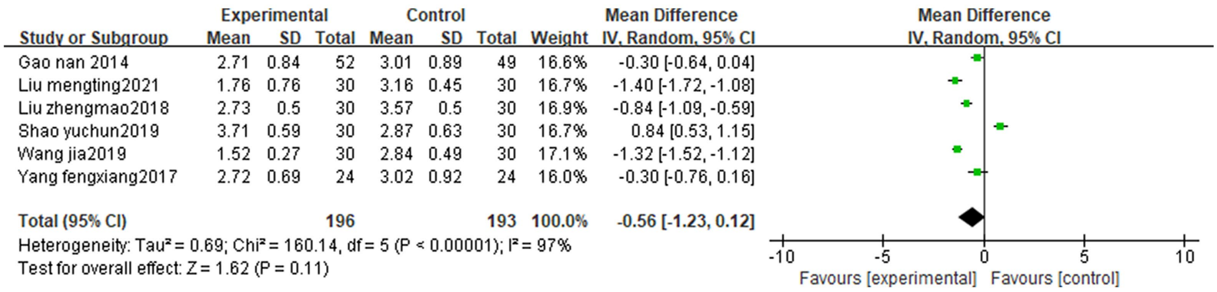

FIGURE 5
Sub-water test of tongue acupuncture for post-stroke dysphagia.

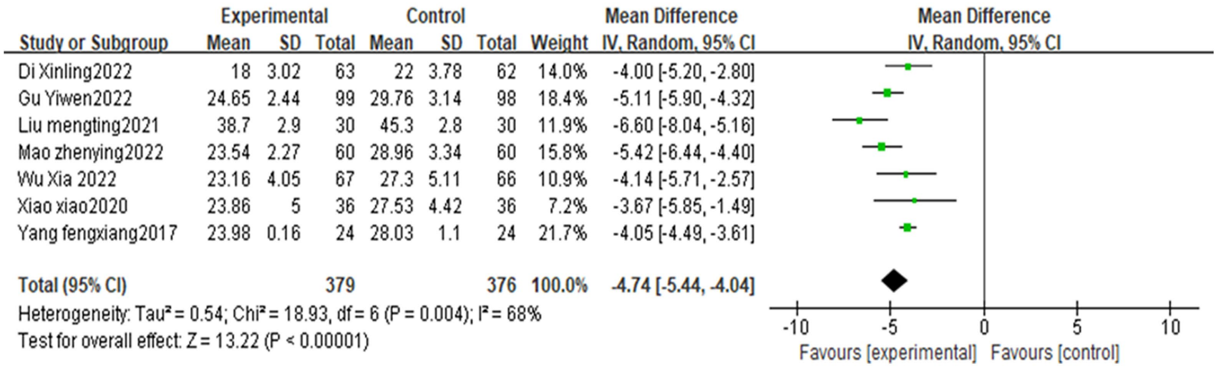

FIGURE 6
Meta-analysis of the swallowing function assessment scale after stroke treated with acupuncture.

4.4.1. Publication bias of clinical efficacy

The clinical efficacy of the 13 included studies [19, 20, 21, 22, 23, 24, 25, 26, 29, 30, 31, 32, 33] was evaluated for publication bias, and the funnel plot pattern was approximately symmetrical to the left and right, which indicated that publication bias may not exist. See Figure 7 for details.

5. Discussion

According to the statistical data from the American Heart Association, stroke has become the second leading cause of death in the world, characterized by high rates of morbidity, mortality, disability, and recurrence. Health education guidelines emphasize that

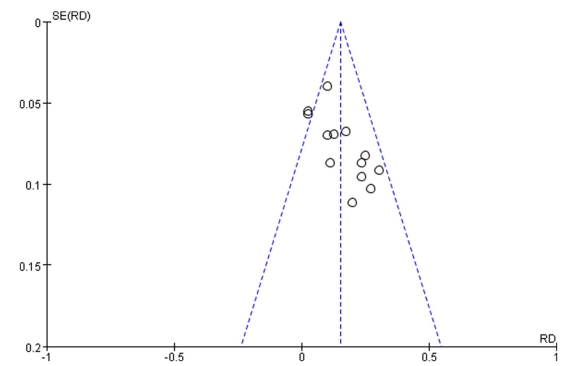

FIGURE 7
Publication bias of clinical efficacy.

rational prevention and timely treatment are indispensable components of the clinical diagnosis and treatment strategy for stroke. Dysphagia is one of the accompanying symptoms of stroke patients. Acupuncture can effectively ameliorate swallowing impairments after a stroke. Acupuncture can increase the sensorimotor stimuli of these nerve-controlling muscles, and these repetitive stimuli can help to activate the central nervous system related to swallowing and enhance neuromuscular excitability. In China, acupuncture is more commonly used in the treatment of post-stroke swallowing disorders. Acupuncture can promote the pharynx, replenishing qi and dredging collateral. The stimuli of the acupuncture points on the tongue can unblock the meridians, qi, and blood, improve the motor function of the tongue, improve the pharyngeal nerve response, promote the construction of the swallowing reflex arc, restore the regulation of the cortical brain bundle, and improve the swallowing function and the quality of life. The randomized controlled studies' literature included in this study were related to tongue acupuncture for the treatment of post-stroke dysphagia. The clinical observation shows that tongue acupuncture can improve dysphagia after stroke, which has certain clinical significance. The aim of this meta-analysis was to provide high-quality evidence-based medical evidence for the clinical treatment of stroke dysphagia.

There are some limitations to this study: (1) All included articles were reported in China, and no relevant clinical reports were found in foreign language databases, which may affect the promotion and application of tongue acupuncture in foreign countries; (2) The quality of included articles was relatively low, and no relevant clinical reports were found. Concealment of configuration and partial mention of blinding methods may affect the credibility of the results; (3) No study reported follow-up data, and none mentioned the reasons for loss of follow-up, so it is difficult to predict long-term efficacy; and (4) Clinical studies of post-stroke dysphagia were mostly observed using subjective indicators, and while SSA is an internationally recognized tool for the assessment of dysphagia, WST is the most classical and concise screening method for dysphagia with the advantages of easy accessibility and patient tolerance. VFSS and FEES are the gold standards for the diagnosis of dysphagia. Electromyography can record the muscle activity of superior and inferior hyoid muscles (Zhang et al., 2022). According to the literature (Yang, 2019; Di et al., 2022; Gu et al., 2022; Wu et al., 2022), VFSS and EMG were used as observation indexes to evaluate the curative effect. However, the stability of the results is not satisfactory, and this may be related to the combination of acupuncture of the tongue with other therapies and the intensity of the acupuncture treatment. More objective indicators should be used in the future, and further studies are still needed for further analysis and validation.

This study still has some limitations. According to the Cochrane Risk of Bias tool, which uses randomization, allocation concealment, blind assessment, none of them mentioned assigning hidden. Due to the inclusion of relatively small sample sizes with a maximum of 100 cases and a minimum sample size of 24 cases, and the deficiency of an estimate of sample size, with experimental protocols not rigorously designed and baseline treatments not explicitly mentioned, this may have led to some heterogeneity.

6. Conclusion

The meta-analysis indicated that tongue acupuncture or tongue acupuncture combined with other therapies is clinically effective in the treatment of post-stroke dysphagia. However, there were some shortcomings in the literature included in this study. Because the evaluation of the methodological quality and quality of evidence is a subjective process and different researchers make independent judgments on each factor, the results of the studies may vary somewhat. In addition, acupuncture is difficult for the blind method in its implementation, and most experimental protocols are single-blind. In the future, randomized clinical studies with high quality, multi-center, large samples, and regular follow-up should be further carried out to improve the research quality. Strict design of the experimental scheme and adopting scientific research methods are also crucial to provide more meaningful evidence for the clinic.

Author contributions

LL, PZ, and ZW revised the manuscript. LL and FX identified studies and conducted data collection, extraction, and analyzed all the data. PK performed validation of data. LL completed the first draft. PZ provided guidelines for this meta-analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effectiveness of non-pharmacological traditional Chinese medicine combined with conventional therapy in treating fibromyalgia: a systematic review and meta-analysis

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Objective: Fibromyalgia is a chronic musculoskeletal disorder characterized by generalized pain, which is also known as "muscular rheumatism" in Chinese medicine. We undertook this systematic review to evaluate the effectiveness of non-pharmacological traditional Chinese medicine (TCM) combined with conventional therapy on pain, health status, depression, and the quality of life of fibromyalgia patients.

Methods: Studies were retrieved from five electronic databases (PubMed, the Cumulative Index to Nursing and Allied Health, Cochrane Library, Embase, and Web of Science) with publication date up to August 2022. We included randomized controlled trials examining the effects of a combination of non-pharmacological TCM and conventional therapy on pain intensity, health status, depression, and quality of life.

Results: Four randomized controlled trials with 384 fibromyalgia patients met the inclusion criteria. Results of the meta-analysis showed that non-pharmacological TCM combined with conventional therapy exerted significant positive effects on alleviating pain at the post-intervention time point than conventional therapy only (visual analog scale $WMD_1 = -1.410$, $P < 0.01$; pressure pain threshold $WMD_2 = 0.830$, $P < 0.001$, respectively). Significant differences in pain assessment were also observed between the two groups after a long-term follow-up (12 months) ($WMD_1 = -1.040$ and $WMD_2 = 0.380$, all $P < 0.05$). The combination therapy group also showed a greater reduction in fibromyalgia impact questionnaire than the control group after a long-term follow-up ($WMD = -6.690$, $P < 0.05$). Depression and pain-related quality of life showed no difference between groups (all $P > 0.05$).

Conclusion: Non-pharmacological TCM combined with conventional therapy may be more effective in alleviating pain and improving health status than conventional therapy only. However, it remains some concerns over the safety and clinic application.

Systematic review registration: Identifier: CRD42022352991.

KEYWORDS

fibromyalgia, traditional Chinese medicine, pain, depression, quality of life, systematic review

1. Introduction

Fibromyalgia is a chronic musculoskeletal disorder characterized by diffuse pain, fatigue, and sleep disturbances (Clauw, 2014; Arnold et al., 2019). It has been the second most common rheumatologic disorder after osteoarthritis, affecting at least 2 to 4% of the population worldwide (Häuser et al., 2015). The core symptom of fibromyalgia is variable and multifocal pain, which occurs at different intensities and multiple sites during the disease. Individuals with fibromyalgia are more vulnerable to hyperalgesia or allodynia (Chinn et al., 2016), thus leading to cognitive impairment, emotional disorders (depression or anxiety), and somatic symptoms (headaches) (Bair and Krebs, 2020).

Conventional therapy, which is a multidisciplinary and non-invasive treatment, is the preferred choice for fibromyalgia patients according to the guidelines in different countries (Fitzcharles et al., 2013; Macfarlane et al., 2017; Ariani et al., 2021). Conventional therapy includes exercise, education, cognitive behavioral therapy (CBT) and drug therapy. As European League Against Rheumatism (EULAR) revised recommendations suggested (Macfarlane et al., 2017), patient education can be used as a basic treatment, and exercise is a "strong for" recommendation for improving pain and physical function. Psychological therapies, especially CBT, may help to ease pain-related negative emotions, such as depression and anxiety. Besides, as one of the recommended treatments, pharmacotherapy may also be a beneficial supplement for pain and depression relief, which includes gabapentinoids, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRI). These conventional therapies mentioned above recommended by the EULAR revised recommendations are widely recognized and used in clinical practice for fibromyalgia.

Non-pharmacological TCM (traditional Chinese medicine, such as Qigong and acupuncture) is also considered as an effective alternative therapy in managing fibromyalgia recommended by the latest two practice guidelines (Ariani et al., 2021; Qian, 2021). It has been well-accepted among patients with fibromyalgia due to high safety, simple operation, fewer adverse reactions, and no addiction (Deare et al., 2013; Sarzi-Puttini et al., 2020). TCM has obvious superiority in the treatment of chronic pain and concomitant mental disorders as it is based on the concept of wholism and harmony of body and mind (Bushnell et al., 2013; Patel et al., 2020). From the TCM point of view, fibromyalgia is generally classified as "muscular rheumatism". The pathogenesis includes the internal factor (deficiency of vital Qi) and the external factor (invasion of pathogenic Qi). It leads to the stagnation of blood vessels and loss of muscle nourishment (Yun, 2022a). The negative mood state is a main clinical manifestation of fibromyalgia, and the liver dominates emotions. In order to relieve patients' psychiatric and somatic symptoms, the treatment for fibromyalgia should focus on how to dredge the liver meridian and manage emotions (Yang, 2022; Yun, 2022b).

Although non-pharmacological TCM (such as Qigong and acupuncture) proved to be effective (Sarzi-Puttini et al., 2020), it remains unclear whether a combination of non-pharmacological TCM and conventional therapy is more effective than conventional therapy only in treating fibromyalgia in clinical settings. This systematic review aims to figure out the analgesic effect of integrated TCM and conventional therapy on the health status, depression, and pain-related quality of life of patients with fibromyalgia.

2. Methods

The protocol of this systematic review was registered in PROSPERO (No. CRD42022352991) and the work adheres to PRISMA guidelines (Moher et al., 2009).

2.1. Search strategy

Systematic searches were conducted in the databases PubMed, the Cumulative Index to Nursing and Allied Health, Cochrane Library, Embase, and Web of Science. We used search terms such as "traditional Chinese medicine", "TCM", and "fibromyalgia" to find relevant studies published until August 2022, and the full search strategy was listed in the Supplementary Table 1.

2.2. Eligibility criteria

Studies published in English were eligible if they met the following inclusion criteria: (1) Participants: patients over 17 years of age with a diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) criteria or the ACTTION-American Pain Society Pain Taxonomy (AAPT) criteria. (2) Interventions: non-pharmacological TCM combined with conventional therapy. (3) Comparisons: conventional therapy in treating fibromyalgia (such as exercise, psychological therapies, patient education, pharmacotherapy). (4) Outcome measures: Primary outcome measures: ① Pain intensity: visual analog scale (VAS), and pressure pain threshold (PPT) (Fischer, 1987). Secondary outcome measures: ① Health status: total Fibromyalgia Impact Questionnaire (FIQ) score (Williams and Arnold, 2011). ② Depression: Hamilton test score (HAM) and Beck Depression Inventory (BDI) (Beck et al., 1961; Ramos-Brieva and Cordero-Villafafila, 1988). ③ Pain-related quality of life: the bodily pain score of the short form-36 (SF-36). ④ Adverse events: specific adverse events reported during the treatment and follow-up (Bair and Krebs, 2020). ⑤ Study design: Randomized Controlled Trial (RCT).

Studies were excluded if they were: (1) Self-reported diagnosis without clinical confirmation. (2) Participants in the combination therapy group were treated concomitantly with herbal medicine. (3) Participants in the control group received TCM treatment.

2.3. Data extraction

Two reviewers (ZC and LC) independently screened the enrolled articles through title and abstract screening and full-text reading. Extracted data included: source, setting and language, study type, demographics, symptom duration and severity of fibromyalgia, interventions, outcome measures, adverse events, time points, and overall dropout rate. Disagreements were resolved through discussion with a third reviewer (QD).

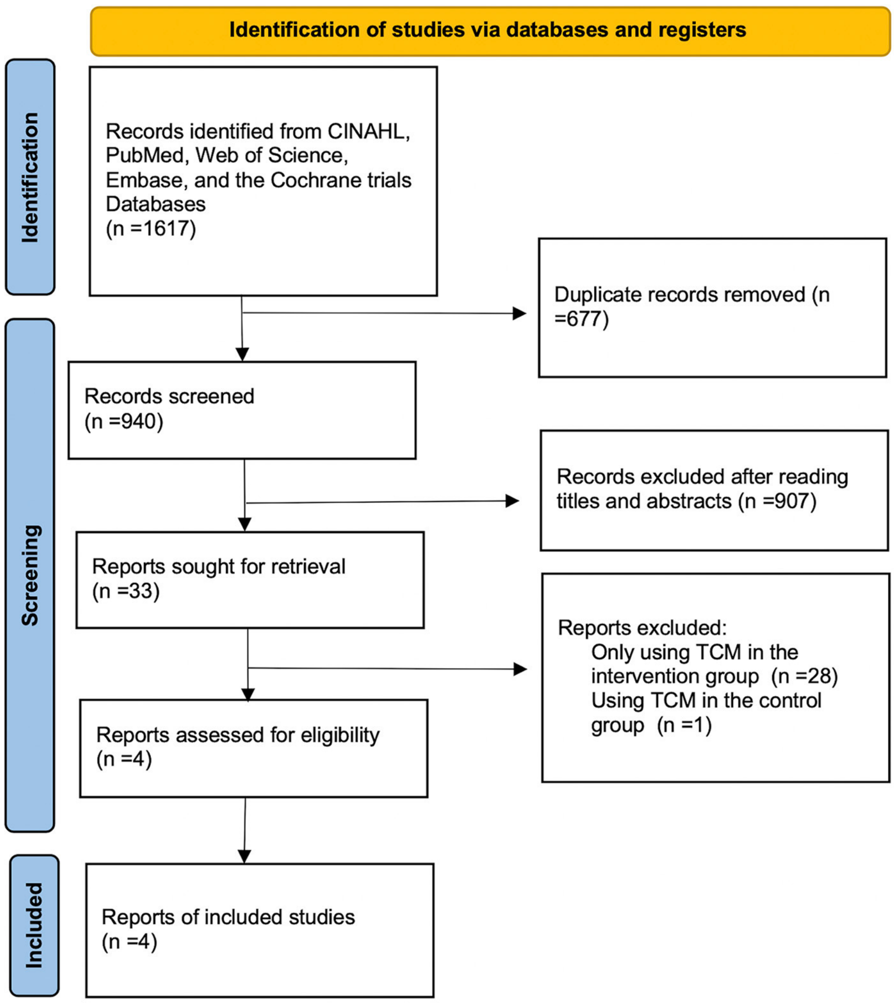

FIGURE 1
Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

2.4. Risk of bias assessment

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias Tool 2.0 (Rob 2.0). Grading of Recommendation Assessment, Development, and Evaluation (GRADE) was used to assess the quality of the evidence. JL, YS, and HY performed the quality assessment.

2.5. Statistical analysis

Data analysis was performed using Review Manager (RevMan, Version 5.4. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020). A fixed-effects model was used for the quantitative analysis if $I^2 \leq 50\%$, which represented low to moderate heterogeneity, while a random-effects model was used when $I^2 > 50\%$, to reduce the impact of substantial heterogeneity. The results would be presented as weighted mean difference (WMD) or standardized mean difference (SMD) and 95% confidence interval (CI) with a significance value set as 0.05.

3. Results

3.1. Identification of studies

The flow diagram of the study selection was provided in Figure 1. Our search retrieved 1617 relevant articles from the five databases. Following the removal of duplicates, the remaining 940 articles were evaluated based on their relevance and publication type. In total, 907 articles with obvious irrelevant topics or non-RCTs were excluded. After the full-text reading, 28 studies only using TCM in the intervention group and 1 study using TCM in the control group were excluded. Four RCTs (Astin et al., 2003; Mannerkorpi and Arndorw, 2004; Targino et al., 2008; Vas et al., 2016) finally met the eligibility criteria.

3.2. Studies' characteristics

The baseline characteristics of enrolled patients, a summary of outcome measures, and adverse events in included studies were shown in Table 1. The intervention method, treatment frequency, treatment duration, and follow-up of the combination therapy group or control group were shown in Table 2.

This review included 4 articles published from 2003 to 2016, and data from 4 studies were included in the meta-analysis. All included studies were RCTs in English. In total, 197 patients were allocated to the combination therapy group and 187 patients received control intervention.

The duration of intervention for fibromyalgia patients ranged from 8 weeks to 3 months, and the frequency of treatment ranged from once to twice a week. Patients in the combination therapy group were treated with non-pharmacological TCM in addition to conventional therapy. Non-pharmacological TCM treatment included Qigong (Astin et al., 2003; Mannerkorpi and Arndorw, 2004) and acupuncture (Targino et al., 2008; Vas et al., 2016). Conventional therapy included mindfulness meditation training (Astin et al., 2003), body awareness therapy plus pharmacotherapy (Mannerkorpi and Arndorw, 2004), tricyclic antidepressants plus exercise (Targino et al., 2008), and conventional pharmacotherapy (Vas et al., 2016).

3.3. Primary outcomes

3.3.1. Pain intensity

Two trials assessed pain intensity using VAS and PPT (Targino et al., 2008; Vas et al., 2016). Targino et al. (2008) reported a significant decrease in VAS score and increase in PPT after 3-month and 12-month acupuncture treatment combined with antidepressants and exercise. The same conclusion could be drawn from another article (Vas et al., 2016). The pain intensity reduction was also greater in the acupuncture plus medication group than in the sham acupuncture group after 10-week and 12-month follow-up.

The pooled data showed that the combination therapy group exhibited a more significant decrease in VAS score than the control group after intervention (WMD −1.410; 95% CI −2.31 to −0.50, $P < 0.01$, $I^2 = 36.0\%$) (Figure 2A) and after a long-term follow-up (WMD −1.040; 95%CI −1.77 to −0.31, $P < 0.01$, $I^2 = 0.0\%$) (Figure 2B).

PPT was assessed in two studies (Targino et al., 2008; Vas et al., 2016). As shown in Figures 3A, B, patients in the combination therapy group demonstrated a substantially better improvement in PPT than those in the control group after intervention (WMD 0.830; 95% CI 0.54 to 1.11, $P < 0.001$, $I^2 = 0.0\%$) and after a long-term follow-up (WMD 0.380; 95% CI 0.16 to 0.61, $P < 0.001$, $I^2 = 0.0\%$).

3.4. Secondary outcomes

3.4.1. Health status

Health status was investigated in 3 studies by using the total FIQ score (Astin et al., 2003; Mannerkorpi and Arndorw, 2004; Vas et al., 2016). FIQ is a 10-item questionnaire to measure the health status of patients with fibromyalgia, with higher scores indicating worse function and symptoms (Burckhardt et al., 1991).

Astin et al. (2003) reported that both Qigong plus mindfulness meditation training group and the control group registered statistically significant improvements after 8-week and 24-week follow-up, but no statistically significant between-group difference for FIQ score was detected. Mannerkorpi and Arndorw (2004) also pointed out that no differences were found between groups after a 3-month follow-up. However, Vas et al. (2016) obtained a result that the FIQ score of the patients in the acupuncture plus medication group was significantly better than in the sham acupuncture group after 10-week and 12-month follow-up.

When the results were pooled, no significant differences were shown between the combination therapy group and control group after intervention (WMD −2.090; 95%CI −7.55 to 3.37, $P = 0.450$, $I^2 = 69.0\%$) (Figure 4A). However, the pooled results showed a greater reduction in total FIQ score than the control group after a long-term follow-up (WMD −6.690; 95%CI −12.18 to −1.21, $P < 0.05$, $I^2 = 42.0\%$) (Figure 4B).

After removing the study from Vas et al. (2016) based on sensitivity analysis, there was no significant statistical heterogeneity and no significant results were found after intervention (WMD 0.66; 95% CI −0.74 to 2.06, $P = 0.36$, $I^2 = 0\%$).

3.4.2. Depression

Regarding the assessment of depression, Astin et al. (2003) used BDI while Vas et al. (2016) measured HAM. Patients with higher scores of BDI and HAM may have more severe depression.

The study from Vas et al. (2016) showed that HAM scores decreased in the acupuncture plus medication group and control group after the 10-week and 6-month treatments, but the difference was not statistically and clinically significant. Astin et al. (2003) also yielded no positive results between Qigong + mindfulness meditation training group and the control group after 8-week and 24-week follow-up.

Compared to the control group, no significant improvement in the combination therapy group was observed in the level of depression after intervention (SMD −0.090; 95% CI −0.35 to 0.17, $P = 0.500$, $I^2 = 0.0\%$) (Supplementary Figure 1A). The results led to a similar conclusion after a long-term follow-up (SMD −0.150; 95%CI −0.41 to 0.11, $P = 0.260$, $I^2 = 0.0\%$) (Supplementary Figure 1B).

3.4.3. Pain-related quality of life

Two studies reported pain-related quality of life using the bodily pain score of the SF-36 (Astin et al., 2003; Targino et al., 2008).

Compared to the control group, the pooled data showed no more improvement in the bodily pain score of the SF-36 in the combination therapy group after intervention (WMD −0.050; 95%CI −7.84 to 7.74, $P = 0.990$, $I^2 = 39.0\%$) and after a long-term follow-up (WMD −0.890; 95%CI −9.84 to 8.06, $P = 0.850$, $I^2 = 0.0\%$). The results are presented in Supplementary Figures 2A, B.

3.4.4. Adverse events

Three studies mentioned adverse events (Mannerkorpi and Arndorw, 2004; Targino et al., 2008; Vas et al., 2016). Over

TABLE 1 Characteristics of included studies.

	Source	Setting; language	Study type	Sample size (% women)	Age: mean (SD)	Symptom duration and severity	Intervention	Outcome measures	Adverse events (% of intervention group)	Time points	Overall dropout rate
1	Astin et al. (2003)	United States; English	RCT	T: 128 (99.2) I: 64 (98.4) C: 64 (100)	T: 47.7 (10.6) yr.	Symptom duration: I: 4.89 (4.15) yr. C: 5.22 (7.31) yr. Severity(FIQ): I: 57.8 (10.8) C: 58.7 (13.5)	Qigong + Mindfulness meditation training	1. Pain: TePsN, Total Myalgic Score 2. Health status: FIQ 3. Quality of life: SF-36 pain score 4. Depression: BDI 5. Function: six minute walk time test 6. Medical care history 7. Coping Strategies Questionnaire	Not provided	I: Baseline 8 weeks 14 weeks 24 weeks C: Baseline 8 weeks 14 weeks 24 weeks	I: 50% C: 48.4% T: 49.2%
2	Mannerkorpi and Arndorw (2004)	Sweden; English	RCT	T: 36 (100) I: 19 (100) C: 17 (100)	T: 45 (8.3) yr.	Symptom duration: 10 (8.5) yr. Severity(FIQ): I: 6.0 (1.8) C: 6.5 (1.9)	Qigong + Body awareness therapy + Medication	1. BARS 2. Health status: FIQ 3. Function: Chair Test and Hand Grip	Increased pain in low back and hips while standing still (54.5)	I: Baseline 3 months C: Baseline 3 months	I: 37% C: 41% T: 38.9%
3	Targino et al. (2008)	Brazil; English	RCT	T: 58 (100) I: 34 (100) C: 24 (100)	I: 52.09 (10.97) yr. C: 51.17 (11.20) yr.	Symptom duration: I: 118.8 (117.3) mo. C: 93.0 (75.25) mo. Severity(VAS): I: 8.0 (4.0-10.0) C: 8.0 (4.0-10.0)	Acupuncture + Tricyclic antidepressant and Exercise	1. Pain: VAS, TePsN, PPT 2. Quality of life: SF-36	Temporary edema (5.8)	I: Baseline 3 months 6 months 12 months 24 months C: Baseline 3 months 6 months 12 months 24 months	I: 5.9% C: 4.2% T: 5.2%
4	Vas et al. (2016)	Spain; English	RCT	T: 162 (100) I: 80 (100) C: 82 (100)	I: 52.3 (9.6) yr. C: 53.2 (9.6) yr.	Symptom duration: I: 70.7 (44.5) mo. C: 69.2 (43.7) mo. Severity(VAS): I: 79.3 (11.0) C: 75.8 (13.3)	Acupuncture + pharmacotherapy	1. Pain: VAS, TePsN, PPT 2. Depression: HAM 3. Health status: FIQ 4. Quality of life: SF-12	Post-acupuncture pain (1.4) Post-acupuncture bruising (2.6) Post-acupuncture vagal symptoms (0.7)	I: Baseline 10 weeks 6 months 12 months C: Baseline 10 weeks 6 months 12 months	I: 8.8% C: 2.5% T: 5.6%

RCT, Randomized Controlled Trial; SD, standard deviation; T, total participants; I, intervention group; C, control group; FIQ, Fibromyalgia Impact Questionnaire; BDI, Beck Depression Inventory; BARS, Body Awareness Rating Scale; HAM, Hamilton test score; VAS, visual analog scale; PPT, pressure pain threshold; TePsN, number of tender points; SF-36, short form 36 questionnaire; SF-12, short form 12 questionnaire.

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TABLE 2 Interventions in the included trials.

	Source	Intervention group	Control group	Duration	Follow-up
1	Astin et al. (2003)	**Qigong:** *Dance of the Phoenix* (a Chinese master). 1h/ time, 1 time/ week. **+ Mindfulness meditation training:** 2 formal meditation practices (a body scan and sitting meditation). 1.5h/ time, 1 time/ week.	**Education/support:** Short lectures on topics from the book "Your personal guide to living well with fibromyalgia: A handbook for self-care and treatment". 2.5h/ time, 1 time/ week.	8 weeks	14 weeks 24 weeks
2	Mannerkorpi and Arndorw (2004)	**Qigong:** Relaxation, grounding and concentration. 20minutes/ time, 1 time/ week. **+ Body awareness therapy:** Breathing and postural techniques. 70minutes/ time, 1 time/ week. **+ Pharmacotherapy:** Analgesics, anti-depressive medicines or sedatives.	**Normal daily activities without any changes.** **+ Pharmacotherapy:** Analgesics, anti-depressive medicines or sedatives.	3 months	/
3	Targino et al. (2008)	**Acupuncture:** Ex-HN-3, and LR3, LI4, PC6, GB34, SP6 on both sides. 20 min/ time, 2 times/ week. **+ Standard care:** Same as the control group.	**Standard care:** 12.5-75mg tricyclic antidepressants. 1 time/ day. 30 min walk + 30 min breathe and mental relaxation exercise. 2 times/ week. Stretching exercises. 2 times/ week.	3 months	6 months 12 months 24 months
4	Vas et al. (2016)	**Individualized Acupuncture:** 20 min/ time, 1 time/ week. **+ Pharmacotherapy:** Analgesics or antidepressant medication.	**Sham acupuncture:** An acupuncture simulation on the dorsal and lumbar regions by the guide tubes without needles. 20 min/ time, 1 time/ week. **+ Pharmacotherapy:** Analgesics or antidepressant medication.	10 weeks	6 months 12 months

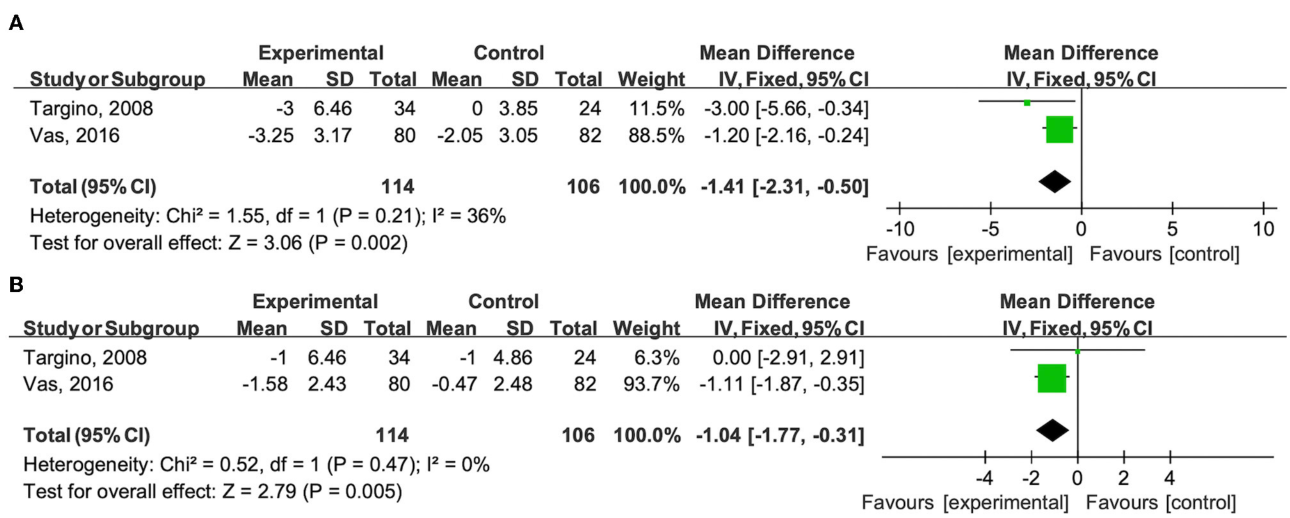

FIGURE 2
(A) Effects of the combination therapy on VAS score in fibromyalgia after the treatment. **(B)** Effects of the combination therapy on VAS score in fibromyalgia after a long-term follow-up.

half of the patients with fibromyalgia in the Qigong group reported increased pain in low back and hips while standing still (Mannerkorpi and Arndorw, 2004). With regard to the adverse events of acupuncture in 2 trials (Targino et al., 2008; Vas et al., 2016), 5.8% of patients with fibromyalgia in the combination therapy group reported temporary oedema, 1.4% reported post-acupuncture pain, 2.6% reported post-acupuncture bruising, and 0.7% reported post-acupuncture vagal symptoms.

3.5. Quality appraisal

The risk of bias assessment is provided in the Supplementary material (Supplementary Figure 3). Two studies had a high risk of bias due to no blinding of participants or personnel and a high dropout rate (Astin et al., 2003; Mannerkorpi and Arndorw, 2004). The other two studies were respectively classified as moderate and low risk of bias (Table 3)

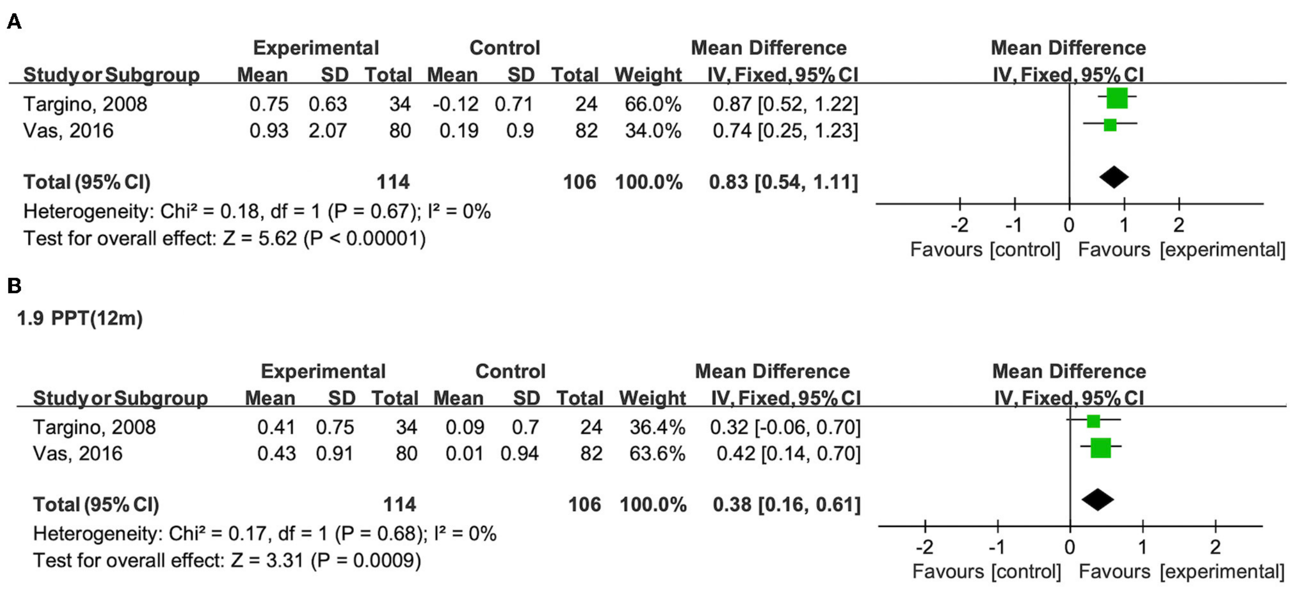

FIGURE 3
(A) Effects of the combination therapy on PPT in fibromyalgia after the treatment. **(B)** Effects of the combination therapy on PPT in fibromyalgia after a long-term follow-up.

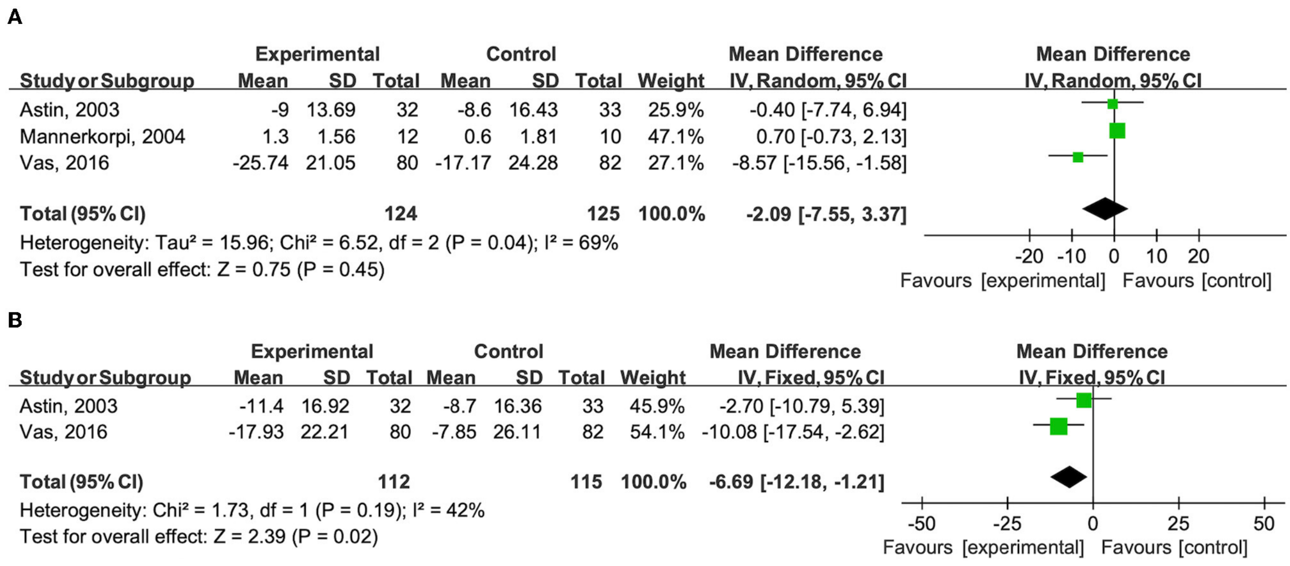

FIGURE 4
(A) Effects of the combination therapy on total FIQ score in fibromyalgia after the treatment. **(B)** Effects of the combination therapy on total FIQ score in fibromyalgia after a long-term follow-up.

(Targino et al., 2008; Vas et al., 2016). The quality of the evidence for each outcome measure was rated from moderate to very low. Outcomes including VAS and PPT showed moderate quality, while the remaining six outcome measures showed very low quality (Supplementary Table 2).

4. Discussion

This meta-analysis evaluated the effect of a combination of non-pharmacological TCM and conventional therapy in treating fibromyalgia compared to conventional therapy only. The

TABLE 3 Risk of bias assessment of the included randomized controlled trials.

	Article, Year	Randomization Process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
1	Astin et al. (2003)	Y/Y/N	Y/Y/N/NA/NA/N/Y	N/PN/PN/NA	N/N/N/NA/NA	NI/NI/NI	High
		Low	High	Low	Low	Some concerns	
2	Mannerkorpi and Arndorw (2004)	NI/NI/N	Y/Y/N/NA/NA/N/ Y	N/PN/PN/NA	N/N/N/NA/NA	NI/NI/NI	High
		Some concerns	High	Low	Low	Some concerns	
3	Targino et al. (2008)	Y/Y/N	Y/Y/N/NA/NA/Y/NA	Y/NA/NA/NA	N/N/N/NA/NA	NI/NI/NI	Some concerns
		Low	Low	Low	Low	Some concerns	
4	Vas et al. (2016)	Y/Y/N	PN/Y/N/NA/NA/Y/NA	Y/NA/NA/NA	N/N/N/NA/NA	Y/N/N	Low
		Low	Low	Low	Low	Low	

Y, Yes; N, No; PY, Probably Yes; PN, Probably No; NI, No Information; NA, Not Applicable.

present meta-analysis of data from 4 RCTs revealed that non-pharmacological TCM combined with conventional therapy was superior to the control intervention in the improvement of pain and health status.

Fibromyalgia is characterized by poor circulation of Qi and blood that could not nourish muscles in the perspective of TCM. The moody state is a prominent external manifestation of this disease, associated with physical dysfunction such as pain and sleep quality. Therefore, focusing on the movement of Qi, mainly in the liver meridian, may be the key to improving the moody state and somatic dysfunctions (Yang, 2022; Yun, 2022b). Blood stasis leads to inadequate blood flow to the liver and stagnation of liver Qi, which hinders the liver meridian from timely regulation of other organs. It may result in various somatic dysfunctions, especially pain. In TCM intervention, the key to alleviating pain is to disperse stagnated liver Qi and eliminate Qi stagnation.

Central sensitization marked by the dysfunction of neuro-circuits is one of the main pathogenesis of fibromyalgia (Siracusa et al., 2021). Central sensitization refers to the enhanced transmission of nociceptive signals in the dorsal horn of the spinal cord. Animal studies showed that acupuncture may activate bioactive chemicals (such as opioids) and inhibit the activation of spinal microglia to modulate the local inflammatory environment to inhibit central sensitization (Lai et al., 2019). In addition, the pathogenesis of fibromyalgia may also link to inflammatory factors (Littlejohn and Guymer, 2018). Moderate-intensity exercise has been proven to decrease fibromyalgia patients' blood levels of cytokines (Bote et al., 2013). Qigong is a moderate-intensity exercise incorporating Qi regulation and supporting the righteous Qi (Jiao et al., 2019), as well regulating breath control and mental adjustment. It may also ameliorate symptoms (especially pain) caused by liver Qi stagnation through physical and emotional regulation in the process of training (Yeung et al., 2018). Meanwhile, clinical practice and the animal experiment proved that stimulating Yintang (Ex-HN-3) may be related to inflammatory pathways, and it is considered effective in improving negative emotions (Armour et al., 2019). Taichong (LR3) and Yanglingquan (GB34) are also classical acupoints employed (WHO, 1991; Qiao et al., 2020).

Our results showed that a significantly more decrease in pain was found in the combination therapy group than that in the control group. However, it seems difficult to define a minimal clinical important difference (MCID) in pain improvement in patients with fibromyalgia. A consensus statement indicated that a 1.0 cm reduction in the 10 cm VAS may represent a "minimal" or "little" change in chronic pain, while a 2.0 to 2.7 cm reduction may be more clinically meaningful (Dworkin et al., 2008). The decrease of VAS scores (WMD = −1.410) in this meta-analysis suggests a "little" difference in pain between the combination therapy group and the control group. Since MCID values varied widely depending on the type of chronic pain and baseline pain intensity (Muñoz-Leyva and Chan, 2020), future studies should focus on the calculation of MCID in pain measurements (e.g., VAS and PPT) in patients with fibromyalgia.

There were no significant differences in depression and pain-related quality of life between the combination therapy group and the control group. A likely explanation is that TCM emphasizes individualized treatment, however, none of the included studies mentioned TCM diagnosis (Mist et al., 2011). Acupuncture points and the frequency or intensity of interventions may focus only on core symptoms such as pain, while the individual needs such as quality of life and improving depression are possibly ignored. Another underlying reason is that though Qigong is effective in regulating body and mind, the exercise requires continuous participation, long-term adherence, and high-level cognitive ability for the patients (Jones and Liptan, 2009; Sawynok and Lynch, 2017). No results showed an improvement in depression and quality of life due to the high dropout rate (37–50%). Moreover, patients with comorbid depression can benefit from specific treatment such as psychopharmacological treatment or cognitive behavioral therapies recommended by the guidelines, but only one article mentioned tricyclic antidepressants were used and no articles included in our systematic review employed CBT as conventional therapy.

Three studies mentioned the adverse events in the combination therapy group, including temporary edema (acupuncture), post-acupuncture pain, post-acupuncture bruising, post-acupuncture vagal symptoms, and increased pain in low back and hips in Qigong exercise (Mannerkorpi and Arndorw, 2004; Targino et al., 2008; Vas et al., 2016). Acupuncture is an invasive treatment, but bleeding and swelling after acupuncture can be relieved by a cold compress. It is necessary to inform patients of the underlying risks before administering needles and apply acupuncture more gently to minimize side effects. It is worth noting that up to 54.5% of patients who took part in Qigong plus body awareness therapy reported increased pain in low back and hips while standing still (Mannerkorpi and Arndorw, 2004). The possible explanation may be that Qigong is a moderate-intensity exercise that may increase the pain and discomfort of patients with fibromyalgia due to exercise-induced fatigue (Lima et al., 2017). Hence, we need to pay more attention to patients and require timely feedback on any discomfort during Qigong intervention. Additionally, to reduce the rate of side effects and increase patient compliance, we should appropriately increase the frequency of rest between training sessions, and guide patients on how to perform relaxation and stretching after training (Garber et al., 2011).

5. Limitations

Some limitations need to be addressed when interpreting the results. First, it may be difficult to draw any sound conclusion because only four eligible RCTs were included in the meta-analysis. Different types of interventions (Qigong, acupuncture, exercise, etc.) and acupoints (standardized or individualized acupuncture) were employed in these studies. The high methodological heterogeneity may restrict the possibility of inferences from the present results and subgroup analysis could not be conducted due to the limited number of studies. A standardized intervention protocol should be developed in the future. Second, two of the included studies showed a high risk of bias due to a high overall dropout rate. Improving the acceptance and comfort of TCM intervention may be a feasible plan to reduce the dropout rate. Future studies should focus on stretching and relaxation after exercise to reduce pain. Online guidance or supervision may be a key way to enhance the adherence of fibromyalgia patients to TCM. Third, although there was a more significant decrease in pain intensity in the combination therapy group than in the control group, it remained unclear whether the effect size reached MCID. Hence the effect of combination therapy on relieving pain should be interpreted with caution and the calculation of MCID in pain measurements warrants further research.

6. Conclusion

Non-pharmacological TCM combined with conventional therapy may be more effective than conventional therapy only in alleviating pain and improving the health status of patients with fibromyalgia. A long-term effect of non-pharmacological TCM combined with conventional therapy was also found in the treatment of pain and health status. However, our results should be applied to the clinic with caution due to the limited number of included studies, methodological heterogeneity, and potential adverse events. To increase the safety and adherence to non-pharmacological TCM, future studies should add stretching and relaxation after exercise and provide online supervision to fibromyalgia patients during the intervention.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LC and ZC conceived the idea and contributed to the writing of the manuscript and screened the enrolled articles and completed the data extraction. LC, JZ, and QW performed the literature search. JL, YS, and HY assessed the risk of bias and the quality of the evidence. LC, ZC, and JL conducted the statistical analyses and interpreted the results. QD and XZ revised the manuscript and gave guidance throughout the process of this study. All authors read and approved the summited and final version of the manuscript to be published.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1097475/full#supplementary-material

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Exploring the potential of mindfulness-based therapy in the prevention and treatment of neurodegenerative diseases based on molecular mechanism studies

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Neurodegenerative diseases (ND) have received increasing attention due to their irreversibility, but there is still no means to completely cure ND in clinical practice. Mindfulness therapy (MT), including Qigong, Tai Chi, meditation, and yoga, etc., has become an effective complementary treatment modality in solving clinical and subclinical problems due to its advantages of low side effects, less pain, and easy acceptance by patients. MT is primarily used to treat mental and emotional disorders. In recent years, evidence has shown that MT has a certain therapeutic effect on ND with a potential molecular basis. In this review, we summarize the pathogenesis and risk factors of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), relating to telomerase activity, epigenetics, stress, and the pro-inflammatory transcription factor nuclear factor kappa B (NF-κB) mediated inflammatory response, and analyze the molecular mechanism basis of MT to prevent and treat ND, to provide possible explanations for the potential of MT treatments for ND.

KEYWORDS

mindfulness therapy, neurodegenerative disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, molecular mechanism

1. Introduction

Neurodegenerative diseases (ND), primarily caused by the loss of specific neurons in the central nervous system, include AD, PD, ALS, and other disorders. The etiology is primarily linked to abnormal protein accumulation, gene mutation, increased reactive oxygen species, neuroinflammation, mitochondrial dysfunction, and apoptosis (Perry et al., 2010; Gómez-Gómez and Zapico, 2019; Hou et al., 2019; Irwin and Vitiello, 2019; Wu et al., 2019; Madore et al., 2020). ND primarily affects individuals over the age of 65, and symptoms generally worsen over time (Qiu and Fratiglioni, 2018). More than 10 million people worldwide now suffer from ND annually, and this number is rising each year along with the world's aging population (Behl et al., 2021). While ND poses a great threat to human health, it also increases the burden on the healthcare system. There is currently no means to completely cure ND in clinical practice, and most drugs can only slow the rate of ND decline and improve the quality of patient survival. The possibility of traditional TCM non-drug therapy for ND is being studied in an increasing number of research studies as TCM gains popularity (Liu et al., 2022).

MT includes qigong, Tai Chi, meditation, yoga, and other forms of physical and mental activities. Even 5,000 years ago, the ancient Chinese had mastered the self-exercise method for optimizing body and mind fitness through meditation and breath regulation. Tai Chi, meditation, yoga, and other forms of alternative medicine have progressively emerged. In a broad sense, mindfulness has been defined as a type of present-centered awareness that is unelaborate, nonjudgmental, and accepts every thought, feeling, or sensation as it arises in the attentional field (Bishop et al., 2004). The MT recommends that practitioners cultivate this awareness through meditation, actively and objectively attend to the present moment with an attitude of acceptance (not over-identification) rather than a reaction attitude, and concurrently collaborate with specific operations to achieve body and mind in order to achieve physical and mental balance. MT has been widely employed in the treatment of depression, anxiety, chronic pain, and sleep disturbances (Figure 1). Research conducted in 2013 by Gao and Xu discovered that long-term regular practice of Qigong exercise by the elderly may slow the rate of mental decline (Gao and Xu, 2013) and that MT has significant efficacy in the treatment of cognitive disorders (Rawtaer et al., 2015; Fam et al., 2020; Jin et al., 2020).

In recent years, the significance of MT in the prevention and treatment of ND has gotten a lot of attention (Dong et al., 2016; Song et al., 2017; Brasure et al., 2018; Kwok et al., 2019; Deuel and Seeberger, 2020; Guzman-Martinez et al., 2021), but its molecular mechanism has not been systematically summarized. Therefore, this paper begins with the proven molecular mechanism of MT and the risk factors for ND in order to investigate the potential molecular mechanism of MT to prevent ND.

2. Brief overview of ND

The term "ND" refers to a broad range of disabling and frequently unpredictable disease groupings that are all caused by neuronal loss and degeneration (Behl et al., 2021).

AD is the most common form of progressive ND, which is usually characterized by physical dysfunction, cognitive dysfunction, memory loss, and a progressive loss of self-care capacity. AD is the most common cause of dementia, accounting for 50–75% of all dementia patients (Yoshiyama et al., 2013). In the world, there are approximately 50 million people who have AD, and the frequency of the disease is increasing due to an aging population, according to a 2018 report from the Alzheimer's Association. There will be 152 million people living with dementia (Livingston et al., 2020). Extracellular β-amyloid (Aβ) deposition and intracellular neurofibrillary tangles are the two pathologically distinctive abnormalities in AD (Yin et al., 2017). Among them, Aβ begins to build up nearly 20 years before dementia manifests, and the ensuing hard plaques interact with acetylcholine to cause inflammatory reactions and impair synaptic transmission, which may further cause the particular protein (tau) to degrade and exacerbate AD.

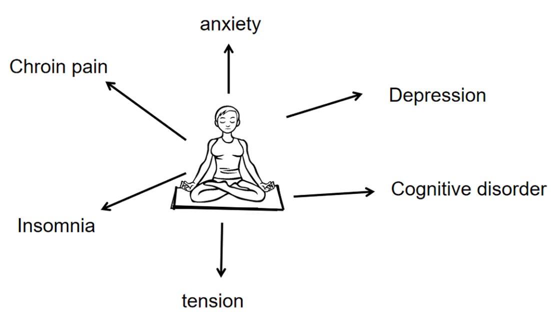

FIGURE 1
Diseases for which MT is currently used to treat.

Neuroinflammation, neuronal loss and death, gliosis, synaptic loss, and impaired main synaptic function are pathogenic features of AD (Tönnies and Trushina, 2017). Along with atrophy in areas like the hippocampus, temporal lobe, parietal lobe, frontal cortex, and thalamus (Knight et al., 2016). AD is also linked to increased oxidative stress, which is considered to be a central factor in AD (Bai et al., 2022), dysregulated gene expression, cytokines, neurotrophins, and stress markers Telomere shortening and deterioration of brain connectivity are also linked to the disease's pathophysiology (Ng et al., 2021).

After AD, PD is the most common ND and the most common severe mobility disability globally (de Lau and Breteler, 2006). It primarily affects older persons and affects 8–18 per 100,000 people annually (de Lau and Breteler, 2006). The prevalence of PD increases with age (Pringsheim et al., 2014). Dyskinesia, with progressive bradykinesia, rigidity, resting tremor, and abnormal posture and gait as its main manifestations, as well as non-motor disorders like hyposmia, constipation, sleep disturbance, depression, and cognitive impairment, are the main clinical characteristics of Parkinson's disease (Greenamyre and Hastings, 2004). PD is a form of multisystem alpha-synucleinopathies characterized by selective loss of dopaminergic neurons and deposition of Lewy bodies in the substantia nigra, resulting in extensive involvement of other central nervous system structures and peripheral tissues (Cacabelos, 2017). Aging appears to be the only significant risk factor for PD development (Rokad et al., 2017). In addition, α-synuclein accumulation, mitochondrial dysfunction, autophagy impairment, and oxidative stress are common factors in PD pathogenesis. Factors such as oxidative stress play a central role in PD (de Lau and Breteler, 2006; Cacabelos, 2017).

ALS is a specific form of ND, but the etiology still remains unclear. ALS impacts the muscles and central nervous system (van Es et al., 2017). The majority of ALS patients, are middle-aged or elderly and above the age of 40. It is a deadly and somewhat uncommon ND. Approximately 3–6 persons out of every 100,000 people have ALS (Chiò et al., 2013). Motor neurons in the spinal cord, brain stem, and motor cortex are the main targets of ALS (Heiman-Patterson et al., 2015). Memory loss, cognitive decline, and decreased speech, swallowing, and respiratory function are all caused by neuronal death (Brown and Al-Chalabi, 2017). Statistics show that Cu/Zn superoxide dismutase gene mutations account for 20% of familial ALS cases (Heiman-Patterson et al., 2015). Aggregation and buildup of the ubiquitinated protein inclusion body TDP-43 in motor neurons are the neuropathological signs of ALS (van Es et al., 2017). The pathogenesis of ALS is also tightly linked to aging, oxidative stress (Aborode et al., 2022), RNA damage repair and axonal development, mitochondrial malfunction and autophagy, and acquired living conditions. And

Oxidative stress is one major contributor to ALS pathogenesis. The result is an increased intracellular level of highly reactive free radicals, combined with defective antioxidant compensation systems that produce oxidative stress.

The aberrant buildup of cytoplasmic or nuclear proteins in the brain is the common pathogenic mechanism for various disorders, despite the fact that their etiologies and sites of lesions differ. Common risk factors include aging, genetic mutations, inflammation, and stress. Early treatment of these risk factors may lower the likelihood of developing ND and/or postpone the disease's onset.

3. Molecular mechanism of MT

3.1. MT lengthens telomeres

MT appears to be a telomere-protective agent. Qigong (Baduanjin) (Tiwari et al., 2014), mindfulness meditation, and yoga (Schutte and Malouff, 2014; Rathore and Abraham, 2018; Dasanayaka et al., 2022) can lengthen telomeres and boost telomerase activity in both white blood cells and peripheral blood mononuclear cells (BPMC). Telomeres are eukaryotic chromosome ends that have repeated DNA sequences and unique cap-like structures that support chromosomal integrity. Telomeres are not fully reproduced because DNA polymerases are unable to complete the replication of the ends of linear molecules. As a result, telomeres shorten with each replication (Shay, 2018), and when they are sufficiently shortened, cells stall until senescence. Despite the fact that short telomeres are a pathogenic cause of senescence, telomerase re-expression can prevent premature senescence caused by telomerase deficiency and the specificity of short telomeres (Bär and Blasco, 2016).

Telomerase is the fundamental nuclear protein reverse transcriptase. Telomerase increases the amount of telomeric DNA at the ends of eukaryotic chromosomes to maintain the length of the telomeres (Epel et al., 2009). MT promotes telomeric DNA synthesis and cell division, counteracts telomere depletion due to cell division, and interrupts the telomere shortening process or lengthens telomeres by increasing telomerase activity and causing telomerase re-expression (Smith et al., 2020). Telomerase re-expression lengthens telomeres, guards against fusion and degeneration of chromosome ends, and is crucial for chromosome placement, replication, and protection, as well as for the regulation of cell growth and lifespan (Anitha et al., 2019).

3.2. MT and DNA methylation

One of the most well researched epigenetic processes, DNA methylation modifies chromatin structure without changing nucleotide base sequences. Particularly in the human brain and blood (García-Campayo et al., 2018), DNA methylation is crucial for controlling the expression of genes (Martínez-González et al., 2020). Long-term MT can methylate genes including FKBP5 (Bishop et al., 2018), SCL6A4 (Stoffel et al., 2019), NR4A2 (García-Campayo et al., 2018), and CLU (Huang et al., 2016), influencing the proteins encoded by these genes, controlling the dynamic process of methylation and demethylation, and enhancing the organism's benefit from the epigenetic process.

3.3. MT and inflammation

Numerous trials have demonstrated that yoga, Tai Chi, and meditation practices can prevent the accumulation of ROS in cells by upregulating the activity of ROS-degrading enzymes through meditation with rhythmic breathing exercises and reducing oxidative stress markers such as ROS and 8-hydroxy-2-deoxyguanosine (Huang et al., 2014; Kumar et al., 2015; Gagrani et al., 2018) and maintaining brain homeostasis. Furthermore, meditation (Wetherell et al., 2017), Tai Chi and qigong (Campo et al., 2015; Klein et al., 2016; Larkey et al., 2016) can reduce stress and lower salivary cortisol levels in people with high baseline levels (Moraes et al., 2018), while having no effect on baseline levels in the normal population. A randomized clinical trial also confirmed that long-term mindfulness training can reduce the accumulation of cortisol and saliva in the hair (Puhlmann et al., 2021), resulting in increased immune responsiveness (Tang et al., 2009; Svetlov et al., 2019). In addition, short-term meditation has been shown to increase side-sympathetic nerve tension and decrease the activity of the sympathetic nervous system. While the reaction of the sympathetic nervous system can drive inflammation, the side neurosympathetic system can inhibit NF-κB and inflammatory reactions by activating acetylcholine (Haroon et al., 2012).

Several studies using gene expression analysis MT have identified downregulation of NF-κB target genes, which can be interpreted as a reversal of the molecular signature of chronic stress effects (Buric et al., 2017). Several randomized controlled trials have confirmed that the expression of the pro-inflammatory genes RIPK2 and COX2 (Kaliman et al., 2014), as well as NF-κB activity, are significantly reduced in PBMC in long-term meditators (Creswell et al., 2012; Black et al., 2015; Bower et al., 2015). In addition, Tai Chi (Irwin et al., 2014; Buric et al., 2017), and yoga (Bower et al., 2015) also reduced levels of the inflammatory markers C-reactive protein (CRP), tumor necrosis factor (TNF-α), and interleukin 6 (IL-6), and had downregulation of several genes involved in leukocyte production and inflammation (Buric et al., 2017).

4. Possible therapeutic mechanisms of MT against ND

4.1. MT delays aging and has the potential to combat ND cognitive impairment

The largest risk factor for the majority of ND is aging. Each lower motor unit cell type is prone to its own unique collection of aging-related phenotypes that may exacerbate the course of the ND disease (Guo and Yu, 2019; Hou et al., 2019; Pandya and Patani, 2020; Liu, 2022). The physiological process of aging produces a multitude of molecular and cellular abnormalities. DNA damage, mitochondrial dysfunction, telomere length loss, and oxidative stress are the four main causes of aging (Wyss-Coray, 2016; Hernandez-Segura et al., 2018), and telomere loss is thought to be the primary cause of aging. Age-related cognitive decline is also linked to shorter telomeres (Bär and Blasco, 2016), and Mendelian randomization research also found a causal link between shorter telomeres and increased risk of AD (Guo and Yu, 2019).

MT delays cellular senescence by increasing telomerase activity to extend telomeres (Campisi and d'Adda di Fagagna, 2007; Blackburn et al., 2015). Genetically or pharmacologically, the reduction of senescent cells improves Aβ peptide and tau protein-induced neuropathology and improves memory in AD model mice (Bussian et al., 2018; Zhang et al., 2019), thus achieving a counteracting effect on cognitive impairment (Hou et al., 2019). Notably, studies have confirmed increased gray matter volume and significantly reduced brain atrophy in the hippocampus and prefrontal cortex in expert meditators (aged 22–77) (Chételat et al., 2017), and Wolkowitz et al. hypothesized that BPMC telomerase activity may correlate with hippocampal enzyme activity and hippocampal volume (Wolkowitz et al., 2015; Deng et al., 2016). Then we can venture to speculate that meditation may have the effect of treating cognitive impairment and promoting memory by increasing telomerase activity and increasing prefrontal cortex gray matter volume as well as hippocampal volume (Cheng et al., 2013), thus reducing the risk of developing AD and/or delaying disease onset. However, this hypothesis is currently controversial and needs further validation.

4.2. The epigenetic potential of ND is controlled by MT

Epigenetic dysregulation can lead to cognitive impairment and neuronal death associated with ND (Hwang et al., 2017).

Long-term meditators' genome-wide alterations in DNA methylation were examined by García-Campayo et al. (2018). The 64 differently methylated areas that meditators produced compared to non-meditators belong to 43 genes, and 48.4% of these regions were determined to be directly related to common human disorders, of which 9 (14%) were in genes linked to ND (AD, PD, and ALS) (García-Campayo et al., 2018). And among these related genes, nuclear receptor family 4 group A member 2 (Nr4a2) is the most differentially methylated. This gene encodes a nuclear transcriptional regulator that has been identified as a key regulator of dopaminergic (DA) neuronal differentiation, survival, and maintenance and as being essential for neuronal development, particularly for the maintenance of the DA system (Jakaria et al., 2019).

Nr4a2 prevents inflammation-mediated DA neuron death and is crucial for hippocampus synaptic plasticity and memory formation (Català-Solsona et al., 2021). It may be possible to treat DA dysfunction-related disorders like PD by promoting the methylation of this gene through meditation. It's interesting to note that new research has discovered that altered Nr4a2 expression is likewise linked to the course of AD, and Nr4a2 agonists can speed up the degradation of Aβ by considerably reducing γ-secretase activity by upregulating an Aβ-degrading enzyme (insulin-degrading enzyme). The characteristic AD symptoms were significantly reduced in the agonist-treated mouse model of AD, and cognitive performance was significantly enhanced (Jakaria et al., 2019; Moon et al., 2019).

Additionally, the CpG sites of FKBP5 GREs in intron 7 and the promoter region speed up age-related demethylation in AD patients, increasing the expression of FKBP51 mRNA and protein with aging. Tau cannot be separated into less toxic tangles due to FKBP51's interference with tau degradation and promotion of tau oligomer formation. This increases neurotoxic tau, which advances AD (Blair et al., 2013). Long-term meditation increases FKBP5 DNA methylation and decreases FKBP51 expression, which reduces tau neurotoxicity and slows the course of AD. In contrast, decreased FKBP5 DNA methylation increases FKBP51 expression.

Epel et al. also discovered that CLU gene expression and PSEN1 gene expression were both decreased following meditation (Epel et al., 2016; Huang et al., 2016). Reduced CLU gene expression can lower the risk of AD and PD, according to genome-wide correlation studies that have identified the CLU gene as a well-established risk gene related to AD and PD (Karch and Goate, 2015; Lin et al., 2021). Although PSEN1 encodes the -secretase necessary for the synthesis of Aβ peptides, PSEN1's decreased expression leads to insufficient synthesis of the γ-secretase complex, which may be caused by a decrease in the synthesis of Aβ peptides as a result of meditation and a relative decrease in the γ-secretase needed for the hydrolysis of Aβ peptides.

By examining blood markers after meditation, Epel et al. also discovered that the level of $A\beta_{40}$ in the blood of meditators decreased (Epel et al., 2016). Since CLU induces the deposition and removal of Aβ (Maturana-Candelas et al., 2021), meditation may lower the level of $A\beta_{40}$ by reducing the expression of the CLU gene, thereby lowering the $A\beta_{42}$ /$A\beta_{40}$ ratio and lowering the risk of AD (Chouraki et al., 2015). The epigenetic modifications in subtelomeric areas may be related to telomere length, and DNA methylation may also be implicated in the stability of telomere length in long-term meditators' specific subtelomeric regions (Mendioroz et al., 2020).

Long-term meditators, compared to non-meditators, have different areas that are methylated in pathways related to cellular senescence, neurotransmission, lipid and glucose metabolism, immunology, and inflammation (Kaliman, 2019). These genes' methylation may affect ND directly or indirectly. Reduced Aβ deposition has a protective or mitigating effect on cognitive impairment caused by AD and PD. This effect is due to the methylation of ND-related genes resulting from MT, such as the Nr4a2 gene and the CLU gene, whose expression is strongly associated with the deposition and clearance of Aβ and tau.

Through the epigenetic process of DNA methylation, meditation may control the expression of ND-related genes, alleviating symptoms and slowing the course of the disease. However, long-term meditation accumulation might be necessary to regulate gene expression, which short-term meditation cannot do. This hypothesis has to be proven in trials using larger sample sizes.

4.3. MT's potential to combat ND-related neuroinflammation

Chronic oxidative stress results in the accumulation of reactive oxygen species, which damages target molecules like DNA, proteins, and lipid structures. An imbalance in the antioxidant system is one of the key mechanisms causing ND (Tönnies and Trushina, 2017). The antioxidant system may become unbalanced, the brain's equilibrium may be lost, and ND may result if the balance between the production and consumption of reactive oxygen species is upset (Radi et al., 2014; Nissanka and Moraes, 2018; Stefanatos and Sanz, 2018; Collin, 2019; Yeung et al., 2021).

Chronic stress may promote the loss of nigrostriatal cells in PD, hastening the disease's course (van der Heide et al., 2021), and stressful conditions may intensify the condition's motor symptoms, such as tremor.

Additionally, in human ALS fibroblasts and pluripotent stem cell iPSC-motoneurons, prolonged stress stimulates the production of stress granules and pathogenic TDP-43 aggregates, accelerating the course of ALS (Ratti et al., 2020).

Stress also leads to a reduction in hippocampal volume and a decrease in the number of glucocorticoid receptors (GR) in the hippocampus (Frodl and O'Keane, 2013), as well as stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, which promotes the release of glucocorticoids (GC) and catecholamines. The decrease in the number of GR and increased GC release leads to elevated GC levels and brain atrophy, such as in the hippocampus, due to prolonged high levels of GC stimulation, which puts the person in a state of extreme stress and anxiety and exacerbates the progression of AD (Boutrup et al., 2019).

In addition, high levels of GC initiate an immune response in brain microglia, making them pro-inflammatory and promoting a neurotoxic response (Milligan Armstrong et al., 2021). In an AD rat experiment, it was demonstrated that $A\beta_{25\text{-}35}$ amyloid toxicity affects the adaptive response of the HPA axis to stress (Brureau et al., 2013), resulting in chronically high levels of cortisol in patients (Vyas and Maatouk, 2013).

The HPA axis is a crucial neuroendocrine signaling system that regulates physiological homeostasis and stress reactions. It is a well-known characteristic of AD to have a very active HPA axis (Notarianni, 2013), which is indicated by excessive cortisol output. The HPA axis's overproduction of cortisol affects somatic tissues through blood flow, and elevated levels of GC, including cortisol, lead to hemodynamic, endocrine, and immune system problems as well as increased accumulation of Aβ and tau, which cause increased brain atrophy, behavioral deficits, mood disorders (Du and Pang, 2015), and/or cognitive decline (Milligan Armstrong et al., 2021), all of which accelerate the progression of AD and PD (de Pablos et al., 2014; Ennis et al., 2017).

Additionally, it has been demonstrated that chronic inflammation raises the risk of ND (Buric et al., 2017). It is well established that the nuclear factor NF-κB, a transcription factor that promotes inflammation, can be inhibited by the cortisol-GR complex, preventing the transcription of genes that promote inflammation. NF-κB can transcriptionally regulate the expression of cytokines. The transcription factor is closely linked to mammalian aging, inflammation, and stress. As a molecular indicator of chronic stress (Buric et al., 2017), the upregulation of pro-inflammatory genes is thought to cause dysregulation of GC secretion, decreased sensitivity to GR in the brain and immune cells, and a lack of suppression of NF-κB-mediated inflammation (Boutrup et al., 2019). This vicious cycle ultimately increases the risk of developing ND.

Neuroinflammation is associated with ND and is one of the important mechanisms in the development of ND (Kwon and Koh, 2020), and both central inflammation and systemic inflammation can accelerate the progression of ND (Perry et al., 2010; Shih et al., 2015). MT delays aging due to DNA damage by inhibiting NF-κB activity (Tilstra et al., 2012), which in turn delays aging-related neurodegeneration (Tilstra et al., 2012; Álvarez-López et al., 2022).

Long-term practice of meditation, yoga, Tai Chi, and qigong induces downregulation of NF-κB-related upstream and downstream targets, which may reduce stress and inflammatory responses by inhibiting the NF-κB pathway through the RIPK2 pathway (Bhasin et al., 2013), delaying the onset of ND. Animal studies have shown that acute activation of pro-inflammatory cytokine signaling in the brain in response to peripheral immune activation is associated with deficits in hippocampal-dependent memory (Dantzer et al., 2008). MT reduction in stress can reduce the hyperactivity of the HPA axis, resulting in a decrease in the level of GC accumulated in the nuclei of neurons in different brain regions, especially the hippocampus, hypothalamus, and amygdala, which are rich in GR. Brain shrinkage and memory impairment may be delayed as a result of MT's lowering of pro-inflammatory cytokines. Regular MT training can have beneficial effects on ND by improving neuroendocrine stress responses, improving HPA axis stress responses (Khalsa, 2015), and nuclear receptor-mediated transcriptional changes to reduce neuroinflammation (Figure 2).

5. Discussion

Current research finds that the mechanisms affecting the onset and development of diseases mainly include: incorrect folding and aggregation of proteins, neuropathy, cellular procedural death and aging. Circadian rhythm disorder, nutritional inadequacies, stress, inflammatory reactions, age, and gene mutations are typical risk factors for ND (Perry et al., 2010; Gómez-Gómez and Zapico, 2019; Hou et al., 2019; Irwin and Vitiello, 2019; Wu et al., 2019; Madore et al., 2020). MT can intervene in these risk variables to prevent and treat ND. By increasing telomerase activity to postpone aging, lowering anxiety and depression to regulate circadian rhythms (Yingwei et al., 2019), lowering stress and NF-κB-induced neuroinflammatory responses, and changing DNA methylation relevant to ND to regulate gene expression, MT can prevent and reduce the progression of ND. In turn, these processes engage in mutually beneficial interactions. Telomerase, for instance, possesses antioxidant, anti-apoptotic, neurotrophic, and neurogenesis-promoting properties that help restore brain cell suppleness and viability in addition to lengthening telomeres to delay aging. Additionally, oxidative stress and inflammation can shorten telomeres and speed up aging (Bär and Blasco, 2016). Antioxidants have neuroprotective effects (Hou et al., 2019), and MT can reduce the occurrence of neuroinflammation and slow down the aging process by reducing oxidative stress. Meanwhile, bioinformatic analysis predicted that epigenetic responses to MT exercises may regulate inflammatory pathways dependent on tumor necrosis factor α and NF-κB signaling. Through these mechanisms, MT can create a positive cycle that will improve the symptoms of ND and slow the ND process.

The clinical effects of MT on ND have demonstrated that MT can enhance patients' quality of life, improve symptoms like anxiety and depression, and slow the progression of the disease. However, the majority of these trials evaluated the effectiveness using a scale. According to the current study of mind-based brain area research, inflammatory factor research, and the subjective score table (Newberg et al., 2014; Lou, 2017; Kwok et al., 2019), and less frequently with biological markers. Extensive experimental research is still needed to understand the mechanism of MT activity in ND. Future research should explore if MT intervention at a younger age would lower the incidence of ND. More clinical trials are also required to determine whether traditional Chinese medicine offers unique, superior benefits for ND prevention and treatment. Mind-based physical and mental therapy is an interesting and beneficial way, in the modern society,

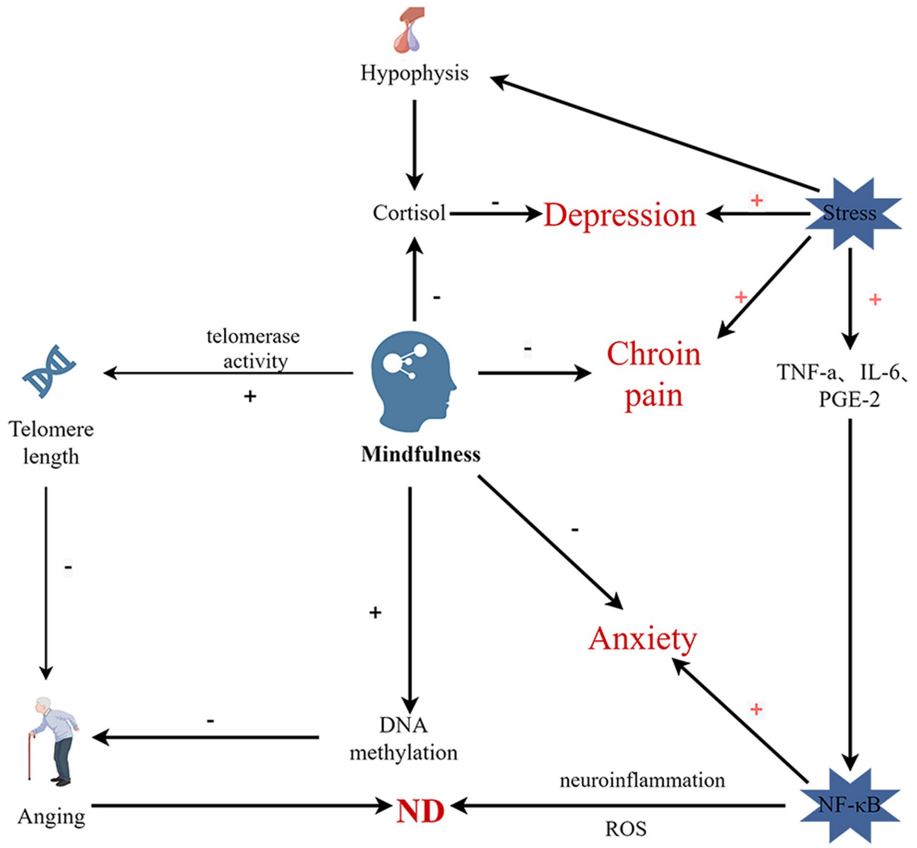

FIGURE 2
Schematic diagram of hypothesized pathway of the effects of MT on mental and physical wellbeing and aging. NF-kB-Nuclear Factor kappa B; IL-6-Interleukin-6; TNF-α-Tumor Necrosis Factor-alpha; PGE-2-prostaglandin E2; ROS-Reactive Oxygen Species. Stress activates the HPV axis, releasing cortisol, and increased cortisol and oxidative stress lead to increased stress. MT can prevent and treat ND by promoting telomerase activity, thereby lengthening telomeres and slowing aging, and by promoting DNA methylation associated with ND and reducing neuroinflammation (By Figdraw).

where public health awareness is generally enhanced, early and continuous mind intervention will play a role in disease with age to prevent and delay illness, and it is worth our study.

Author contributions

CW drafted the manuscript. YF revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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