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# Therapeutic potential of quercetin in depressive symptoms: a systematic review and meta-analysis of preclinical studies

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**Background:** Depression is a common and severe mental disorder. Quercetin, a natural flavonoid compound, has been shown in several studies through animal experiments to improve depressive symptoms, demonstrating significant antidepressant potential.

**Objective:** This study represents the first preclinical meta-analysis on quercetin and depression, aiming to systematically evaluate the antidepressant effects of quercetin in animal studies. Methods: This study conducted a systematic search of the PubMed, EMBASE, Cochrane Library, and Web of Science electronic databases, with the search period covering from the inception of the databases to January 2025. Subsequently, the SYRCLE risk of bias assessment tool was used for quality evaluation, and data analysis was performed using RevMan 5.4 software.

**Results:** This systematic review included 52 animal studies for random-effects meta-analysis. The results indicated that, compared to the control group, quercetin significantly reduced the immobility time in the forced swimming test and tail suspension test, as well as the time spent in the closed arms of the elevated plus maze. Simultaneously, it increased sucrose preference, swimming time in the forced swimming test, total distance traveled in the open field test, time spent in the central area, and the number of entries into the central area. In the elevated plus maze test, quercetin also increased the time spent in the open field test. Moreover, quercetin increased the levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and brain-derived neurotrophic factor (BDNF), while reducing the levels of malondialdehyde (MDA), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and corticosterone (CORT).

**Conclusion:** This meta-analysis indicates that quercetin significantly improves depressive symptoms. However, further high-quality studies are needed to explore the role of quercetin in antidepressant research.

#### Systematic Review Registration: http://inplasy.com/, Identifier: INPLASY202530047.

KEYWORDS

quercetin, depression, systematic review, meta-analysis, preclinical studies

## **1** Introduction

Depression is a common and highly recurrent mental disorder globally, characterized by persistent low mood, anxiety, anhedonia, and cognitive impairments (Burcusa and Iacono, 2007; Malhi and Mann, 2018). According to reports by the World Health Organization (WHO), over 300 million people worldwide suffer from depression. More than 700 000 people die due to suicide every year (World Health Organization, 2020). It is expected that by 2030, depression will become the leading cause of disability worldwide (Chen et al., 2024), placing a significant psychological and economic burden on individuals, families, and society. In recent years, treatment methods for depression have continuously evolved, including pharmacotherapy, psychotherapy, neuromodulation technologies, AI-assisted diagnosis and treatment, and lifestyle interventions (Sampogna et al., 2024). However, pharmacological intervention remains the cornerstone of depression treatment, with most currently used antidepressants exhibiting limitations such as a single mechanism of action, slow onset, and significant side effects (Pannu et al., 2021). Therefore, there is an urgent need to develop safe and effective antidepressants that target multiple pathways and mechanisms.

Quercetin (3,3',4',5,7-hydroxyflavone) is a natural flavonoid compound widely found in plants such as apples, onions, broccoli, wine, green tea, and ginkgo (Williamson and Manach, 2005; Mirza et al., 2023). Many studies have shown that quercetin exhibits various biological activities, including antioxidant (Xu et al., 2019), anti-inflammatory (Wu et al., 2024), and anticancer properties (Maleki et al., 2021), and can protect the nervous system (Cardozo et al., 2021; Fideles et al., 2023) as well as improve cognitive function (Ebrahimpour et al., 2020). In recent years, research on quercetin's antidepressant effects has been gradually increasing. Current studies indicate that quercetin enhances the expression of BDNF in the prefrontal cortex and hippocampus of mice, improving anxiety, depression, and cognitive deficits induced by psychosocial stress (Ugwu et al., 2022). Other studies suggest that quercetin regulates Acetyl-H3K9 and inhibits astrocyte ferroptosis, significantly improving depressive-like behaviors in a perimenopausal depression rat model (Wang et al., 2024c). Furthermore, Ge et al. discovered that quercetin reduces apoptosis in the hippocampus and prefrontal cortex of chronic unpredictable stress (CUS) model mice, upregulates Nrf2 protein expression, and increases the phosphorylation levels of ERK and CREB, improving depressive



#1	" depression " [MeSH] OR" depressive disorder " [MeSH]
#2	<pre>((((((((((((((((((((((((((((((((((((</pre>
#3	#1 OR #2
#4	" Quercetin " [MeSH]
#5	(((((Quercetin [Title/Abstract]) OR (Pentahydroxyflavone [Title/Abstract])) OR (Dikvertin [Title/Abstract])) OR (Quercetins [Title/Abstract])) OR (Quercetins [Title/Abstract])) OR (Quercetins [Title/Abstract])) OR (Sophoretin [Title/Abstract])
#6	#4 OR #5
#7	#3 AND #6

#### TABLE 1 Search strategy on PubMed.

behaviors in mice, similar to the effects of the antidepressant fluoxetine (Ge et al., 2024).

Despite increasing evidence confirming the effectiveness of quercetin in treating depression (Chen et al., 2022), some controversial results remain in the published studies. To clarify the clinical indications of quercetin for depression, a comprehensive and scientific evaluation of animal experimental studies is crucial. Therefore, we have summarized the existing evidence and, for the first time, conducted a meta-analysis of preclinical studies on quercetin's antidepressant effects, which may provide important clues for future clinical research.

## 2 Materials and methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA guidelines (Page et al., 2021) and the Cochrane Collaboration's principles. To avoid duplication with ongoing systematic reviews, we first searched for similar reviews on the INPLASY website and subsequently registered our study (registration number: INPLASY202530047).

#### 2.1 Search strategy

We systematically searched four electronic databases (PubMed, EMBASE, Cochrane Library, Web of Science) for data from the inception of the databases through January 2025. The search strategy utilized terms related to quercetin and depression to identify preclinical studies assessing the impact of quercetin on depression. The search algorithm employed only terms relevant to the topic of interest and filtered unique keywords to database (Reshma et al., 2024). The detailed search strategy is provided in Table 1 (using PubMed as an example).

## 2.2 Inclusion and exclusion criteria

Based on the PICOS principle, the studies included in this review adhered to the following criteria: (P) Population: Animal studies, with preparation requiring ethical approval, and no restrictions on species, gender, age, or weight of the animals; (I) Intervention: Studies involving quercetin treatment, either alone or in combination, with no restrictions on the route of administration, duration, dosage, or formulation; (C) Comparison: Control groups with either blank controls or standard treatments; (O) Outcome: Primary outcome measures included the forced swimming test (FST), tail suspension test (TST), sucrose preference test (SPT), open field test (OFT), and elevated plus maze (EPM); secondary outcome measures included corticosterone (CORT), brain-derived neurotrophic factor (BDNF), catalase (CAT), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ); (S) Study Design: Animal experiments.

The exclusion criteria were as follows: (1) Review articles, case reports, editorials/letters, patents, abstracts, and other informal journals; (2) *In vitro* studies, computer simulation studies, and all clinical trials; (3) Republished and irrelevant literature; (4) Studies on quercetin derivatives; (5) Experimental studies lacking a control group; (6) Studies with missing original articles or incomplete original data; (7) Studies where outcome data cannot be extracted or merged.

### 2.3 Research selection

The literature was screened and excluded using EndNote reference management software. Two researchers independently reviewed the titles and abstracts of the studies, excluded those that did not meet the inclusion criteria, and determined which studies to include. The remaining studies were then read in full by both researchers to further confirm their inclusion. Throughout the screening process, both researchers worked independently, and the final list of included studies was compared. If the studies matched, they were included; if there was a discrepancy, a third researcher discussed and resolved the differences.

## 2.4 Data extraction

The following information was independently extracted from the included studies by two researchers: (1) First author's name and publication year; (2) Animal characteristics described in the



intervention and control groups, including animal model, species, sex, and the number of animals per group; (3) Treatment information, including the drug dosage, route of administration, and duration of the intervention; (4) Outcome measures: Two researchers independently extracted data from each study, initially attempting to extract numerical data from tables or text. If these were not reported, quantitative data were extracted from graphs using Engauge Digitizer.

### 2.5 Quality assessment

Two researchers independently assessed the risk of bias in each included study using the SYRCLE risk of bias assessment tool (Hooijmans et al., 2014), specifically analyzing the following types of bias: selection bias (random sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases. Each type of bias was classified as high risk, low risk, or unclear. In the event of a discrepancy, the issue was resolved through discussion with a third researcher.

### 2.6 Data analysis

In this meta-analysis, the outcome measures were continuous data. Due to differences in animal species and models, standardized mean differences (SMD) and 95% confidence intervals (CIs) were used for analysis. The heterogeneity of the data was assessed using the  $I^2$  statistic. When  $I^2 <50\%$  and p > 0.05, low heterogeneity was assumed, and a fixed-effect model was used; otherwise, a random-effects model was applied. Sensitivity analysis was performed when more than 10 studies were included in an outcome measure, and funnel plots, along with Begg's and Egger's tests, were used to assess publication bias. A p-value <0.05 was considered statistically significant. All data analyses were performed using Review Manager 5.4 and STATA 15.1 software.

## **3** Results

## 3.1 Study selection

Based on the predefined search strategy, a total of 1,331 articles were retrieved. After excluding 533 duplicates, 798 articles remained. By reviewing the titles and abstracts, we further excluded conference abstracts and reviews (n = 137), technological achievements (n = 54), studies not measuring depression (n = 297), human studies (n = 46), in vitro studies (n = 13), network pharmacology studies (n = 63), and studies on quercetin metabolites, derivatives, or precursors (n = 122). Finally, 66 articles were selected for full-text screening. Afterward, we excluded studies with no full text (n = 3), studies with inconsistent outcome measures (n = 6), studies with unclear data (n = 3), and studies involving fixed-dose combinations with other drugs (n = 2), resulting in the inclusion of 52 articles (Anjaneyulu et al., 2003; Sah et al., 2011; Liu et al., 2013; Rinwa and Kumar, 2013; Jain and Gangshettiwar, 2014; Merzoug et al., 2014; Holzmann et al., 2015; Mehta et al., 2017; Rebai et al., 2017; Singh et al., 2017; Quraishi et al., 2018; Samad et al., 2018; Anggreini et al., 2019; Fang et al., 2019; Khan et al., 2019; Sriram and Ravichandra, 2019; Toumi et al., 2019; Boudia et al., 2020; Donoso et al., 2020; Sadighparvar et al., 2020; Ahin et al., 2020; Zhang et al., 2020; Bicca et al., 2021; Bin-Jaliah, 2021; Eduviere et al., 2021; Guan T. et al., 2021; Guan Y. et al., 2021; Ma et al., 2021; Madiha et al., 2021; Wang et al., 2021; Tan et al., 2022; Ugwu et al., 2022; Yang et al., 2022; Adeoluwa et al., 2023; Balasubramanian et al., 2023; Ge et al., 2023; Jia et al., 2023; Adeoluwa et al., 2024; Bappi et al., 2024; Du et al., 2024; Ge et al., 2024; Kore et al., 2024; Li B. et al., 2024; Li Y. et al., 2024; Makhdoomi et al., 2024; Su et al., 2024; Tavakol et al., 2024; Wang et al., 2024c; Wang et al., 2024a; Wang et al., 2024b; Zhu et al., 2024; Hou et al., 2025) for the comprehensive analysis. The detailed literature search and screening process is shown in Figure 1.

# 3.2 Characteristics and quality of included studies

A total of 52 studies included in this meta-analysis were published between 2003 and 2025, and their main characteristics are summarized in Table 2. Of these, 21 studies were conducted in

#### TABLE 2 Characteristics of the 52 studies included in the meta-analysis.

First author	Publication year	Country	Species	Weight	Sex	Numbers in each group (QE/Ctrl)	Model	Experimental group	Dose of quercetin	Control group	Method of administration	Administration time	Outcome measures
Muragundla Anjaneyulu	2003	India	Laka mice	20-30 g	male	6/6	Streptozotocin- Induced Diabetic	quercetin + Diabetic	100 mg/kg	vehicle + Diabetic	i.p	60min	А
Sangeeta Pilkhwal Sah	2011	India	Wistar albino rat	150-200 g	-	6/6	LPS	quercetin + LPS	25 mg/kg	vehicle + LPS	i.p	2w	BEFGKL
Jianxiang Liu	2013	China	ICR mice	21-25 g	male	15/15	-	quercetin	20 mg/kg	blank control	i.g	1 h	С
Puneet Rinwa	2013	India	Wistar rat	250-300 g	male	6/6	Olfactory bulbectomy (OBX)	quercetin + OBX	80 mg/kg	OBX	p.o	2w	ABFGJKLMN
Dilpesh Jain	2014	India	Wistar rat	200-250 g	male	6/6	3-nitropropionic acid (3-NP)- induced Huntington's disease	quercetin+3-NP	50 mg/kg	3-NP	p.o	14 d	A
Sameha Merzoug	2014	Algeria	Wistar rat	_	male	5/5	Adriamycin (ADR)	quercetin + ADR	60 mg/kg	ADR	i.p	24 h	ABEJKL
Iandra Holzmann	2015	Brazil	Swiss mice	25-30 g	female	6/6	Olfactory bulbectomy (OB)	quercetin + OB	25 mg/kg	vehicle + OB	p.o	14 d	ABCKN
Vineet Mehta	2017	India	Swiss albino mice	20-25 g	-	8/8	CUS	quercetin + CUS	30 mg/kg	CUS	p.o	21 d	BDELM
Redouane Rebai	2017	Algeria	Wistar rat	180–210 g	male	7/6	Streptozotocin- Induced Diabetic	quercetin + Diabetic	10 mg/kg	vehicle + Diabetic	i.p	4w	AB
Tanveer Singh	2017	India	Swiss albino mice	22–28 g	male	6/6	Pentylenetetrazole induced kindling	quercetin + levetiracetam + kindled	40 mg/kg	levetiracetam + kindled	р.о	15 d	CDJ
Mustajab Quraishi	2018	India	Wistar rat	180–220 g	male	6/6	CUMS	quercetin + CUMS	50 mg/kg	saline + CUMS	p.o	lw	ABDJ
Noreen Samad	2018	Pakistan	Albino Wistar mice	20 ± 5 g	male	6/6	2 h immobilization stress	quercetin + stress	20 mg/kg	vehicle + stress	i.p	14 d	AELMN
Khadeeja Khan	2019	India	Swiss albino mice	25-30 g	male	5/5	CUMS	quercetin + CUMS	25 mg/kg	saline + CUMS	p.o	4w	ABCFGKMN
Putri Anggreini	2019	Indonesia	ICR mice	25-30 g	male	6/6	Predatory stress	quercetin + Predatory stress	50 mg/kg	Predatory stress	i.p	3 d	CE
SRIRAM BS	2019	India	Mice	25-30 g	male	6/6	Monosodium glutamate (MSG)	quercetin + MSG	100 mg/kg	MSG	p.o	13 d	FI
Mohamed Lamine Toumi	2019	Algeria	Wistar rat	255 ± 5 g	male	7/7	Alloxan Induced Diabetic	quercetin + Diabetic	100 mg/kg	vehicle + Diabetic	p.o	24 h	ABE
Fang Ke	2019	China	SD rat	_	male	3/3	LPS	quercetin + LPS	40 mg/kg	LPS	i.g	14 d	ABDFI
Fella Boudiaf	2020	Algeria	Wistar rat	210 ± 20 g	_	6/6	_	quercetin	5 mg/kg	blank control	i.g	7 d	В

(Continued on following page)

#### TABLE 2 (Continued) Characteristics of the 52 studies included in the meta-analysis.

First author	Publication year	Country	Species	Weight	Sex	Numbers in each group (QE/Ctrl)	Model	Experimental group	Dose of quercetin	Control group	Method of administration	Administration time	Outcome measures
Francisco Donoso	2020	Ireland	SD rat	250-300 g	female	10/12	Maternal separation (MS)	quercetin + MS	20 mg/kg	MS	p.o	8w	BEIJ
Jiajia Zhang	2020	China	C57BL/6J mice	_	male	24/22	Chronic social defeat stress (CSDS)	quercetin + CSDS	2 g/kg	CSDS	p.o	54 d	BCDE
Shirin Sadighparvar	2020	Iran	Wistar rat	90 ± 10 g	male	6/6	1,2- dimethyhydrazine (DMH)-induced colorectal cancer	quercetin + exercise + DMH	50 mg/kg	exercise + DMH	i.g	12w	ABGHI
Tuğçe DemirtaşŞahin	2020	Turkey	Wistar albino rat	250-300 g	male	8/8	CUMS	quercetin + CUMS	30 mg/kg	vehicle + CUMS	i.p	5w	ADJKLMN
Ismaeel Bin- Jaliah	2021	Saudi Arabia	Wistar rat	150–200 g	male	6/6	CUS	quercetin + CUS	50 mg/kg	saline + CUS	i.p	3w	LN
Anthony Taghogho Eduvière	2021	Nigeria	Albino Swiss mice	22.0 ± 2.0 g	male	6/6	72 h active sleep disruption	quercetin + sleep- deprived	50 mg/kg	vehicle + sleep- deprived	р.о	7 d	CMN
Tong Guan	2021	China	SD rat	190–220 g	male	10/10	CUMS	quercetin + CUMS	50 mg/kg	vehicle + CUMS	i.g	8w	DGHKMN
Yuechen Guan	2021	China	Kunming mice	18-22 g	male	10/10	CUMS	quercetin + CUMS	40 mg/kg	double distilled water + CUMS	i.g	21 d	ABDKLN
Zhong-Xuan Ma	2021	China	ICR mice	22-24 g	male	3/3	CUMS	quercetin + CUMS	30 mg/kg	CUMS	i.g	3w	BCDI
Syeda Madiha	2021	Pakistan	Wistar rat	150-200 g	male	8/8	-	quercetin	50 mg/kg	blank control	p.o	14 d	DKLMN
Guoli Wang	2021	China	C57BL/6J mice	_	female	6/6	ERa-KO	quercetin + ERa-KO	100 mg/kg	vehicle + ERα-KO	p.o	10w	ACI
Diogo Ferreira Bicca	2021	Brazil	Swiss mice	_	male	7/7	Glyphosate-based herbicide (GBH)	quercetin + GBH	30 mg/kg	vehicle + GBH	i.g	30 d	ADEK
Zihu Tan	2022	China	C57BL/ 6 mice	24-30 g	male	6/6	Bilateral carotid artery stenosis (BCAS)/chronic restraint stress (CRS)	quercetin + BCAS/CRS	60 mg/kg	vehicle + BCAS/CRS	i.p	14 d	ABCDEGH
Princewill Ikechukwu Ugwu	2022	Nigeria	Swiss albino mice	25-30 g	male	7/7	Social defeat stress (SDS)	quercetin + SDS	100 mg/kg	vehicle + SDS	i.p	14 d	CFGIJKLMN
Yanrong Yang	2022	China	SD rat	180–200 g	male	10/10	Middle cerebral artery embolization (MCAO)-induced post-stroke depression (PSD)	quercetin + exercise + PSD	50 µg/kg	exercise + PSD	p.o	12w	CDGHI
Ramya Balasubramanian	2023	India	C57BL/6J mice	_	male	6/6		quercetin + rmTBI	50 mg/kg	rmTBI	p.o	7 d	А
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#### TABLE 2 (Continued) Characteristics of the 52 studies included in the meta-analysis.

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First author	Publication year	Country	Species	Weight	Sex	Numbers in each group (QE/Ctrl)	Model	Experimental group	Dose of quercetin	Control group	Method of administration	Administration time	Outcome measures
							Repeated mild traumatic brain injury (rmTBI)						
Olusegun Adebayo Adeoluwa	2023	Nigeria	Rat	_	male	6/6	LPS	quercetin + LPS	50 mg/kg	vehicle + LPS	р.о	7 d	FG
Chenjie Ge	2023	China	C57BL/6J mice	18–20 g	male	6/6	Corticosterone (CORT)	quercetin + CORT	80 mg/kg	saline + CORT	i.g	2w	ABEFGHIKM
Siqi Jia	2023	China	SD rat	190-220 g	male	16/16	CUMS	quercetin + CUMS	50 mg/kg	vehicle + CUMS	i.g	8w	KLN
Olusegun Adebayo Adeoluwa	2024	Nigeria	Swiss mice	20–25 g	male	5/5	_	quercetin	100 mg/kg	vehicle	p.o	60min	AC
Mehedi Hasan Bappi	2024	Bangladesh	Swiss Albino mice	24–28 g	male	6/6	-	quercetin	50 mg/kg	vehicle	p.o	0.5 h	А
Dan Wang-1	2024	China	Wistar rat	190–230 g	female	12/12	Ovariectomy combined with chronic unpredictable mild stress (OVX- CUMS)	quercetin + OVX- CUMS	50 mg/kg	vehicle + OVX- CUMS	i.g	4w	DKLMN
Dan Wang-2	2024	China	Wistar rat	190–230 g	female	9/9	Perimenopausal depression	quercetin + Perimenopausal depression	50 mg/kg	vehicle + Perimenopausal depression	i.g	4w	ABEK
Longfei Du	2024	China	C57BL/6J mice	25-30 g	male	6/6	CUS	quercetin + CUS	75 mg/kg	vehicle + CUS	i.p	2w	ACDFGH
Chenjie Ge	2024	China	C57BL/ 6 mice	18–22 g	male	6/6	CUMS	quercetin + CUMS	50 mg/kg	saline + CUMS	i.g	4w	ACD
Mikhil Santosh Kore	2024	India	Swiss albino mice	20-25 g	male	8/8	CUMS	quercetin + CUMS	20 mg/kg	CUMS	p.o	3w	ACEFGHIJ
Bozhi Li	2024	China	Wistar rat	180–220 g	male	12/12	CUMS	quercetin + CUMS	50 mg/kg	pure water + CUMS	i.g	8w	ADE
YUANYUAN LI	2024	China	SD rat	180-220 g	male	10/10	CUMS	quercetin + CUMS	52.08 mg/kg	saline + CUMS	i.g	6w	BDFGH
Sajjad Makhdoomi	2024	Iran	BALB/c mice	20 ± 5 g	male	6/6	_	quercetin	25 mg/kg	blank control	p.o	21 d	ABCELMN
Qing Zhu	2024	China	BALB/c mice	_	female	5/5	4T1 cells and CORT to create a BCRD model	quercetin + BCRD	8 mg/kg	BCRD	i.g	25 d	ACD
Pan Su	2024	China	ICR mice	20 ± 2 g	male	10/10	LPS	quercetin + LPS	50 mg/kg	vehicle + LPS	i.g	14 d	BCD

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Outcome measures	AB	ABCDIJ	GHKL	ted stress; LPS,
Administration time	45min	4w	4w	s; CUS, chronic unpredic
Method of administration	i.p	i.g	i. B	Abbreviations: Ctrl, control; QE, quercetin; SD, Sprague-Dawley; min, minute; d, days, w, weeks, i.g., intragastric injection; i.p., intraperitoneal injection; p.o., oral administration; CUMS, chronic unpredictable mild stress, CUS, chronic unpredicted stress, LPS, ipopolysaccharide.
Control group	saline + SIS	CUMS	vehicle + OVX- ig CUMS	on; CUMS, chronic
Dose of quercetin	40 mg/kg	60 mg/kg	50 mg/kg	oral administrati
Experimental group	quercetin + SIS	quercetin + CUMS	quercetin + OVX- CUMS	eritoneal injection; p.o.,
Model	Social isolation stress (SIS)	CUMS	Ovariectomy (OVX) combined with CUMS	c injection; i.p., intrap
Numbers in each group (QE/Ctrl)	6/6	3/3	12/12	ks; i.g., intragastri
Sex	male	male	female	ys; w, wee
Weight	10-12 g	140–160 g	190 ± 20 g	minute; d, da
Species	NMRI mice 10-12 g	SD rat	Wistar rat	e-Dawley; min
Country	Iran	China	China	etin; SD, Sprague
Publication Country Species Weight year	2024	2024	2025	, control; QE, querce
First author	Fatemeh Tavakol 2024	Mingyan Wang	Yali Hou	Abbreviations: Ctrl, lipopolysaccharide.

EPM; F. IL-6, levels; G, TNF-a, levels; H, IL-1β levels; I, BDNF, levels; I, CORT, levels; K, GSH, levels; L, MDA, levels; M, CAT, levels; and N, SOD, levels FST; B, OFT; C, TST; D, SPT; E, Notes: A, China, 11 in India, 4 in Nigeria and Algeria, 3 in Iran, 2 in Brazil and Pakistan, and one each in Indonesia, Bangladesh, Saudi Arabia, Ireland, and Turkey. Twenty-five studies induced depression in animals through stress, 15 through chemical induction, 5 through surgical induction, and 1 through genetic knockout. The sample size of each study ranged from 3 to 24 animals. Of the included studies, 28 used mice (weighing 10-30 g), and 24 used rats (weighing 80-300 g). Except for 10 studies, the remaining all used male animals. The quercetin dosage ranged from 50 µg/kg to 2 g/kg. Twenty-one studies administered quercetin orally, 19 via gavage, and the remaining 12 via intraperitoneal injection. The duration of quercetin supplementation ranged from 0.5 h to 12 weeks. Among the 52 included studies, the baseline characteristics were evenly distributed between the experimental and control groups in all studies. Random sequence generation was reported in 41 studies (78.8%), but none of the studies mentioned allocation concealment or blinding of animal breeders and researchers. Seven studies performed blinded outcome assessment. In addition, all studies reported the completeness of outcome data, with all animals undergoing the same assessments during the experiment, and no selective reporting was detected. Overall, the quality of the included studies primarily ranged from moderate to low risk of bias. There was a high number of "unclear risk" or "high risk" bias sources in allocation concealment and blinding, but most studies showed a low risk of bias in random sequence generation, outcome assessment, and other biases, providing a certain level of reliability to the metaanalysis results. However, caution should still be taken when interpreting and applying these results due to the potential impact of these biases. The detailed information on the quality assessment of the literature is presented in Table 3.

## 3.3 Behavioral tests

## 3.3.1 FST

The meta-analysis of FST, 29 studies (Anjaneyulu et al., 2003; Rinwa and Kumar, 2013; Jain and Gangshettiwar, 2014; Merzoug et al., 2014; Holzmann et al., 2015; Rebai et al., 2017; Quraishi et al., 2018; Samad et al., 2018; Fang et al., 2019; Khan et al., 2019; Toumi et al., 2019; Ahin et al., 2020; Sadighparvar et al., 2020; Bicca et al., 2021; Guan T. et al., 2021; Wang et al., 2021; Tan et al., 2022; Ge et al., 2023; Adeoluwa et al., 2024; Bappi et al., 2024; Du et al., 2024; Ge et al., 2024; Kore et al., 2024; Li B. et al., 2024; Makhdoomi et al., 2024; Tavakol et al., 2024; Wang et al., 2024c; Wang et al., 2024b; Zhu et al., 2024) on immobility time (involving 435 animals) and 6 studies (Merzoug et al., 2014; Rebai et al., 2017; Khan et al., 2019; Toumi et al., 2019; Balasubramanian et al., 2023; Ge et al., 2023) on swimming time (involving 77 animals) were included. The results indicated that, compared to the control group, quercetin treatment significantly reduced immobility time (SMD = -2.65; 95% CI = [-3.22, -2.08]; p < 0.001;  $I^2 = 74\%$ ) and increased swimming time  $(SMD = 3.83; 95\% CI = [2.51, 5.15]; p < 0.001; I^2 = 56\%)$ . The forest plot showing the effect of quercetin on FST is presented in Figure 2.

## 3.3.2 OFT

As for the OFT, 11 studies (Merzoug et al., 2014; Rebai et al., 2017; Quraishi et al., 2018; Fang et al., 2019; Toumi et al., 2019; Boudia et al., 2020; Donoso et al., 2020; Makhdoomi et al., 2024; Su

#### TABLE 3 Quality assessment of included studies.

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Muragundla Anjaneyulu	2003	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Low risl
Sangeeta Pilkhwal Sah	2011	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low ris
Jianxiang Liu	2013	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Low risl
Puneet Rinwa	2013	Low risk	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risl
Dilpesh Jain	2014	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Sameha Merzoug	2014	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Iandra Holzmann	2015	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Vineet Mehta	2017	Low risk	Low risk	Unclear risk	High risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Redouane Rebai	2017	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Tanveer Singh	2017	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Unclea: risk
Mustajab Quraishi	2018	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclea risk
Noreen Samad	2018	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclea risk
Khadeeja Khan	2019	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Putri Anggreini	2019	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
SRIRAM BS	2019	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Mohamed Lamine Toumi	2019	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Unclea risk
Fang Ke	2019	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low ris
Fella Boudiaf	2020	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Unclea: risk
Francisco Donoso	2020	Low risk	Low risk	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	Low ris
Jiajia Zhang	2020	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low ris
Shirin Sadighparvar	2020	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	Low ris
Tuğçe DemirtaşŞahin	2020	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Ismaeel Bin-Jaliah	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
nthony Taghogho Eduvière	2021	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris
Tong Guan	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low ris

(Continued on following page)

#### TABLE 3 (Continued) Quality assessment of included studies.

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Yuechen Guan	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Zhong-Xuan Ma	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Syeda Madiha	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Guoli Wang	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Diogo Ferreira Bicca	2021	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Zihu Tan	2022	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
Princewill Ikechukwu Ugwu	2022	Low risk	Low risk	Unclear risk	High risk	High risk	Low risk	High risk	Low risk	Low risk	High risk
Yanrong Yang	2022	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Ramya Balasubramanian	2023	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Olusegun Adebayo Adeoluwa	2023	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Chenjie Ge	2023	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Siqi Jia	2023	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Olusegun Adebayo Adeoluwa	2024	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Mehedi Hasan Bappi	2024	Unclear risk	Low risk	High risk	Unclear risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Dan Wang-1	2024	Low risk	Low risk	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Dan Wang-2	2024	Low risk	Low risk	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Longfei Du	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chenjie Ge	2024	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Mikhil Santosh Kore	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Bozhi Li	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
YUANYUAN LI	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Sajjad Makhdoomi	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Qing Zhu	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk
Pan Su	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Fatemeh Tavakol	2024	Low risk	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk

(Continued on following page)

TABLE 3 (Continued) Quality assessment of included studies.

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Mingyan Wang	2024	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Yali Hou	2025	Low risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Unclear risk

Notes: (1) Random sequence generation; (2) Baseline characteristics; (3) Allocation concealment; (4) Random housing; (5) Blinding (for animal breeders and researchers); (6) Random outcome assessment; (7) Blinding (for outcome evaluators); (8) Incomplete outcome data; (9) Selective outcome reporting; (10) Other risk of bias.

## (A)

		erimenta			Control	T	141.1.1.1	Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean		Total	Mear			Weight		IV, Random, 95% CI
Bozhi Li 2024	83.19					12	4.7%		
Chenjie Ge 2023	90.33			173.8		8	2.6%		
Chenjie Ge 2024	105.775			158.646		6	3.0%		
Dan Wang-2 2024	113.326			144.102		12	4.0%		
Dilpesh Jain 2014	176.962			239.349		6	4.0%		
Diogo Ferreira Bicca 2021	90.786			162.8		8	4.0%		
Fang Ke 2019	36.696			84.842		9	4.4%		
Fatemeh Tavakol 2024	52.184			145.612		6	2.0%		
Guoli Wang 2021	37.61	21.335		83.568		6	3.9%		
landra Holzmann 2015	49.7			156.1		6	3.5%		the second se
Khadeeja Khan 2019	16.782	3.6135	5	42.429		5	2.7%		and the second sec
Longfei Du 2024	166.4	13.02	10	188.71	26.72	10	4.6%	-1.02 [-1.96, -0.07]	-
Mehedi Hasan Bappi 2024	61.5	7.7894	6	95.4	13.031	6	3.4%	-2.91 [-4.73, -1.10]	
dikhil Santosh Kore 2024	132.613	16.238	8	136.14	5.3344	8	4.5%	-0.28 [-1.26, 0.71]	-
Mingyan Wang 2024	13.441	9.516	8	50.699	10.215	8	3.5%	-3.57 [-5.30, -1.84]	100 million (100 million)
Mohamed Lamine Toumi 2019	196.29	4.6036	7	225.21	7.3023	7	2.9%	-4.44 [-6.64, -2.23]	
Muragundla Anjaneyulu 2003	1.34952	0.12367	6	3.15109	0.44142	6	2.4%	-5.13 [-7.88, -2.38]	
Mustajab Quraishi 2018	35.697	4.9896	6	72.95	16.5	6	3.5%	-2.82 [-4.60, -1.04]	
Noreen Samad 2018	52.11	11.84	6	193.66	15.24	6	1.1%	-9.57 [-14.38, -4.77]	
Olusegun Adebayo Adeoluwa 2024	54.625	13.884	5	156.75	15.885	5	1.6%		
Puneet Rinwa 2013	96.625		12	192.971	31.336	12	4.1%		
Qing Zhu 2024	90.605	8.796	5	111.885	8.985	5	3.5%		
Redouane Rebai 2017	62.92	16.1	7	127	23	6	3.5%		
Sajjad Makhdoomi 2024	62.678			67.672	28.36	6	4.4%		
Sameha Merzoug 2014	146.24	3.8947	6	190.59	4.5561	6	1.1%		
Shirin Sadighparvar 2020	120.23			147.88		6	3.6%		<u> </u>
Tuğçe DemirtaşŞahin 2020	172.43			233.16		10	4.3%		
Yuechen Guan 2021	103.283					10	4.5%		
Zihu Tan 2022	104.71	51.545		148.31		10	4.6%		+
Total (95% CI)			218			247	100.0%	-2.65 [-3.22, -2.08]	•
	00.06 df - 2	0 /0 - 0 0		2 - 740		211	100.070	-2.03 [-3.22, -2.00]	
	00001								Favours [experimental] Favours [control]
Test for overall effect: Z = 9.16 (P < C	).00001)								
Fest for overall effect: Z = 9.16 (P < 0		imental		Cor	trol		Sto	I. Mean Difference	Std. Mean Difference
Fest for overall effect: Z = 9.16 (P < 0		imental SD T	otal	Cor Mean	trol SD Tot	al We		1. Mean Difference IV. Random, 95% Cl	Std. Mean Difference IV. Random, 95% Cl
Test for overall effect: Z = 9.16 (P < 0 B) Study or Subgroup	Exper Mean					111 - 11 - 11 - 11 - 11 - 11 - 11 - 11		IV, Random, 95% Cl	
Heterogeneity: Tau <sup>2</sup> = 1.59; Chi <sup>2</sup> = 1; Test for overall effect: Z = 9.16 (P < 0 B) Study or Subgroup Chenjie Ge 2023 Khadeeia Khan 2019	Exper Mean 128.02	<u>SD</u> T 13.29	8	Mean 44.67	SD Tot 5.81	8 10	eight ).9%	IV, Random, 95% Cl 7.68 [4.46, 10.90]	
Test for overall effect: Z = 9.16 (P < 0 <b>B)</b> <u>Study or Subgroup</u> Chenjie Ge 2023 Khadeeja Khan 2019	Exper Mean 128.02 272.62 3	<u>SD</u> T 13.29 0.075	8 5 1	Mean 44.67 95.59 4	SD Tot 5.81 0.831	8 10 5 20	eight ).9% ).7%	IV. Random, 95% Cl 7.68 [4.46, 10.90] 1.94 [0.29, 3.59]	
Test for overall effect: Z = 9.16 (P < 0 <b>B)</b> <u>Study or Subgroup</u> Chenjie Ge 2023 Khadeeja Khan 2019 Mohamed Lamine Toumi 2019	Exper Mean 128.02 272.62 3 42.851 3	<u>SD</u> T 13.29 0.075 .2014	8 5 1 7 2	Mean 44.67 95.59 4 9.564 4	<u>SD Tot</u> 5.81 0.831 3126	8 10 5 20 7 19	eight ).9% ).7% ).7%	IV, Random, 95% Cl 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05]	
Test for overall effect: Z = 9.16 (P < 0 <b>Study or Subgroup</b> Chenjie Ge 2023 Khadeeja Khan 2019 Mohamed Lamine Toumi 2019 Ramya Balasubramanian 2023	Exper Mean 128.02 272.62 3 42.851 3 180.11 2	<b>SD T</b> 13.29 0.075 0.2014 8.365	8 5 1 7 2 6	Mean 44.67 95.59 4 9.564 4 52.99 1	<b>SD Tot</b> 5.81 0.831 3126 3.543	8 10 5 20 7 19 6 13	eight ).9% ).7% ).7% ).7%	IV, Random, 95% CI 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05] 4.90 [2.25, 7.54]	
Fest for overall effect: Z = 9.16 (P < 0 <b>Study or Subgroup</b> Chenjie Ge 2023 Khadeeja Khan 2019 Mohamed Lamine Toumi 2019 Ramya Balasubramanian 2023 Redouane Rebai 2017	Exper Mean 128.02 272.62 3 42.851 3 180.11 2 117.4	<b>SD T</b> 13.29 0.075 2.2014 8.365 19.89	8 5 1 7 2 6 7	Mean 44.67 95.59 4 9.564 4 52.99 1 58.74	<b>SD</b> Tot 5.81 0.831 3126 3.543 12.41	8 10 5 20 7 19 6 13 6 19	eight ).9% ).7% ).7% ).7% ).2%	IV, Random, 95% CI 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05] 4.90 [2.25, 7.54] 3.23 [1.38, 5.07]	
Test for overall effect: Z = 9.16 (P < 0 B) Study or Subgroup	Exper Mean 128.02 272.62 3 42.851 3 180.11 2	<b>SD T</b> 13.29 0.075 2.2014 8.365 19.89	8 5 1 7 2 6 7	Mean 44.67 95.59 4 9.564 4 52.99 1	<b>SD</b> Tot 5.81 0.831 3126 3.543 12.41	8 10 5 20 7 19 6 13 6 19	eight ).9% ).7% ).7% ).7%	IV, Random, 95% CI 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05] 4.90 [2.25, 7.54]	
Test for overall effect: Z = 9.16 (P < 0 <b>Study or Subgroup</b> Chenjie Ge 2023 Khadeeja Khan 2019 Mohamed Lamine Toumi 2019 Ramya Balasubramanian 2023 Redouane Rebai 2017	Exper Mean 128.02 272.62 3 42.851 3 180.11 2 117.4	<b>SD T</b> 13.29 0.075 2.2014 8.365 19.89	8 5 1 7 2 6 7	Mean 44.67 95.59 4 9.564 4 52.99 1 58.74	<b>SD</b> Tot 5.81 0.831 3126 3.543 12.41 3295	8 10 5 20 7 19 6 13 6 19	eight ).9% ).7% ).7% ).7% ).2% j.8%	IV, Random, 95% CI 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05] 4.90 [2.25, 7.54] 3.23 [1.38, 5.07]	
Test for overall effect: Z = 9.16 (P < 0 <b>Study or Subgroup</b> Chenjie Ge 2023 Khadeeja Khan 2019 Mohamed Lamine Toumi 2019 Ramya Balasubramanian 2023 Redouane Rebai 2017 Sameha Merzoug 2014	Exper Mean 128.02 272.62 3 42.851 3 180.11 2 117.4 96.609 4	<u>SD T</u> 13.29 0.075 0.2014 8.365 19.89 0.5022	8 5 1 7 2 6 7 6 8 <b>39</b>	Mean 44.67 95.59 41 9.564 4. 52.99 11 58.74 0.507 2.	<b>SD</b> Tot 5.81 0.831 3126 3.543 12.41 3295	8 10 5 20 7 19 6 13 6 19 6 15	eight ).9% ).7% ).7% ).7% ).2% j.8%	IV. Random, 95% Cl 7.68 [4.46, 10.90] 1.94 [0.29, 3.59] 3.28 [1.50, 5.05] 4.90 [2.25, 7.54] 3.23 [1.38, 5.07] 4.15 [1.83, 6.47]	

Forest plot for the effect of quercetin on the forced swimming test. (A) the immobility time; (B) the swimming time.

et al., 2024; Wang et al., 2024c; Wang et al., 2024b) on total distance traveled (involving 175 animals), 13 studies (Merzoug et al., 2014; Mehta et al., 2017; Quraishi et al., 2018; Fang et al., 2019; Khan et al., 2019; Toumi et al., 2019; Donoso et al., 2020; Zhang et al., 2020; Ma et al., 2021; Tan et al., 2022; Ge et al., 2023; Li B. et al., 2024; Su et al.,

2024) on time spent in the central area (involving 242 animals), 6 studies (Mehta et al., 2017; Rebai et al., 2017; Quraishi et al., 2018; Donoso et al., 2020; Makhdoomi et al., 2024; Wang et al., 2024c) on the number of entries into the central area (involving 91 animals), and 10 studies (Sah et al., 2011; Rinwa and Kumar, 2013; Merzoug

### (A)

	Expe	rimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Dan Wang-2 2024	2,254.1	106.1	12	1,854.1	168	12	9.4%	2.75 [1.58, 3.92]	
Fang Ke 2019	12.0842	4.2453	9	9.8267	6.8517	9	10.1%	0.38 [-0.56, 1.31]	
Fella Boudiaf 2020	663.39	410.9	6	932.89	208.23	6	9.3%	-0.76 [-1.96, 0.43]	
Francisco Donoso 2020	2,915.4	662.81	10	3,113.4	685.55	12	10.4%	-0.28 [-1.13, 0.56]	
Mingyan Wang 2024	2,370.1	237.8	8	1,274.5	355.4	8	7.8%	3.43 [1.74, 5.11]	
Mohamed Lamine Toumi 2019	346.11	22.092	7	314.99	22.092	7	9.3%	1.32 [0.12, 2.51]	
Mustajab Quraishi 2018	16.855	5.286	6	6.115	2.8904	6	8.1%	2.33 [0.72, 3.93]	
Pan Su 2024	2,057.2	327.3	10	2,126.7	431.65	10	10.3%	-0.17 [-1.05, 0.70]	
Redouane Rebai 2017	989.9	132.2	7	464.3	123.4	6	6.7%	3.81 [1.75, 5.88]	
Sajjad Makhdoomi 2024	2,050.8	221.2	6	2,063.6	177.4	6	9.5%	-0.06 [-1.19, 1.07]	
Sameha Merzoug 2014	10.8872	2.8806	6	7.843	1.3938	6	9.1%	1.24 [-0.04, 2.53]	-
Total (95% CI)			87			88	100.0%	1.12 [0.30, 1.94]	•
Heterogeneity: Tau <sup>2</sup> = 1.52; Chi <sup>2</sup>	= 53.27, df =	= 10 (P <	0.0000	01); I <sup>2</sup> = 81	96				
Test for overall effect: Z = 2.67 (P		<u>,</u>							-4 -2 U 2 4
1									Favours [experimental] Favours [control]

## **(B)**

	Expe	rimental		С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chenjie Ge 2023	67.227	6.83	8	38.116	4.243	8	5.7%	4.84 [2.67, 7.01]	
ang Ke 2019	0.67672	0.9526	9	0.04787	0.0237	9	9.3%	0.89 [-0.09, 1.87]	+
rancisco Donoso 2020	6.873	4.1837	10	3.088	2.941	12	9.5%	1.02 [0.12, 1.93]	+
liajia Zhang 2020	37.864	13.532	24	29.543	14.004	22	10.4%	0.59 [0.00, 1.19]	-
Khadeeja Khan 2019	8.3927	1.5597	5	8.2146	3.6837	5	8.5%	0.06 [-1.18, 1.30]	+
Aohamed Lamine Toumi 2019	9.339	1.7118	7	5.389	0.4683	7	7.1%	2.95 [1.29, 4.61]	
Mustajab Quraishi 2018	55.199	1.3619	6	35.248	1.2762	6	1.0%	13.95 [7.05, 20.86]	
Pan Su 2024	14.592	3.3805	10	6.387	1.5748	10	8.1%	2.98 [1.63, 4.33]	-
Sameha Merzoug 2014	14.31	3.5224	6	2.417	1.5138	6	5.4%	4.05 [1.77, 6.33]	
/ineet Mehta 2017	66.328	48.349	8	24.708	22.268	8	9.0%	1.05 [-0.02, 2.11]	+
YUANYUAN LI 2024	23.786	2.365	10	19.422	2.957	10	9.2%	1.56 [0.53, 2.59]	-
Zhong-Xuan Ma 2021	55.765	6.9692	8	26.964	9.0142	8	7.1%	3.38 [1.71, 5.05]	-
Zihu Tan 2022	34.941	16.931	10	24.021	13.588	10	9.5%	0.68 [-0.23, 1.59]	+
Total (95% CI)			121			121	100.0%	1.88 [1.14, 2.63]	•
Heterogeneity: Tau <sup>2</sup> = 1.29; Chi <sup>2</sup>	= 56.95, df :	= 12 (P <	0.0000	01); I <sup>2</sup> = 79	%			S 101 S	
Fest for overall effect: Z = 4.98 (P				320					-20 -10 0 10 20 Favours [experimental] Favours [control]

## (C)

	Exp	erimenta	ıl	(	Control			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV	, Random, 95% Cl	
Francisco Donoso 2020	24.916	11.261	10	12.689	9.793	12	20.4%	1.12 [0.21, 2.04]			
Mingyan Wang 2024	9.0085	2.1413	8	2.5533	1.3955	8	11.9%	3.38 [1.71, 5.04]			
Mustajab Quraishi 2018	5.4695	1.0447	6	3.2975	1.2091	6	14.1%	1.77 [0.35, 3.20]			
Redouane Rebai 2017	2.85	2.03	7	1.16	1.17	6	17.0%	0.93 [-0.24, 2.10]			
Sajjad Makhdoomi 2024	43.885	13.984	6	42.519	8.334	6	17.5%	0.11 [-1.02, 1.24]		1 m m	
Vineet Mehta 2017	13.651	5.0827	8	8.965	8.0497	8	19.1%	0.66 [-0.36, 1.67]		a the second sec	
Total (95% CI)			45			46	100.0%	1.18 [0.44, 1.92]		•	
Heterogeneity: Tau <sup>2</sup> = 0.48	3; Chi <sup>2</sup> = 1	1.77, df =	5 (P =	0.04); 12 =	= 58%				<u> </u>		
Test for overall effect: Z = 3	3.13 (P = 0	).002)							-4 -2 Favours [experin	u 2 4 mental] Favours [control]	

## **(D)**

	Expe	erimental		C	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Fang Ke 2019	11.268	5.4552	9	8.0119	3.5049	9	11.0%	0.68 [-0.28, 1.63]	+	
Fatemeh Tavakol 2024	21.5605	2.8964	6	6.8914	3.1835	6	7.0%	4.45 [2.00, 6.90]		
landra Holzmann 2015	36.4	17.881	6	51.7	9.798	6	10.3%	-0.98 [-2.21, 0.25]	· · · · · · · · · · · · · · · · · · ·	
Khadeeja Khan 2019	38.158	8.0454	5	23.858	6.7194	5	9.3%	1.74 [0.16, 3.32]		
Puneet Rinwa 2013	21.2	8.487	12	43.5	12.332	12	10.8%	-2.03 [-3.05, -1.02]		
Sameha Merzoug 2014	11.9966	2.1639	6	10.4666	2.3956	6	10.4%	0.62 [-0.55, 1.79]		
Sangeeta Pilkhwal Sah 2011	11.75	2.6944	6	4	3.7232	6	9.4%	2.20 [0.64, 3.76]		
Shirin Sadighparvar 2020	7.8534	1.164	6	6.8753	1.0854	6	10.4%	0.80 [-0.40, 2.00]		
YUANYUAN LI 2024	25.746	2.318	10	20.312	3.454	10	10.7%	1.77 [0.70, 2.84]		
Yuechen Guan 2021	27.804	10.445	10	10.768	5.0375	10	10.6%	1.99 [0.88, 3.10]		
Total (95% CI)			76			76	100.0%	0.98 [-0.01, 1.98]	•	
Heterogeneity: Tau <sup>2</sup> = 2.13; Ch	i <sup>2</sup> = 58.15, 0	df = 9 (P <	0.000	01); I <sup>2</sup> = 86	5%			11 A A A A A A A A A A A A A A A A A A	<u> </u>	
Test for overall effect: Z = 1.93	(P = 0.05)			80					-4 -2 U 2 4 Favours [experimental] Favours [control]	

#### FIGURE 3

Forest plot for the effect of quercetin on the open field test. (A) Total distance traveled; (B) the time spent in the central area; (C) the number of entries into the central; (D) the number of standing episodes.

et al., 2014; Holzmann et al., 2015; Fang et al., 2019; Khan et al., 2019; Sadighparvar et al., 2020; Guan T. et al., 2021; Li B. et al., 2024; Tavakol et al., 2024) on the number of standing episodes (involving

152 animals) were included. The results showed that, compared to the control group, quercetin treatment significantly increased the total distance traveled (SMD = 1.12; 95% CI = [0.30, 1.94]; p = 0.008;

	Expe	rimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
itudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
nthony Taghogho Eduvière 2021	137.102	22.533	6	190.745	9.5481	6	4.7%	-2.86 [-4.66, -1.06]	
henjie Ge 2024	105.49	7.81	6	194.76	16.23	6	2.4%	-6.47 [-9.83, -3.12]	
Juoli Wang 2021	77.128	29.044	6	131.133	15.341	6	5.3%	-2.15 [-3.69, -0.60]	
andra Holzmann 2015	53.4	36.007	6	120.5	15.922	6	5.2%	-2.22 [-3.79, -0.66]	
iajia Zhang 2020	61.6	21.17	24	79.72	25.84	22	7.2%	-0.76 [-1.36, -0.16]	+
ianxiang Liu 2013	100.93	35.244	15	163.47	36.638	15	6.8%	-1.69 [-2.54, -0.84]	+
(hadeeja Khan 2019	89.204	18.841	5	145.804	9.2171	5	3.8%	-3.45 [-5.75, -1.14]	
ongfei Du 2024	151.15	26.44	10	184.63	9.05	10	6.4%	-1.62 [-2.66, -0.58]	+
1ikhil Santosh Kore 2024	170.41	15.132	8	190.5	8.853	8	6.1%	-1.53 [-2.69, -0.38]	-
1ingyan Wang 2024	43.273	16.165	8	103.112	19.78	8	5.2%	-3.13 [-4.72, -1.54]	
)lusegun Adebayo Adeoluwa 2024	28.21	8.01	5	181.58	10.77	5	0.5%	-14.60 [-22.91, -6.29]	
'an Su 2024	52.404	19.603	10	105.034	14.256	10	5.7%	-2.94 [-4.28, -1.60]	
rincewill Ikechukwu Ugwu 2022	86.29	22.145	7	157.75	30.029	7	5.3%	-2.54 [-4.06, -1.01]	
utri Anggreini 2019	101.132	55.961	6	143.673	34.734	6	6.0%	-0.84 [-2.05, 0.36]	-
ing Zhu 2024	72.048	6.536	5	89.727	5.968	5	4.5%	-2.55 [-4.45, -0.65]	
ajjad Makhdoomi 2024	130.83	23.18	6	114.62	39.53	6	6.1%	0.46 [-0.69, 1.62]	+
anveer Singh 2017	88	13.007	6		19.326	6	1.1%	-11.19 [-16.76, -5.61]	
anrong Yang 2022	87.91	6.83	10	113.22	9.71	10	5.7%	-2.89 [-4.22, -1.56]	
hong-Xuan Ma 2021	43.779	13.568	8	84.603	10.485	8	5.1%	-3.18 [-4.79, -1.58]	
iihu Tan 2022	119.51	66.692	10	156.28	56.478	10	6.7%	-0.57 [-1.47, 0.33]	
otal (95% CI)			167			165	100.0%	-2.19 [-2.82, -1.56]	•
leterogeneity: Tau <sup>2</sup> = 1.35; Chi <sup>2</sup> = 77.	91, df = 19	(P < 0.00	001); P	²= 76%				-	-20 -10 0 10 20
est for overall effect: Z = 6.80 (P < 0.)	00001)								Favours [experimental] Favours [control]
GURE 4 Prest plot for the effect of que	weetin ou				haak				

 $I^2 = 81\%$ ), time spent in the central area (SMD = 1.88; 95% CI = [1.14, 2.63]; p < 0.001;  $I^2 = 79\%$ ), and the number of entries into the central area (SMD = 1.18; 95% CI = [0.44, 1.92]; p = 0.002;  $I^2 = 58\%$ ). However, quercetin treatment did not show a statistically significant effect on the number of standing episodes (SMD = 0.98; 95% CI = [-0.01, 1.98]; p = 0.05;  $I^2 = 85\%$ ). The forest plot showing the effect of quercetin on OFT is presented in Figure 3.

#### 3.3.3 TST

In the TST, 20 studies (Liu et al., 2013; Holzmann et al., 2015; Singh et al., 2017; Anggreini et al., 2019; Khan et al., 2019; Zhang et al., 2020; Eduviere et al., 2021; Ma et al., 2021; Wang et al., 2021; Tan et al., 2022; Ugwu et al., 2022; Yang et al., 2022; Adeoluwa et al., 2024; Du et al., 2024; Ge et al., 2024; Kore et al., 2024; Makhdoomi et al., 2024; Su et al., 2024; Wang et al., 2024c; Zhu et al., 2024) on immobility time (involving 332 animals) were included. The results indicated that, compared to the control group, quercetin treatment significantly reduced immobility time (SMD = -2.19; 95% CI = [-2.82, -1.56]; p < 0.001;  $I^2$  = 76%). The forest plot showing the effect of quercetin on TST is presented in Figure 4.

#### 3.3.4 SPT

Regarding SPT, 21 studies (Mehta et al., 2017; Singh et al., 2017; Quraishi et al., 2018; Fang et al., 2019; Ahin et al., 2020; Zhang et al., 2020; Bicca et al., 2021; Guan T. et al., 2021; Guan Y. et al., 2021; Ma et al., 2021; Madiha et al., 2021; Tan et al., 2022; Yang et al., 2022; Du et al., 2024; Ge et al., 2024; Li B. et al., 2024; Li B. et al., 2024; Su et al., 2024; Wang et al., 2024c; Wang et al., 2024a; Zhu et al., 2024) on sucrose preference (involving 398 animals) were included. The results indicated that, compared to the control group, quercetin treatment significantly increased sucrose preference in animals (SMD = 1.91; 95% CI = [1.40, 2.42]; p < 0.001;  $I^2 = 75\%$ ). The forest plot showing the effect of quercetin on SPT is presented in Figure 5.

#### 3.3.5 EPM

In terms of the EPM, 15 studies (Sah et al., 2011; Merzoug et al., 2014; Mehta et al., 2017; Samad et al., 2018; Anggreini et al., 2019; Toumi et al., 2019; Donoso et al., 2020; Zhang et al., 2020; Bicca et al., 2021; Tan et al., 2022; Ge et al., 2023; Kore et al., 2024; Li B. et al., 2024; Makhdoomi et al., 2024; Wang et al., 2024b) on time spent in the open arms (involving 274 animals), 9 studies (Sah et al., 2011; Merzoug et al., 2014; Anggreini et al., 2019; Donoso et al., 2020; Bicca et al., 2021; Tan et al., 2022; Ge et al., 2023; Makhdoomi et al., 2024; Wang et al., 2024b) on the number of entries into the open arms (involving 146 animals), and 5 studies (Merzoug et al., 2014; Toumi et al., 2019; Donoso et al., 2020; Kore et al., 2024; Wang et al., 2024b) on time spent in the closed arms (involving 88 animals) were included. The results showed that, compared to the control group, quercetin treatment significantly increased the time spent in the open arms (SMD = 1.53; 95% CI = [0.91, 2.15]; p < 0.001;  $I^2 = 76\%$ ), the number of entries into the open arms (SMD = 1.58; 95% CI = [0.72, 2.44]; p < 0.001;  $I^2 = 78\%$ ), and decreased the time spent in the closed arms (SMD = -1.99; 95% CI = [-3.39, -0.58]; p = 0.006;  $I^2$  = 84%). The forest plot showing the effect of quercetin on EPM is presented in Figure 6.

#### 3.4 Biochemical assay

#### 3.4.1 Oxidative stress

To investigate the antioxidant effects of quercetin treatment, 16 studies (Sah et al., 2011; Rinwa and Kumar, 2013; Merzoug et al., 2014; Holzmann et al., 2015; Khan et al., 2019; Ahin et al., 2020; Bicca et al., 2021; Guan T. et al., 2021; Guan Y. et al., 2021; Madiha et al., 2021; Ugwu et al., 2022; Ge et al., 2023; Jia et al., 2023; Wang et al., 2024a; Wang et al., 2024b; Hou et al., 2025) on glutathione (GSH) (involving 266 animals), 14 studies (Rinwa and Kumar, 2013; Holzmann et al., 2015; Samad et al., 2018; Khan et al., 2019; Ahin et al., 2020; Bin-Jaliah, 2021; Eduviere et al., 2021; Guan T. et al.,

	Exp	erimental		0	Control			Std. Mean Difference	Std. Mean Difference
study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
lozhi Li 2024	65.562	22.967	12	42.49	17.812	12	5.8%	1.08 [0.22, 1.95]	-
henjie Ge 2024	42.26	2.649	6	34.295	2.199	6	3.6%	3.02 [1.16, 4.88]	
)an Wang-1 2024	63.579	11.272	12	50.701	7.443	12	5.7%	1.30 [0.41, 2.20]	
)iogo Ferreira Bicca 2021	71.728	3.6939	8	73.252	19.239	8	5.5%	-0.10 [-1.08, 0.88]	
ang Ke 2019	0.76191	0.09537	9	0.44279	0.21615	9	5.2%	1.82 [0.68, 2.96]	
iajia Zhang 2020	72.565	12.698	24	70.212	16.007	22	6.4%	0.16 [-0.42, 0.74]	+
ongfei Du 2024.	67.115	7.864	10	49.563	12.57	10	5.4%	1.60 [0.57, 2.64]	
lingyan Wang 2024	75.709	6.39	8	52.289	8.071	8	4.2%	3.04 [1.48, 4.60]	
lustajab Quraishi 2018	34.159	5.1978	6	15.908	1.8028	6	2.7%	4.33 [1.93, 6.73]	
an Su 2024	76.212	7.4282	10	59.091	5.9894	10	5.0%	2.43 [1.22, 3.64]	
ing Zhu 2024	68.716	2.639	5	55.015	1.586	5	1.7%	5.68 [2.25, 9.12]	
yeda Madiha 2021	93.382	1.658	8	90.577	1.106	8	4.9%	1.88 [0.65, 3.12]	
anveer Singh 2017	86.885	10.212	6	67.992	14.89	6	4.8%	1.37 [0.05, 2.68]	
ong Guan 2021	70.748	15.851	10	39.048	14.529	10	5.2%	2.00 [0.88, 3.11]	
uğçe DemirtaşŞahin 2020	36.084	8.5508	10	19.98	5.6067	10	5.1%	2.13 [0.99, 3.28]	
ineet Mehta 2017	65.699	8.6578	8	51.24	11.195	8	5.2%	1.37 [0.24, 2.49]	
anrong Yang 2022	73.287	2.725	10	57.899	4.375	10	4.0%	4.04 [2.39, 5.69]	
UANYUAN LI 2024	85.964	7.1	10	70.18	8.356	10	5.2%	1.95 [0.84, 3.06]	
uechen Guan 2021	81.355	5.8913	10	64.439	4.3734	10	4.6%	3.12 [1.73, 4.51]	
hong-Xuan Ma 2021	77.402	5.456	8	45.929	11.116	8	4.0%	3.40 [1.73, 5.07]	
ihu Tan 2022	74.465	38.393	10	55.179	39.965	10	5.7%	0.47 [-0.42, 1.36]	+
otal (95% CI)			200			198	100.0%	1.91 [1.40, 2.42]	•
leterogeneity: Tau <sup>2</sup> = 0.98; C	hi² = 79.01,	df = 20 (P	< 0.00	001); I <sup>2</sup> = 7	'5%				+ + + + + -10 -5 0 5 10
est for overall effect: Z = 7.31	(P < 0.000	01)							Favours [experimental] Favours [control]
URE 5									

2021; Guan Y. et al., 2021; Madiha et al., 2021; Ugwu et al., 2022; Jia et al., 2023; Makhdoomi et al., 2024; Wang et al., 2024a) on superoxide dismutase (SOD) (involving 224 animals), 12 studies (Rinwa and Kumar, 2013; Mehta et al., 2017; Samad et al., 2018; Khan et al., 2019; Ahin et al., 2020; Eduviere et al., 2021; Guan T. et al., 2021; Madiha et al., 2021; Ugwu et al., 2022; Ge et al., 2023; Makhdoomi et al., 2024; Wang et al., 2024a) on catalase (CAT) (involving 176 animals), and 14 studies (Sah et al., 2011; Rinwa and Kumar, 2013; Merzoug et al., 2014; Mehta et al., 2017; Samad et al., 2018; Ahin et al., 2020; Bin-Jaliah, 2021; Guan T. et al., 2021; Madiha et al., 2021; Ugwu et al., 2022; Jia et al., 2023; Makhdoomi et al., 2024; Wang et al., 2024a; Hou et al., 2025) on malondialdehyde (MDA) (involving 232 animals) were included. The results indicated that, compared to the control group, quercetin treatment significantly increased GSH levels in animals (SMD = 2.85; 95% CI = [2.02, 3.67]; p < 0.001;  $I^2$  = 79%), SOD levels (SMD = 2.57; 95% CI = [1.63, 3.50]; p < 0.001;  $I^2$  = 82%), and CAT levels (SMD = 2.36; 95% CI = [1.32, 3.40]; p < 0.001;  $I^2 = 82\%$ ), while decreasing MDA levels (SMD = -2.42; 95% CI = [-3.08, -1.76]; p < 0.001;  $I^2 = 67\%$ ). The forest plot showing the effect of quercetin on oxidative stress markers is presented in Figure 7.

#### 3.4.2 Inflammatory cytokines

In the case of inflammatory cytokines, 14 studies (Sah et al., 2011; Rinwa and Kumar, 2013; Khan et al., 2019; Sadighparvar et al., 2020; Guan T. et al., 2021; Tan et al., 2022; Ugwu et al., 2022; Yang et al., 2022; Adeoluwa et al., 2023; Ge et al., 2023; Du et al., 2024; Kore et al., 2024; Li B. et al., 2024; Hou et al., 2025) on tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (involving 208 animals), 11 studies (Sah et al., 2011; Rinwa and Kumar, 2013; Fang et al., 2019; Khan et al., 2019; Sriram and Ravichandra, 2019; Ugwu et al., 2022; Adeoluwa et al., 2023; Ge et al., 2023; Gu et al., 2024; Li B. et al., 2024; Kore et al., 2024; Li B. et al., 2024; Kore et al., 2024; Li B. et al., 2024; Kore et al., 2024; Li B. et al., 2024; Mou et al., 2024; Li B. et al., 2024) on interleukin-6 (IL-6) (involving 150 animals), and 10 studies (Sah et al., 2011; Sadighparvar et al., 2020; Guan T. et al., 2021; Tan et al., 2022; Yang et al., 2022; Ge et al., 2023; Du et al., 2023; Du et al., 2024; Core et al., 2023; Du et al., 2024; Core et al., 202

2024; Kore et al., 2024; Li B. et al., 2024; Hou et al., 2025) on interleukin-1 $\beta$  (IL-1 $\beta$ ) (involving 160 animals) were included in the meta-analysis. The results indicated that, compared to the control group, quercetin treatment significantly reduced TNF- $\alpha$  levels in animals (SMD = -4.16; 95% CI = [-5.39, -2.93]; p < 0.001;  $I^2$  = 82%), IL-6 levels (SMD = -2.49; 95% CI = [-3.48, -1.50]; p < 0.001;  $I^2$  = 76%), and IL-1 $\beta$  levels (SMD = -2.17; 95% CI = [-3.09, -1.24]; p < 0.001;  $I^2$  = 77%). These results suggest that quercetin has significant anti-inflammatory effects. The forest plot showing the effect of quercetin on inflammatory cytokine levels is presented in Figure 8.

#### 3.4.3 BDNF and CORT

Eleven studies (Fang et al., 2019; Sriram and Ravichandra, 2019; Donoso et al., 2020; Sadighparvar et al., 2020; Ma et al., 2021; Wang et al., 2021; Ugwu et al., 2022; Yang et al., 2022; Ge et al., 2023; Kore et al., 2024; Wang et al., 2024c) on brain-derived neurotrophic factor (BDNF) (involving 138 animals) and 9 studies (Rinwa and Kumar, 2013; Merzoug et al., 2014; Singh et al., 2017; Quraishi et al., 2018; Donoso et al., 2020; Ahin et al., 2020; Ugwu et al., 2022; Kore et al., 2024; Wang et al., 2024c) on corticosterone (CORT) (involving 142 animals) were included. The results indicated that, compared to the control group, quercetin treatment significantly increased BDNF levels (SMD = 1.46; 95% CI = [0.67, 2.26]; p < 0.001;  $I^2 = 66\%$ ) and decreased CORT levels in animals (SMD = -2.12; 95% CI = [-3.10, -1.14]; p < 0.001;  $I^2 = 76\%$ ). The forest plot showing the effect of quercetin on BDNF and CORT levels is presented in Figure 9. The effects of quercetin on all behavioral and biochemical endpoints are summarized in Table 4.

### 3.5 Sensitivity analysis and publication bias

In the sensitivity analysis with the exclusion of one study, the overall effects for all outcomes remained consistent, except for the

## (A)

	Expe	erimental		(	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bozhi Li 2024	117.994	76.622	12	70.939	52.824	12	8.6%	0.69 [-0.14, 1.52]	
Chenjie Ge 2023	32.687	2.436	8	15.735	2.436	8	3.3%	6.58 [3.78, 9.38]	
Dan Wang-2 2024	73.551	14.954	12	54.393	15.887	12	8.4%	1.20 [0.32, 2.08]	
Diogo Ferreira Bicca 2021	97.557	9.594	8	82.325	15.392	8	7.8%	1.12 [0.05, 2.20]	
Francisco Donoso 2020	26.992	9.8821	10	22.301	10.094	12	8.5%	0.45 [-0.40, 1.30]	+-
Jiajia Zhang 2020	39.239	12.718	24	32.283	11.521	22	9.3%	0.56 [-0.03, 1.15]	+
Mikhil Santosh Kore 2024	119.336	9.3932	8	112.266	9.6958	8	8.0%	0.70 [-0.32, 1.72]	+
Mohamed Lamine Toumi 2019	17.092	3.6406	7	5.723	1.516	7	5.0%	3.82 [1.85, 5.79]	
Noreen Samad 2018	156.371	17.867	6	65.379	8.872	6	2.8%	5.95 [2.84, 9.07]	
Putri Anggreini 2019	54.775	47.131	6	9.038	9.6755	6	7.1%	1.24 [-0.04, 2.52]	
Sajjad Makhdoomi 2024	15.9781	1.1478	6	16.0105	2.09855	6	7.6%	-0.02 [-1.15, 1.11]	
Sameha Merzoug 2014	22.69	3.0423	6	12.576	2.136	6	4.7%	3.55 [1.48, 5.62]	
3angeeta Pilkhwal Sah 2011	180	14.305	6	108.5	6.8586	6	2.9%	5.88 [2.80, 8.97]	
/ineet Mehta 2017	46.108	11.314	8	30.465	12.355	8	7.7%	1.25 [0.15, 2.35]	
Zihu Tan 2022	33.443	20.156	10	24.835	13.901	10	8.4%	0.48 [-0.42, 1.37]	
Total (95% CI)			137			137	100.0%	1.53 [0.91, 2.15]	•
Heterogeneity: Tau <sup>2</sup> = 0.98; Chi <sup>2</sup> =	= 57.75, df =	= 14 (P <	0.0000	1); l <sup>2</sup> = 76	%				
Fest for overall effect: Z = 4.85 (P							-10 -5 0 5 10 Favours [experimental] Favours [control]		

## **(B)**

	Exp	erimental		C	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chenjie Ge 2023	40.58	4.793	8	20.662	3.048	8	7.9%	4.69 [2.58, 6.80]	
Dan Wang-2 2024	14.627	2.178	12	4.724	1.313	12	8.9%	5.32 [3.49, 7.15]	
Diogo Ferreira Bicca 2021	8.4859	3.4495	8	5.3745	2.8007	8	12.2%	0.94 [-0.11, 1.99]	+
Francisco Donoso 2020	8.0398	1.6529	10	5.8245	2.587	12	12.8%	0.96 [0.07, 1.86]	
Putri Anggreini 2019	4.8548	2.73	6	2.5299	1.9865	6	11.5%	0.90 [-0.31, 2.11]	+
Sajjad Makhdoomi 2024	50.079	10.9405	6	45.544	10.023	6	11.8%	0.40 [-0.75, 1.55]	
Sameha Merzoug 2014	3.6621	1.2105	6	2.1626	1.1486	6	11.3%	1.17 [-0.10, 2.44]	
Sangeeta Pilkhwal Sah 2011	7	4.899	6	1	1.1758	6	10.8%	1.55 [0.19, 2.92]	
Zihu Tan 2022	55.777	44.958	10	39.02	41.704	10	12.9%	0.37 [-0.52, 1.26]	
Total (95% CI)			72			74	100.0%	1.58 [0.72, 2.44]	•
Heterogeneity: Tau <sup>2</sup> = 1.30; Ch	i <sup>2</sup> = 36.16,	df = 8 (P <	0.000	1); I <sup>2</sup> = 78	1%				
Test for overall effect: Z = 3.59	(P = 0.000	3)							-4 -2 U 2 4 Favours [experimental] Favours [control]

## (C)

	Experim				ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Dan Wang-2 2024	160.68	22.38	12	206.61	27.25	12	23.3%	-1.78 [-2.75, -0.81]	
Francisco Donoso 2020	34.402	6.1443	10	35.876	10.389	12	24.0%	-0.16 [-1.00, 0.68]	-
Mikhil Santosh Kore 2024	180.328	10.598	8	187.002	8.2816	8	23.1%	-0.66 [-1.68, 0.35]	
Mohamed Lamine Toumi 2019	242.89	5.1592	7	275.02	5.5561	7	13.5%	-5.61 [-8.28, -2.94]	
Sameha Merzoug 2014	237.7	5.7563	6	262.6	6.1237	6	16.0%	-3.87 [-6.07, -1.67]	
Total (95% CI)			43			45	100.0%	-1.99 [-3.39, -0.58]	•
Heterogeneity: Tau <sup>2</sup> = 1.96; Chi <sup>2</sup> =	= 24.40, df =	= 4 (P < 0	.0001);	I <sup>2</sup> = 84%					
Test for overall effect: Z = 2.76 (P	= 0.006)								-10 -5 0 5 1 Favours [experimental] Favours [control]

FIGURE 6

Forest plot for the effect of quercetin on the elevated plus maze. (A) The time spent in the open arms; (B) the number of entries into the open arms; (C) the time spent closed arms.

number of standing episodes in the open field test. In the analysis of standing episodes, after excluding the study by Iandra Holzmann et al., the results changed. Heterogeneity decreased, and a significant effect was observed (SMD = 1.21; 95% CI = [0.17, 2.25]; p = 0.02;  $I^2$  = 84%). After excluding the study by Puneet Rinwa et al., the results also changed. Heterogeneity decreased, and a significant effect was

observed (SMD = 1.28; 95% CI = [0.51, 2.06]; p = 0.001;  $I^2$  = 70%). The detailed results of the sensitivity analysis are presented in Supplementary Figure S1.

Funnel plots, Begg's test, and Egger's test were conducted for 15 outcome measures, including FST immobility time, total distance traveled in OFT, number of standing episodes in

Study or Subgroup	Experimental Mean SD Tot	Contro al Mean	SD Total		Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV. Random, 95% Cl
Chenjie Ge 2023			98 6	5.2%	4.03 [1.76, 6.30]	
Dan Wang-1 2024			.67 12	6.3%	4.86 [3.16, 6.56]	
Dan Wang-2 2024			.27 9	6.0%	4.32 [2.48, 6.17]	
Diogo Ferreira Bicca 2021		7 224.58 58.		7.0%	1.83 [0.51, 3.15]	
landra Holzmann 2015 Khadeeja Khan 2019		6 2,650 271 5 1.1831 0	.89 6 .43 5	7.3% 5.4%	-0.58 [-1.74, 0.59] 3.17 [1.00, 5.34]	
Princewill Ikechukwu Ugwu 2022		7 1.6494 0.8		5.8%	3.79 [1.83, 5.75]	
Puneet Rinwa 2013		6 0.015 0.0		5.1%	4.17 [1.84, 6.49]	
Sameha Merzoug 2014	12.3209 1.4503	5 9.0311 1.2	66 5	6.2%	2.17 [0.43, 3.91]	
Sangeeta Pilkhwal Sah 2011		6 38.106 5.5		3.4%	6.77 [3.27, 10.26]	
Siqi Jia 2023		6 7.8932 1.3		7.9%	1.29 [0.52, 2.07]	
Syeda Madiha 2021 Tong Guan 2021		8 104.057 2. 0 24.055 3.	135 10	6.5% 7.2%	3.04 [1.48, 4.61] 2.43 [1.21, 3.64]	
Tuğçe DemirtaşŞahin 2020		8 0.40189 0.1		7.2%	1.74 [0.54, 2.94]	
Yali Hou 2025	178.93 13.06 1	2 108.48 12		6.0%	5.30 [3.48, 7.13]	
Yuechen Guan 2021	53.456 7.2891 1	0 42.563 7.8	i19 10	7.6%	1.38 [0.38, 2.37]	
Total (05% CI)	42	2	422	100.0%	2 95 12 02 2 671	•
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 2.08; Chi <sup>2</sup> = 7	13 2 42 df = 15 (P < 0.000)		133	100.0%	2.85 [2.02, 3.67]	
Test for overall effect: Z = 6.76 (P < 0		17,1 = 10.0				-10 -5 0 5 10
						Favours [experimental] Favours [control]
<b>(B)</b>						
	Experimental	Contro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean SD Tot		D Total		IV, Random, 95% Cl	IV, Random, 95% Cl
Anthony Taghogho Eduvière 2021	20.67 2.3025	6 10.32 2.3		6.0%	4.13 [1.82, 6.44]	
Dan Wang-1 2024	43.943 5.777 1	2 33.462 9.8	36 12	8.8%	1.25 [0.36, 2.14]	
landra Holzmann 2015		6 0.64 0.17		8.3%	-0.66 [-1.84, 0.52]	
Ismaeel Bin-Jaliah 2021		6 11.076 0.7		4.2%	6.54 [3.15, 9.92]	
Khadeeja Khan 2019 Noreen Samad 2018		5 2.4529 1.14 6 45.156 8.6		8.2% 4.3%	0.45 [-0.81, 1.72] 6.41 [3.09, 9.74]	
Princewill Ikechukwu Ugwu 2022		7 1.2083 0.26		8.4%	0.96 [-0.17, 2.09]	
Puneet Rinwa 2013		6 0.29 0.07		5.2%	5.24 [2.44, 8.04]	
Sajjad Makhdoomi 2024		6 48.04 1.		8.3%	0.93 [-0.29, 2.15]	
Sigi Jia 2023 Strado Modilao 2021		6 62.313 9.8		8.9%	1.77 [0.94, 2.61]	
Syeda Madiha 2021 Tong Guan 2021		8 53.798 3. 0 51.633 5.6		7.9% 6.6%	2.58 [1.16, 4.00] 5.27 [3.25, 7.29]	
Tuğce DemirtaşŞahin 2020		8 1.9953 0.53		7.2%	3.55 [1.83, 5.27]	
Yuechen Guan 2021		0 89.08 22.8		7.6%	3.65 [2.12, 5.19]	
Total (95% CI)	11	2	143	100.0%	2.57 [1.63, 3.50]	<b>▲</b>
Heterogeneity: Tau <sup>2</sup> = 2.36; Chi <sup>2</sup> = 7			112	100.070	2.57 [1.05, 5.50]	
Test for overall effect: Z = 5.40 (P <		017,1 = 02.10				-10 -5 0 5 10
	,					Favours [experimental] Favours [control]
	,					Favours [experimental] Favours [control]
(C)						Favours [experimental] Favours [control]
	Experimental	Contr			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Experimental Mean SD Tol	tal Mean	SD Total		IV, Random, 95% Cl	
<u>Study or Subgroup</u> Anthony Taghogho Eduvière 2021	Experimental Mean SD Tot 32.6 9.0876	tal Mean 6 15.87 4	<u>SD Total</u> 752 6	8.7%	IV, Random, 95% Cl 2.13 [0.59, 3.67]	Std. Mean Difference
<u>Study or Subgroup</u> Anthony Taghogho Eduvière 2021 Chenjie Ge 2023	Experimental Mean SD Tol 32.6 9.0876 83.09 10.341	tal Mean 6 15.87 4 6 43.796 7	<u>SD Total</u> 752 6 542 6	8.7% 7.1%	IV, Random, 95% Cl 2.13 [0.59, 3.67] 4.01 [1.75, 6.27]	Std. Mean Difference
<u>Study or Subgroup</u> Anthony Taghogho Eduvière 2021	Experimental Mean SD Tol 32.6 9.0876 83.09 10.341	tal Mean 6 15.87 4 6 43.796 7	<u>SD Tota</u> 752 6 542 6 057 12	8.7% 7.1%	IV, Random, 95% Cl 2.13 [0.59, 3.67]	Std. Mean Difference
<u>Study or Subgroup</u> Anthony Taghogho Eduvière 2021 Chenije de 2023 Dan Wang-1 2024 Khandeeja Khan 2019 Noreen Samad 2018	Experimental <u>Mean SD Tot</u> 32.6 9.0870 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7	Mean           6         15.87         4.           6         43.796         7.           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1	SD         Total           752         6           542         6           557         12           471         5           734         6	8.7% 7.1% 9.4% 6.6% 7.5%	IV, Random, 95% Cl 2.13 [0.59, 3.67] 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64]	Std. Mean Difference
<u>Study or Subgroup</u> Anthony Taghogho Eduvière 2021 Chenijie Ge 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022	Experimental Mean SD Tor 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7 1.0277 0.269	Mean           6         15.87         4.           6         43.796         7.           12         10.141         3.           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1	SD         Total           752         6           542         6           057         12           471         5           734         6           318         7	8.7% 7.1% 9.4% 6.6% 7.5% 8.7%	IV, Random, 95% Cl 2.13 [0.59, 3.67] 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64] 2.56 [1.03, 4.09]	Std. Mean Difference
Study or Subgroup Anthony Taghogho Eduvière 2021 Chenije de 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill ikechtukwu Ugwu 2022 Puneet Rinwa 2013	Experimental <u>Mean SD Tor</u> 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7695 2.7 1.0277 0.2069 0.49 0.0245	Mean           6         15.87         4.           6         43.796         7.           12         10.141         3.           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1           6         0.11         0.0	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 5.1%	IV, Random, 95% Cl 2.13 (0.59, 3.67] 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64] 2.56 [1.03, 4.09] 6.40 [3.08, 9.73]	Std. Mean Difference
Study or Subgroup Anthory Taghogho Eduvière 2021 Chenija Ge 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2019 Princewill Ikechukwu Ugwu 2022 Puneet Rirwa 2013 Sajad Makdoomi 2024	Experimental Mean 5D Tol 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7 1.0277 0.2069 0.49 0.0245 8.8 0.72	Mean           6         15.87         4.           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.7           7         0.4953         0.1           6         0.11         0.0           6         8.3         3	SD         Total           752         6           542         6           557         12           471         5           734         6           818         7           735         6           .04         6	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 5.1% 9.5%	IV, Random, 95% Cl 2.13 (0.59, 3.67) 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64] 2.56 [1.03, 4.09] 6.40 [3.08, 9.73] 0.52 [-0.64, 1.68]	Std. Mean Difference
Study or Subgroup Anthony Taghogho Eduvière 2021 Chenije de 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rirwa 2013 Sajiad Makhdoom1 2024	Experimental Mean SD Tof 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7 1.0277 0.2069 0.49 0.0245 8.8 0.72 12.639 1.254	Mean           6         15.87         4.           6         43.796         7.           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1           6         0.11         0.0           6         8.3         8           8         14.13         0	SD         Total           752         6           542         6           557         12           471         5           734         6           818         7           735         6           .04         6           627         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 5.1% 9.5% 9.5%	V, Random, 95% Cl 2,13 [0,59, 3,67] 4,01 [1,75, 6,27] 2,98 [1,76, 4,20] 3,89 [1,37, 6,40] 3,57 [1,49, 5,64] 2,56 [1,03, 4,09] 6,40 [3,08, 9,73] 0,52 [-0,64, 1,68] -1,42 [-2,55, -0,29]	Std. Mean Difference
Study or Subgroup Anthory Taghogho Eduvière 2021 Chenija Ge 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2019 Princewill Ikechukwu Ugwu 2022 Puneet Rirwa 2013 Sajad Makdoomi 2024	Experimental Mean SD Tol 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7 1.0277 0.269 0.49 0.0245 8.8 0.72 12.639 1.254	Mean           6         15.87         4.           6         43.796         7.           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1           6         0.11         0.0           6         8.3         8           8         14.13         0	SD         Total           752         6           542         6           057         12           471         5           734         6           318         7           735         6           .04         6           627         8           408         10	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 5.1% 9.5% 9.5%	IV, Random, 95% Cl 2.13 (0.59, 3.67) 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64] 2.56 [1.03, 4.09] 6.40 [3.08, 9.73] 0.52 [-0.64, 1.68]	Std. Mean Difference
Study or Subgroup Anthory Taghogho Edwiver 2021 Chenije 62 2023 Dan Wang-1 2024 Khađeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puncet Rirwa 2013 Sajjad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021	Experimental           Mean         SD         Tot           32.6         9.0876         9.0876           13.09         10.341         1.62           13.1392         1.2804         1.62           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         2.003         3.18	Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1           6         8.1         1.0           6         8.3         1.1           7         0.4953         0.1           6         8.3         0.1           10         10.611         2	SD         Total           752         6           542         6           057         12           471         5           734         6           318         7           735         6           627         8           408         10           542         8	8.7% 9.4% 6.6% 7.5% 8.7% 5.1% 9.5% 9.5% 9.0% 9.6%	V, Random, 95% C1 2.13 [0.59, 3.67] 4.01 [1.75, 6.27] 2.98 [1.76, 4.20] 3.89 [1.37, 6.40] 3.57 [1.49, 5.64] 2.56 [1.03, 4.09] 6.40 [3.08, 9.73] 0.52 [-0.64, 1.88] -1.42 [-2.55, 0.29] 3.23 [1.81, 4.65]	Std. Mean Difference
Study or Subgroup Anthory Taghogho Edwiver 2021 Chenije Ge 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rimwa 2013 Sajad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tuğçe DemirtaşŞahin 2020 Vincet Mehta 2017	Experimental           Mean         SD         Tot           32.6         9.0876         9.0876           83.09         10.341         1.62           17.68         1.62         2.7           12.7595         2.7         1.0277           1.0277         0.2069         0.49           0.49         0.0245         8.8           0.72         1.2639         1.254           1.0853         0.5223         3.38           1.0853         0.5223         86.545	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           7         0.4953         0.1           6         0.11         0.0           6         8.3         8           10         10.611         2           8         16.5284         0.0           8         65.208         10	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6           627         8           627         8           608         10           542         8           417         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.0% 9.6% 9.2%	IV. Random. 95% cl:           2:13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]	Std. Mean Difference
Study or Subgroup Anthow Taghogho Edwière 2021 Chenije 62 2023 Dan Wang-1 2024 Khadegia Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajiad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tugge DemirtaşŞahin 2020 Vineet Metha 2017 Total (95% CI)	Experimental           Mean         SD         Tot           32.6         9.0876         8.09         10.341           17.68         1.62         1.27595         2.7           1.0277         0.2069         2.7         1.0277         1.0245           8.8         0.72         1.2639         1.254         1.0853         0.5223           86.545         7.996         1.24         1.24         1.24         1.24	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         -0.11         0.0           6         0.11         0.0           6         0.11         0.0           10         10.611         2           8         0.55364         0.0           8         0.55208         10           98         65.208         10	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6           627         8           627         8           608         10           542         8           417         8	8.7% 9.4% 6.6% 7.5% 8.7% 5.1% 9.5% 9.5% 9.0% 9.6%	IV. Random, 95% CI           2.13 (0.59, 3.67)           4.01 (1.75, 6.27)           2.98 (1.76, 4.20)           3.89 (1.37, 6.40)           3.67 (1.44, 5.64)           2.56 (1.03, 4.09)           6.40 (3.06, 9.73)           0.52 (1.064, 1.68)           -1.42 [-2.55, -0.29)           3.23 (1.81, 4.65)           1.35 (0.23, 2.47)	Std. Mean Difference IV. Random, 95% CI
Study of Subgroup Anthory Taghogho Eduvière 2021 Chenjie Ge 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rimwa 2013 Sajaid Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tugge DemirtaşŞahin 2020 Vineet Mehta 2017	Experimental           Mean         SD         Tof           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         0.03         3.136           1.0853         0.5223         86.545         7.996           1.7.6, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         -0.11         0.0           6         0.11         0.0           6         0.11         0.0           10         10.611         2           8         0.55364         0.0           8         0.55208         10           98         65.208         10	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6           627         8           627         8           608         10           542         8           417         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.0% 9.6% 9.2%	IV. Random. 95% cl:           2:13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]	Std. Mean Difference
Study or Subgroup Anthory Taghogho Eduvière 2021 Chenije 62 0203 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puncet Rimwa 2013 Sajjad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tuĝce Demintaşşahin 2020 Vineet Mehta 2017 Total (95% CI) Heterogeneity: Tau" = 2.64; Chi" = 6	Experimental           Mean         SD         Tof           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         0.03         3.136           1.0853         0.5223         86.545         7.996           1.7.6, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         -0.11         0.0           6         0.11         0.0           6         0.11         0.0           10         10.611         2           8         0.55364         0.0           8         0.55208         10           98         65.208         10	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6           627         8           627         8           608         10           542         8           417         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.0% 9.6% 9.2%	IV. Random. 95% cl:           2:13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]	Std. Mean Difference IV. Random, 95% CI
Study or Subgroup Anthory Taghogho Eduvière 2021 Chenije 62 0203 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puncet Rimwa 2013 Sajjad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tuĝce Demintaşşahin 2020 Vineet Mehta 2017 Total (95% CI) Heterogeneity: Tau" = 2.64; Chi" = 6	Experimental           Mean         SD         Tof           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         0.03         3.136           1.0853         0.5223         86.545         7.996           1.7.6, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         -0.11         0.0           6         0.11         0.0           6         0.11         0.0           10         10.611         2           8         0.55364         0.0           8         0.55208         10           98         65.208         10	SD         Total           752         6           542         6           057         12           471         5           734         6           818         7           735         6           627         8           627         8           608         10           542         8           417         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.0% 9.6% 9.2%	IV. Random. 95% cl:           2:13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]	Std. Mean Difference IV. Random, 95% CI
Study or Subgroup Anthory Taghogho Edwiver 2021 Chenije 62023 Dan Wang-1 2024 Khadegia Khan 2019 Noreen Samad 2018 Princewill Ikechtikwa Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Syeda Madiha 2021 Tong Guan 2021 Tugge DemitaşŞahin 2020 Vineet Mehta 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 6 Test for overall effect Z = 4.43 (P < 0	Experimental           Mean         SD         Tof           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         0.03         3.136           1.0853         0.5223         86.545         7.996           1.7.6, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         0.11         0.0           6         0.11         0.11           6         0.11         0.11           10         10.611         2           8         14.13         0           10         10.611         2           8         0.55384         0.0           8         65.208         10           38         8         15.208	SD         Total           752         6           542         6           557         12           471         5           734         6           318         7           318         7           6027         8           408         100           542         8           4117         8	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.6% 9.2%	IV. Random. 95% cl:           2:13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]	Std. Mean Difference IV. Random, 95% CI
Study or Subgroup Anthony Taghogho Eduvière 2021 Chenije 62 2023 Dan Wang-1 2024 Knadegia Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajiad Makhdoomi 2024 Syeda Madha 2021 Tong Guan 2021 Tong G	Experimental Mean SD Tol 32.6 9.0876 83.09 10.341 17.68 1.62 13.1392 1.2804 12.7595 2.7 1.0277 0.2069 0.49 0.0245 2.7 12.639 1.254 8.8 0.72 1.0633 0.5223 86.545 7.996 1.766, df = 11 (P < 0.0000 0.00001) Experimental Mean SD Tot	Image         Mean           6         1587         4           6         43.796         7           10.141         3         5           8.6263         0.7         6           7         0.4953         0.1           6         4.7165         1.1           6         0.71         0.4953         0.1           6         8.14.13         0         10.1611         2           8         14.13         0         10.611         2           8         0.55364         0.6         88           11); F = 82%         10         10         10.611           8         0.55384         0.6         30         10           8         0.55384         0.6         30         10           9         0.55384         0.6         30         10           88         11; F = 82%         10         10         10           9         0.65384         0.6         30         10           9         0.65384         0.6         30         10	SD         Total           752         6           542         6           557         12           471         5           318         7           735         6           0.04         6           327         8           408         10           542         88           \$417         8           \$57         5           \$6         5           \$75         5           \$6         5           \$608         10           5         88           \$17         8           \$27         5           \$28         5           \$27         5           \$27         8           \$417         8	8.7% 7.1% 9.4% 6.6% 7.5% 9.5% 9.5% 9.5% 9.2% 100.0%	IV. Random. 95% cl:           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.657 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [-0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]           2.36 [1.32, 3.40]           Std. Mean Difference           IV. Random. 95% cl	Std. Mean Difference IV. Random, 95% Cl
Study or Subgroup         Anthory Taghogho Eduvière 2021         Chenije 62 2023         Dan Wang-1 2024         Khadeeja Khan 2019         Noreen Samad 2018         Princewill Ikechtukwu Ugwu 2022         Punetet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tugge Demitsgahin 2020         Vineet Mehta 2017         Total (95% CI)         Heterogeneity: Tau" = 2.64; Chi" = 6         Test for overall effect: Z = 4.43 (P < CI	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           8.8         0.72         1.2634         1.264           2.0.03         3.136         1.0853         0.5223           86.545         7.996         1.76, df = 11 (P < 0.0000	al Mean 6 15.87 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 7 0.4963 0.1 6 0.11 0.0 6 8.3 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.55364 0.0 8 0.55208 10 38 11); F = 82% Contra al Mean 2 13.243 2.	SD         Total           752         6           542         6           057         12           771         5           334         6           618         7           735         6           627         8           008         10           542         8           417         8           \$         88           \$         88           \$         92           12         12	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.6% 9.2% 100.0%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.89 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.06, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.35 [0.32, 2.47]           2.36 [1.32, 3.40]           Std. Mean Difference IV. Random, 95% C1           -3.07 [-4.31, -1.83]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthomy Taghogho Eduvière 2021         Chenije 62 2023         Dan Wang-1 2024         Knadeeja Khan 2019         Noreen Samad 2018         Princesvill kechtukvu Ugwu 2022         Puneet Rinwa 2013         Sajiad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tugge DemitaşŞahin 2020         Vineet Mehta 2017         Total (95% C)         Heterogenely: Tau" = 2.64; Chi" = 6         Test for overall effect: Z = 4.43 (P < C	Experimental           Mean         SD         Tot           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           12.639         1.254         0.33         3.136           1.0853         0.5223         86.545         7.996           41.76, df = 11 (P < 0.00000)	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 6 0.11 0.0 8 0.55364 0.0 8	SD         Total           752         6           542         6           557         12           471         5           318         7           735         6           507         8           827         8           408         10           542         8           \$         88           \$         88           \$         92           102         12           337         6	8.7% 7.1% 9.4% 6.6% 7.5% 9.5% 9.5% 9.0% 9.6% 9.2% 100.0%	IV. Random. 95% c1           2.13 (0.69, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [-0.54, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]           2.36 [1.32, 3.40]           Std. Mean Difference           IV. Random. 95% c1           -3.07 [-4.31, -1.83]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthory Taghogho Eduvière 2021         Chenije 62 2023         Dan Wang-1 2024         Khadeeja Khan 2019         Noreen Samad 2018         Princewill Ikechtukwu Ugwu 2022         Punetet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tugge Demitsgahin 2020         Vineet Mehta 2017         Total (95% CI)         Heterogeneity: Tau" = 2.64; Chi" = 6         Test for overall effect: Z = 4.43 (P < CI	Experimental           Mean         SD         Tot           32.6         9.0876         13.1392         1.2804           13.1392         1.2804         12.799         2.7           1.0277         0.2069         0.49         0.0245           8.8         0.72         1.2634         1.264           1.0653         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	al Mean 6 15.87 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 7 0.4963 0.1 6 0.11 0.0 6 8.3 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.55364 0.0 8 0.55208 10 38 11); F = 82% Contra al Mean 2 13.243 2.	SD Total 752 6 542 6 557 12 471 5 734 6 818 7 735 6 6 27 8 408 10 827 8 417 8 88 417 8 88 50 Total 92 12 137 6 36 6	8.7% 7.1% 9.4% 6.6% 7.5% 8.7% 9.5% 9.5% 9.5% 9.6% 9.2% 100.0%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.89 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.06, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.35 [0.32, 2.47]           2.36 [1.32, 3.40]           Std. Mean Difference IV. Random, 95% C1           -3.07 [-4.31, -1.83]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthory Taghogho Eduvière 2021         Chenije 62023         Dan Wang-1 2024         Khadeeja Khan 2019         Noreen Samad 2018         Princevill Ikechukwu Ugwu 2022         Puneet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madina 2021         Tong Guan 2021         Tudye Demitasgaahin 2020         Vineet Mehta 2017         Total (95% CI)         Heterogeneity: Tau" = 2.64; Chi" = 6         Test for overall effect: Z = 4.43 (P < C	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         1.27595         2.7           1.0277         0.2069         2.7         1.0277           1.0277         0.2069         2.7         1.0277           1.0353         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           10.141         3         5           8.6263         0.7         6           7         0.4953         0.1           6         0.7165         1.1           7         0.4953         0.1           6         0.11         0.0           6         8.3         8           0.10         10.611         2           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.52364         0.0           8         0.52364         0.0           8         0.52364         0.0           8         0.52364         0.0           8         6.5208         10           8         9.615         1.1           7         2.8854         0.8           8         9.015         1.1           7         2.8854         0.41	SD Total 752 6 542 6 557 12 471 5 6 18 7 735 6 0.04 6 327 8 408 10 542 8 408 10 542 8 408 10 542 8 417 8 8 8 8 8 9 50 Total 192 12 137 6 36 6 37 7 47 6	8.7% 7.1% 9.4% 6.6% 7.5% 9.5% 9.5% 9.5% 9.2% 100.0% Weight 8.2% 1.8% 5.1% 7.8%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.65 [1.37, 6.40]           3.65 [1.34, 6.97]           0.55 [0.64, 1.68]           1.42 [5.25, 0.29]           3.23 [1.81, 4.65]           1.35 [0.32, 2.47]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           3.07 [4.31, -183]           9.14 [1.374, 4.54]           -3.81 [5.99, -1.63]           -2.00 [-3.36, -0.63]           -2.00 [-3.8, -0.63]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup Anthony Taghogho Eduvière 2021 Chenije de 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Pruneet Rinwa 2013 Sajad Makhdoomi 2024 Syeda Madiha 2021 Tudge Dernitaşşahin 2020 Vineet Henta 2017 Total (95% CI) Helerogeneihy Tau" = 2.64; Chi" = 6 Test for overall effect Z = 4.43 ( $P < O$ (D) Study or Subgroup Dan Wang-1 2024 Ismaeet Bin-Jaliah 2021 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024	Experimental           Mean         SD         Tof           32.6         9.0876         9.0341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           1.053         1.254         2.003         3.136           1.0853         0.5223         86.545         7.996           1.766, df = 11 (P < 0.0000	al Mean 6 15.87 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 6 0.11 0.0 6 8.3 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.55364 0.0 8 0.55364 0.0 8 0.55364 0.0 8 0.55364 0.0 8 0.53364 0.0 8 0.53364 0.0 8 0.53364 0.0 8 0.53164	SD Total 752 6 557 12 771 5 734 6 318 7 735 6 0.04 6 327 8 408 10 542 8 417 8 88 417 8 88 417 8 88 417 6 6 37 7 6	8.7% 7.1% 9.4% 9.4% 8.7% 5.1% 9.5% 9.5% 9.5% 9.5% 9.2% 100.0%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.657 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.06, 9.73]           0.52 [0.64, 1.68]           3.23 [1.81, 4.65]           1.52 [0.32, 2.47]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           3.37 [4.4], 1.83]           -9.14 [+13.74, -4.54]           -3.37 [4.38], 9.163]           -2.00 [-3.36, -0.63]           -1.61 [-2.99, 0.24]           -3.07 [-2.01, 1.08]	Std. Mean Difference N. Random, 95% Cl
Anthory Taghogho Edwiver 2021 Chenije 62 0203 Dan Wang-1 2024 Khadeja Khan 2019 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Syeda Madha 2021 Tong Guan 2021 Tuge Demitaşşahin 2020 Vineet Mehta 2017 Total (95% CI) Heterogeneity: Tau" = 2.64; Chi" = 6 Test for overall effect Z = 4.43 (P < C (D) Study of Subgroup Dan Wang-1 2024 Ismaee Bin-Jaliah 2021 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Sameha Merzoug 2014	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         1.31392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           1.0633         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           6         0.47165         1.1           6         0.11         0.0           6         8.14.13         0           0         10.611         2           8         0.55364         0.0           8         0.55364         0.0           88         11); I" = 82%         10           88         12         13.243         2           2         13.243         2         2.3243         0.8           6         2.3703         0.1         6         8.9615         1.1           7         2.8654         0.8         0.41         0.6         5.28         0.0           6         5.241         0.0         5         8.67.24         0.0	<u>SD Total</u> 752 6 157 12 157 157 12 157 157 12 157 157 12 157 157 157 157 157 157 157 157 157 157	8.7% 7.1% 8.6% 8.7% 9.5% 9.5% 9.0% 9.2% 100.0% 100.0%	IV. Random. 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.657 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [-0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]           2.36 [1.32, 3.40]           Std. Mean Difference           IV. Random. 955 C1           -3.07 [-4.31, -1.83]           -2.04 [-3.47, 4.54]           -38 [-5.99, -1.63]           -2.07 [-3.48, -0.69]           -1.61 [-2.89, -0.24]           -0.07 [-1.20, 1.06]           -2.43 [-4.28, -0.59]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthony Taghogho Eduvière 2021         Chenije 62 2023         Dan Wang-1 2024         Khadeeja Khan 2019         Noreen Samad 2018         Princewill Ikechukwu Ugwu 2022         Punetef Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuğe DemitaşŞahin 2020         Vineel Mehta 2017         Total (95% CI)         Heterogeneily: Tau" = 2.64; Chi" = 6         Test for overall effect. Z = 4.43 (P < C	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           8.8         0.72         1.2634         1.0624           8.8         0.72         1.2639         1.254           2.003         3.136         1.0653         0.5223           86.545         7.996         1.76, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         15.87         4           6         43.786         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           6         0.716         0.063           6         0.11         0.0           6         8.3         8           10         10.611         2           8         0.55364         0.0           8         0.55284         10           38         1.1         1.82%           11); IP = 82%         10           38         6.208         10           38         6.3733         2.           6         2.3703         0.1           7         2.8954         0.8           8         0.41         0.           6         5.28         (           5         8.6741         0.           6         150.491         11.	<u>SD Total</u> <u>SD Total <u>SD Total</u> <u>SD Tot</u></u>	8.7% 7.1% 9.4% 6.6% 8.7% 5.1% 9.5% 9.5% 9.5% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.5% 9.5% 9.5% 9.0% 9.18% 8.7% 8.7% 8.7% 8.7% 8.6%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.50 [0.32, 2.47]           2.36 [1.32, 3.40]           V. Random, 95% C1           -3.07 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.81 [+5.98, -1.63]           -2.00 [+3.36, -0.63]           -1.69, -0.24]           -3.81 [+2.98, -0.24]           -0.07 [+1.20, 1.06]           -3.34 [+2.88, -0.58]           -3.34 [+2.88, -0.58]           -3.34 [+3.38, -1.38]	Std. Mean Difference N. Random, 95% Cl
Anthory Taghogho Eduvière 2021 Chenije 62 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechulwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Syeda Madha 2021 Tong Guan 2021 Total (95% CI) Helerogeneily. Tau" = 2.64; Chi" = 6 Test for overail effect. Z = 4.43 (P < C (D) Study or Subgroup Dan Wang-1 2024 Ismaeel Bin-Jaliah 2021 Noreen Samad 2018 Princewill Kechulwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Sameha Merzoug 2014 Sangeeta Pilkhwal San 2011 Siqi Ja 2023	Experimental           Mean         SD         Tof           32.6         9.0876         83.09         10.341           17.66         1.62         13.1392         1.2804           12.7595         2.7         1.0275         0.269           0.49         0.245         8.8         0.72           12.639         1.254         0.33         3.136           1.0853         0.5223         86.545         7.996           1.76, df = 11 (P ≤ 0.0000         0.00001)         1.1454         0.4887           1.1454         0.1129         3.39303         1.3138           1.1454         0.4887         0.1487           0.153         0.147         5.23         0.69           6.5687         0.8938         10.8914         11.192	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 6 0.11 0.0 8 0.55364 0.0 10 0.041 0.0 5 8.6741 ( 6 1.4054 0.2	SD         Total           SD         752         6           SD         752         6           SD         752         6           SD         734         6           SD         734         6           SD         735         6           SD         735         6           SD         764         88           SD         7643         88           SD         7643         6           SD         7643         6           SE         77         6           SD         7643         6           SE         88         6           SE         86         5           SE         86         5           SE         88         5           SE         7         16	8.7% 7.1% 9.4% 8.8% 8.7% 5.1% 9.5% 9.5% 9.5% 9.0% 9.2% 9.0% 9.2% 100.0%	IV. Random. 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [-0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           -1.35 [0.32, 2.47]           2.17 [0.86, 3.48]           2.36 [1.32, 3.40]           Std. Mean Difference           IV. Random, 95% c1           -3.07 [-4.31, -1.83]           -2.01 [-3.6, -0.63]           -1.61 [-2.99, -0.24]           -0.07 [-1.20, 1.06]           -0.07 [-1.20, 1.06]           -0.07 [-1.20, 1.06]           -3.38 [-5.39, -1.38]           -3.38 [-5.39, -1.38]           -3.38 [-5.39, -1.38]           -3.38 [-5.39, -1.38]           -3.38 [-5.39, -1.38]           -1.76 [-2.68, 0.93]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthony Taghogho Eduvière 2021         Chenije 62 2023         Dan Wang-1 2024         Khadeeja Khan 2019         Noreen Samad 2018         Princewill Ikechukwu Ugwu 2022         Punetef Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuğe DemitaşŞahin 2020         Vineel Mehta 2017         Total (95% CI)         Heterogeneily: Tau" = 2.64; Chi" = 6         Test for overall effect. Z = 4.43 (P < C	Experimental Mean         SD         Tot           32.6         9.0876         13.392         1.2804           13.1392         1.2804         12.7995         2.7           1.02779         0.2069         2.7         10.2779           1.0277         0.2069         3.136         1.264           2.033         3.136         1.254         2.03           1.0853         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6263 0.7 6 4.7165 1.1 6 0.11 0.0 8 0.55364 0.0 10 0.041 0.0 5 8.6741 ( 6 1.4054 0.2	SD         Total           SD         Total           542         6           542         6           157         12           734         6           6         27           8         88           417         8           9192         12           136         6           137         6           6         5           66         5           65         5           88         6           65         5           88         6           65         5           88         6           65         5           88         6           65         5	8.7% 7.1% 9.4% 6.6% 8.7% 5.1% 9.5% 9.5% 9.5% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.5% 9.5% 9.5% 9.0% 9.18% 8.7% 8.7% 8.7% 8.7% 8.6%	IV. Random, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.50 [0.32, 2.47]           2.36 [1.32, 3.40]           V. Random, 95% C1           -3.07 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.81 [+5.98, -1.63]           -2.00 [+3.36, -0.63]           -1.69, -0.24]           -3.81 [+2.98, -0.24]           -0.07 [+1.20, 1.06]           -3.34 [+2.88, -0.58]           -3.34 [+2.88, -0.58]           -3.34 [+3.38, -1.38]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthony Taghogho Eduvière 2021         Chenije 62023         Dan Wang-1 2024         Khadeej Khan 2019         Noreen Samad 2018         Princewill Ikechukwu Ugwu 2022         Punet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuge DemitaşŞahin 2020         Vineet Menta 2017         Total (95% CI)         Helerogeneity: Tau" = 2.64; Chr" = 6         Test for overall effect. Z = 4.43 (P < C	Experimental           Mean         SD         Tof           32.6         9.0876         8.3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           0.49         0.0245         8.8         0.72           1.053         1.254         2.033         3.136           1.0853         0.5223         86.545         7.996           1.766, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           6         0.71         0.0           6         0.11         0.0           6         8.3         8           0.11         0.0         10.811           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.5308         10           9         8.23703         0.1           6         2.3703         0.1           6         0.41         0.           6         5.28         0           6         5.28         1           6         5.241         1           6         5.2471         1	SD         Total           SD         752         6           S542         6         6           S167         12         6           S171         6         734         6           S181         7         7         318         7           S277         8         88         88           SD         Total         88           SD         Total         7           G         367         6         65           G65         6         65         6           G65         6         6         6           G72         16         94         8	8.7% 7.1% 8.94% 6.6% 8.7% 8.7% 9.5% 9.5% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0	IV. Randorn, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           3.07 [4.31, -183]           9.14 [1.3.74, 4.54]           -3.81 [-5.99, -1.63]           -0.07 [-1.20, 1.06]           -2.38 [4.5.99, -1.63]           -2.00 [-3.38, [-3.8], -0.83]           -1.81 [-2.89, -0.24]           -0.07 [-1.20, 1.06]           -3.38 [-5.39, -1.38]           -1.76 [-2.59, 0.94]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup Anthory Taghogho Eduvière 2021 Chenije de 2023 Dan Wang-1 2024 Khadeeja Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Pruneet Rinwa 2013 Sajiad Makhdoomi 2024 Syeda Madiha 2021 Tudge Demitaş§ahin 2020 Vineet Meha 2017 Total (95% CI) Heterogeneity: Tau" = 2.64; Chi" = 6 Test for overall effect Z = 4.43 (P < CI (D) Study or Subgroup Dan Wang-1 2024 Ismaeel Bin-Jaliah 2021 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajad Makhdoomi 2024 Sameha Merzoug 2014 Sameha Merzoug 2014 Sangete Pilkhwal Sah 2021 Tudge Demitaş§ahin 2020 Vineet Meha 2017 Tudge Demitaş§ahin 2020 Vineet Meha 2017 Yail Hou 2025	Experimental           Mean         SD         Tot           32.6         9.0876         3.03         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           4.8         0.72         2.63         1.254           2.003         3.136         1.0853         0.5223           86.545         7.996         4.6         0.72           1.76, df = 11 (P < 0.0000	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6226 0.7 6 4.7165 1.1 6 0.11 0.0 8 0.55364 0.0 8 0.5238 0.1 6 2.3703 0.1 6 2.3703 0.1 6 2.3703 0.1 6 8.9615 1.1 7 2.8854 0.8 6 0.241 0.2 8 65.728 ( 5 8.6741 0.0 5 8.6741 11. 6 1.50.491 11. 6 1.9049 11.2 8 0.8712 2.8 8 0.8712 2. 8 0.8712 2. 8 0.8712 2. 8 19.813 1.5 8 1.2708 0.8 1.2708	SD         Total           5/52         6           5/52         6           5/54         6           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         12           5/57         12           5/57         12	8.7% 7.1% 9.4% 8.6% 8.7% 9.5% 9.5% 9.5% 9.5% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0	IV. Randorn, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.87 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.06, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.35 [0.32, 2.47]           2.36 [1.32, 3.40]           V. Random, 95% C1           -3.07 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.07 [4.31, -1.83]           -9.04 [+1.20, 1.06]           -2.00 [-3.36, -0.63]           -3.81 [-5.98, -1.63]           -0.07 [+1.20, 1.06]           -3.38 [-5.39, -1.38]           -1.6 [-2.69, -0.45]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.57]           -4.31 [-5.2, -0.73]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthory Taghogho Eduvière 2021         Chenije 62023         Dan Wang-1 2024         Khadee Athan 2018         Princewill Ikechukwu Ugwu 2022         Puneet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuge DemitaşŞahin 2020         Vineet Mehta 2017         Total (95% Cl)         Heterogeneity: Tau" = 2.64; Chi" = 6         Test for overall effect. Z = 4.43 (P < Cl)	Experimental           Mean         SD         Tot           32.6         9.0876         3.03         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           4.8         0.72         2.63         1.254           2.003         3.136         1.0853         0.5223           86.545         7.996         4.6         0.72           1.76, df = 11 (P < 0.0000	Image         Mean           6         15.87         4           6         15.87         4           6         43.796         7           12         10.141         3           5         8.6263         0.7           6         4.7165         1.1           6         0.41         0.0           6         8.3         8           0.11         0.0         10.611         2           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.55364         0.0           8         0.57364         0.0           8         0.57364         0.0           8         0.57364         0.0           8         0.57373         0.1           6         2.3703         0.1           6         0.411         0.           6         5.28         0.           6         1.4054         0.2           8         8.8712         2.           8         5.4708         <	SD         Total           5/52         6           5/52         6           5/54         6           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         16           5/57         12           5/57         12           5/57         12	8.7% 7.1% 9.4% 6.6% 8.7% 5.75% 9.5% 9.5% 9.5% 9.8% 9.8% 9.8% 9.8% 9.8% 9.8% 5.1% 7.8% 8.7% 5.51% 8.7% 8.7% 8.7% 8.8% 8.8% 8.8%	IV. Randorn, 95% cl.           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.57 [1.49, 5.64]           2.56 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [-0.64, 1.68]           -1.42 [-2.55, -0.29]           3.23 [1.81, 4.65]           1.35 [0.23, 2.47]           2.17 [0.86, 3.48]           2.36 [1.32, 3.40]           Stid. Mean Difference           IV. Random, 95% Cl.           -3.07 [-4.31, -1.83]           -9.14 [1.37, 4.454]           -3.81 [-5.99, -1.63]           -2.03 [-3.8, 0.24]           -0.07 [-1.20, 1.06]           -3.81 [-5.99, -0.24]           -0.07 [-1.20, 1.06]           -3.81 [-5.99, -0.24]           -0.07 [-1.20, 1.06]           -3.81 [-5.99, -0.24]           -0.07 [-1.20, 1.06]           -3.81 [-5.99, -0.24]           -0.07 [-1.20, 1.06]           -3.81 [-5.99, -0.24]           -0.07 [-1.20, 1.06]           -3.38 [-5.39, -0.34]           -1.61 [-2.99, -0.24]           -1.61 [-2.99, -0.24]           -1.65 [-2.90, -0.32]           -1.65 [-2.90, -0.32]           -1.65 [-2.90,	Std. Mean Difference N. Random, 95% Cl
Anthory Taghogho Edwiver 2021 Chenije 62 2023 Dan Wang-1 2024 Knadegia Khan 2019 Noreen Samad 2018 Princewill Ikechukwu Ugwu 2022 Puneet Rinwa 2013 Sajiad Makhdoomi 2024 Syeda Madha 2021 Tong Guan 2021 Tong Guan 2021 Tong Guan 2021 Total (95% CI) Heterogenely: Tau'e 2.64; Chi''e 6 Test for overail effect Z = 4.43 (P < C (D) Study of Subgroup Dan Wang-1 2024 Ismael Bin-Jaliah 2021 Noreen Samad 2018 Princer Rinwa 2013 Sajiad Makhdoomi 2024 Sameha Merzoug 2014 Samgeta Pilkhwal San 2011 Siqi Ja 2023 Syeda Madiha 2021 Tuge DemitaşŞahin 2020 Vineet Meha 2017 Yali Hou 2025 Yuecho Guan 2021 Total (95% CI)	Experimental           Mean         SD         Tof           32.6         9.0876         3.09         10.341           17.66         1.62         -         13.1392         1.2804           12.7595         2.7         1.0277         0.2069         0.49         0.0245           0.49         0.0245         6.8         0.72         1.0277         0.2069           1.0653         0.5223         3.136         -         1.0853         0.5223           86.545         7.996         -         -         -         -           1.766, df = 11 (P < 0.0000	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6228 0.7 6 4.7165 1.1 6 0.11 0.0 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.5281 0 6 2.3703 0.1 6 1.4054 0.2 8 0.8712 0 5 8.6741 0 6 1.4054 0.2 8 0.8712 0 1 1.33537 0.2 6	SD         Total           752         6           0157         12           138         7           735         6           0.4         6           0.27         8           808         10           9192         12           927         8           910         117           912         12           913         6           914         88           915         117           916         6           917         12           918         7           9192         12           9192         12           9192         12           9193         12           9194         8           9195         12           9194         8           912         12           913         12           914         8           915         12           916         12           917         12           918         12           919         10	8.7% 7.1% 9.4% 8.6% 8.7% 9.5% 9.5% 9.5% 9.5% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0% 9.0	IV. Randorn, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.37, 6.40]           3.87 [1.37, 6.40]           3.657 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.06, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.35 [0.32, 2.47]           2.36 [1.32, 3.40]           V. Random, 95% C1           -3.07 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.07 [4.31, -1.83]           -9.04 [+1.20, 1.06]           -2.00 [-3.36, -0.63]           -3.81 [-5.98, -1.63]           -0.07 [+1.20, 1.06]           -3.38 [-5.39, -1.38]           -1.6 [-2.69, -0.45]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.56]           -3.24 [-4.28, -0.57]           -4.31 [-5.2, -0.73]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthory Taghogho Edwiver 2021         Chenije 62 2023         Dan Wang-1 2024         Khadegi Khan 2018         Princewill Ikechtikkwu Ugwu 2022         Puneet Rivma 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuge Demitaş Şahin 2020         Vineet Mehta 2017         Total (95% Cl)         Heterogeneity: Tau" = 2.64; Chi" = 6         Test for overall effect: Z = 4.43 (P < Cl	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           1.0277         0.2069         2.7         1.0277           1.0277         0.2069         3.136         1.263           2.03         3.136         1.264         2.03           1.0653         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6228 0.7 6 4.7165 1.1 6 0.11 0.0 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.5281 0 6 2.3703 0.1 6 1.4054 0.2 8 0.8712 0 5 8.6741 0 6 1.4054 0.2 8 0.8712 0 1 1.33537 0.2 6	SD         Total           752         6           0157         12           138         7           735         6           0.4         6           0.27         8           808         10           9192         12           927         8           910         117           912         12           913         6           914         88           915         117           916         6           917         12           918         7           9192         12           9192         12           9192         12           9193         12           9194         8           9195         12           9194         8           912         12           913         12           914         8           915         12           916         12           917         12           918         12           919         10	8.7% 7.1% 9.4% 8.6% 8.7% 9.5% 9.5% 9.5% 9.5% 9.0% 9.6% 9.0% 9.6% 9.0% 100.0% 100.0%	IV. Randorn, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.52 [0.23, 2.47]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           3.30 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.07 [+4.31, -1.83]           -9.14 [+13.74, -4.54]           -0.07 [+1.20, 1.06]           -3.38 [+5.39, -1.38]           -1.61 [>2.89, 0.24]           -0.07 [+1.20, 1.06]           -2.34 [+2.8, 0.59]           -3.34 [+3.9, 0.14]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+3.9, 0.14]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+3.9, 0.44]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+2.8, 0.59]           -3.34 [+3.9, 0.44]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.62]	Std. Mean Difference N. Random, 95% Cl
Study or Subgroup         Anthony Taghogho Eduvière 2021         Chenjie Ge 2023         Dan Wang-1 2024         Khadeeja Khan 2018         Princewill Ikechukwu Ugwu 2022         Puneet Rinwa 2013         Sajad Makhdoomi 2024         Syeda Madiha 2021         Tong Guan 2021         Tuge DemitaşŞahin 2020         Vineet Metha 2017         Total (95% CI)         Heterogeneily: Tau" = 2.64; Chi" = 6         Test for overall effect Z = 4.43 (P < CI)	Experimental           Mean         SD         Tot           32.6         9.0876         3.09         10.341           17.68         1.62         13.1392         1.2804           12.7595         2.7         1.0277         0.2069           1.0277         0.2069         2.7         1.0277           1.0277         0.2069         3.136         1.263           2.03         3.136         1.264         2.03           1.0653         0.5223         86.545         7.996           1.76, df = 11 (P < 0.0000	tal Mean 6 1587 4 6 43.796 7 12 10.141 3 5 8.6228 0.7 6 4.7165 1.1 6 0.11 0.0 8 14.13 0 10 10.611 2 8 0.55364 0.0 8 0.5281 0 6 2.3703 0.1 6 1.4054 0.2 8 0.8712 0 5 8.6741 0 6 1.4054 0.2 8 0.8712 0 1 1.33537 0.2 6	SD         Total           752         6           0157         12           138         7           735         6           0.4         6           0.27         8           808         10           9192         12           927         8           910         117           912         12           913         6           914         88           915         117           916         6           917         12           918         7           9192         12           9192         12           9192         12           9193         12           9194         8           9195         12           9194         8           9194         8           912         94           912         94           912         94           912         94           912         94           912         91           914         91           915         91	8.7% 7.1% 9.4% 8.6% 8.7% 9.5% 9.5% 9.5% 9.5% 9.0% 9.6% 9.0% 9.6% 9.0% 100.0% 100.0%	IV. Randorn, 95% c1           2.13 (0.59, 3.67)           4.01 [1.75, 6.27]           2.98 [1.76, 4.20]           3.89 [1.37, 6.40]           3.87 [1.49, 5.64]           2.66 [1.03, 4.09]           6.40 [3.08, 9.73]           0.52 [0.64, 1.68]           1.42 [2.55, 0.29]           3.23 [1.81, 4.65]           1.52 [0.23, 2.47]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           2.36 [1.32, 3.40]           3.30 [4.31, -1.83]           -9.14 [+13.74, -4.54]           -3.07 [+4.31, -1.83]           -9.14 [+13.74, -4.54]           -0.07 [+1.20, 1.06]           -3.38 [+5.39, -1.38]           -1.61 [>2.89, 0.24]           -0.07 [+1.20, 1.06]           -2.34 [+2.8, 0.59]           -3.34 [+3.9, 0.14]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+3.9, 0.14]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+3.9, 0.44]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.59]           -3.34 [+2.8, 0.59]           -3.34 [+3.9, 0.44]           -0.07 [+1.20, 1.06]           -2.44 [+2.8, 0.62]	Std. Mean Difference N. Random, 95% Cl

OFT, time spent in the central area of OFT, TST immobility time, sucrose preference in SPT, time spent in the open arms of the EPM, GSH, SOD, CAT, MDA, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and BDNF, to assess publication bias. The results indicated that there is some

publication bias in the study (see Supplementary Figures S2-S3). Despite the positive findings, further research is needed to validate these results due to the potential publication bias in this meta-analysis.

## (A)

	Expe	erimenta	I	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Chenjie Ge 2023	442.38	57.25	6	1,109.99	113.33	6	5.4%	-6.86 [-10.40, -3.33]	
Khadeeja Khan 2019	174.72	12.902	5	254.72	11.136	5	5.4%	-6.00 [-9.59, -2.40]	
_ongfei Du 2024	1,784.8	321.1	6	2,240	206	6	8.8%	-1.56 [-2.92, -0.19]	
likhil Santosh Kore 2024	385.43	159.86	8	537.57	104.28	8	9.2%	-1.07 [-2.13, 0.00]	-
Diusegun Adebayo Adeoluwa 2023	205.97	6.503	6	255.33	15.032	6	7.5%	-3.93 [-6.16, -1.71]	
Princewill Ikechukwu Ugwu 2022	2.1835	0.7368	7	6.7221	1.2655	7	7.7%	-4.10 [-6.18, -2.03]	
Puneet Rinwa 2013	47.361	12.044	6	126.741	10.908	6	5.8%	-6.38 [-9.69, -3.06]	
Sangeeta Pilkhwal Sah 2011	44	24.005	6	130	22.045	6	7.8%	-3.44 [-5.47, -1.42]	
Shirin Sadighparvar 2020	226.22	7.9	6	294.79	5.05	6	4.0%	-9.55 [-14.34, -4.75]	
Tong Guan 2021	219.2	9.33	10	349.28	9.75	10	4.2%	-13.06 [-17.66, -8.46]	
′ali Hou 2025	53.532	22.841	12	117.363	10.095	12	8.9%	-3.49 [-4.83, -2.15]	-
/anrong Yang 2022	264.65	13.16	10	355.37	14.25	10	7.3%	-6.33 [-8.69, -3.98]	-+
/UANYUAN LI 2024	5.0038	0.4595	10	6.1945	0.5677	10	9.1%	-2.21 [-3.37, -1.05]	+
Zihu Tan 2022	2.2792	1.1189	6	3.7585	1.5469	6	9.0%	-1.01 [-2.25, 0.22]	-
Total (95% CI)			104			104	100.0%	-4.16 [-5.39, -2.93]	•
Heterogeneity: Tau <sup>2</sup> = 3.97; Chi <sup>2</sup> = 74.	0.4  df = 1.3	R/P < 0.0	0001)	I <sup>2</sup> = 82%				-	-20 -10 0 10 20

## **(B)**

	Expe	rimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Chenjie Ge 2023	249.49	36.67	6	661.08	65.38	6	4.7%	-7.17 [-10.85, -3.49]	
Fang Ke 2019	152.73	34.17	9	166.65	65.82	9	12.1%	-0.25 [-1.18, 0.68]	
Khadeeja Khan 2019	26.827	2.0281	5	36.078	2.1578	5	7.1%	-3.99 [-6.56, -1.42]	
Longfei Du 2024	1,994.9	398	6	2,931.8	347.6	6	10.0%	-2.31 [-3.91, -0.72]	
Mikhil Santosh Kore 2024	55.433	4.0277	8	64.683	10.559	8	11.7%	-1.09 [-2.17, -0.02]	
Olusegun Adebayo Adeoluwa 2023	12.5194	2.5759	6	18.2251	2.2356	6	10.2%	-2.18 [-3.74, -0.63]	
Princewill Ikechukwu Ugwu 2022	2.2368	0.4606	7	2.7038	0.5813	7	11.6%	-0.83 [-1.94, 0.28]	
Puneet Rinwa 2013	115.93	11.439	6	210.65	14.55	6	5.1%	-6.68 [-10.13, -3.23]	
Sangeeta Pilkhwal Sah 2011	12.34	5.1439	6	69.58	40.906	6	10.6%	-1.81 [-3.25, -0.38]	
SRIRAM BS 2019	26.588	1.171	6	33.021	0.596	6	5.4%	-6.39 [-9.71, -3.07]	
YUANYUAN LI 2024	18.883	3.401	10	30.055	5.188	10	11.3%	-2.44 [-3.66, -1.22]	-
Total (95% CI)			75			75	100.0%	-2.49 [-3.48, -1.50]	•
Heterogeneity: Tau <sup>2</sup> = 1.89; Chi <sup>2</sup> = 42	43, df = 10	(P < 0.00	)001); P	<sup>2</sup> = 76%					
Test for overall effect: Z = 4.92 (P < 0.		,							-10 -5 0 5 10
	/								Favours [experimental] Favours [control]

#### Favours [experimental] Favours [control]

## **(C)**

	Expe	erimental		С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chenjie Ge 2023	112.85	21.97	6	482.36	41.17	6	2.6%	-10.34 [-15.51, -5.17]	
Longfei Du 2024	1,984.4	276.1	6	2,748.6	596.5	6	11.1%	-1.52 [-2.87, -0.17]	
Mikhil Santosh Kore 2024	316.47	135.85	8	378.19	182.43	8	12.5%	-0.36 [-1.35, 0.63]	
Sangeeta Pilkhwal Sah 2011	41	17.146	6	71.65	24.495	6	11.3%	-1.34 [-2.64, -0.03]	
Shirin Sadighparvar 2020	125.52	7.33	6	184.52	7.34	6	4.2%	-7.42 [-11.22, -3.63]	
Tong Guan 2021	31.795	2.826	10	42.116	4.772	10	11.6%	-2.52 [-3.76, -1.28]	
Yali Hou 2025	12.542	3.977	12	24.88	5.5575	12	12.1%	-2.47 [-3.57, -1.36]	-
Yanrong Yang 2022	194.19	20.64	10	266.28	17.44	10	10.4%	-3.61 [-5.14, -2.09]	-+
YUANYUAN LI 2024	21.556	3.027	10	24.842	2.749	10	12.6%	-1.09 [-2.04, -0.13]	*
Zihu Tan 2022	2.1794	1.771	6	3.8955	1.477	6	11.6%	-0.97 [-2.20, 0.26]	-*-
Total (95% CI)			80			80	100.0%	-2.17 [-3.09, -1.24]	•
Heterogeneity: Tau <sup>2</sup> = 1.53; Chi	<sup>2</sup> = 39.30,	df = 9 (P	< 0.000	1); I <sup>2</sup> = 77	'%				
Test for overall effect: Z = 4.58 (	P < 0.000	01)							-10 -5 0 5 10
									Favours [experimental] Favours [control]
GURE 8									
orest plot for the effect of	querceti	n on th	e infla	mmator	v cvtok	ines (	A) TNF-	a. (B)    -6. (C)    -16	

### 3.6 Subgroup analysis

Due to the high heterogeneity among the meta-analyses, we further conducted subgroup analyses of all behavioral tests and biochemical markers according to animal species, dose of quercetin intervention, and duration of treatment. Subgroup analysis demonstrated that, compared to the control group, quercetin

administration at a dose of ≥60 mg/kg significantly increased the total distance traveled in the open field test (OFT) (SMD = 1.88; 95% CI = [0.63, 3.12]; p = 0.003;  $I^2$  = 59%). Conversely, no statistically significant differences were observed in the total distance traveled in the OFT at doses of  $\leq 10$  mg/kg or 10-60 mg/kg. The influence of shorter treatment durations (≤1 week) on total distance traveled was not significant (SMD = 0.97; 95% CI = [-0.29, 2.24]; p = 0.13; I<sup>2</sup> =

## (A)

	Exp	erimental	1	(	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Tota	Weight	t IV, Random, 95% CI	IV, Random, 95% CI
Chenjie Ge 2023	0.22977	0.02382	6	0.18565	0.01806	6	10.6%	1.93 [0.46, 3.40]	
Fang Ke 2019	1.09382	0.2156	3	0.52877	0.1518	3	5.3%	2.42 [-0.41, 5.26]	
Francisco Donoso 2020	337.08	221.61	10	285.42	209.09	12	14.0%	0.23 [-0.61, 1.07]	+
Guoli Wang 2021	73.459	24.458	6	39.748	28.625	6	11.7%	1.17 [-0.10, 2.44]	+
Mikhil Santosh Kore 2024	107.085	10.875	8	108.398	5.9538	8	13.3%	-0.14 [-1.12, 0.84]	+
Mingyan Wang 2024	0.862	0.0426	3	0.4015	0.0274	3	0.6%	10.29 [0.23, 20.35]	
Princewill Ikechukwu Ugwu 2022	3.4696	1.2549	7	1.4162	0.3167	7	11.0%	2.10 [0.71, 3.49]	+
Shirin Sadighparvar 2020	0.82473	0.02182	6	0.77891	0.03818	6	11.4%	1.36 [0.05, 2.67]	+-
SRIRAM BS 2019	27.094	1.629	6	16.636	0.474	6	3.1%	8.05 [3.96, 12.13]	
Yanrong Yang 2022	0.9282	0.0594	10	0.8457	0.0718	10	13.3%	1.20 [0.23, 2.17]	-
Zhong-Xuan Ma 2021	0.85959	0.0297	3	0.58973	0.1352	3	5.8%	2.21 [-0.46, 4.87]	
Total (95% CI)			68			70	100.0%	1.46 [0.67, 2.26]	•
Heterogeneity: Tau <sup>2</sup> = 0.98; Chi <sup>2</sup> = 2	29.27, df = 1	10 (P = 0.0	001); I <sup>z</sup> :	= 66%					-20 -10 0 10 20
Test for overall effect: Z = 3.62 (P =	0.0003)								-20 -10 0 10 20 Favours [experimental] Favours [control]
<b>(B)</b>									
	Expe	erimental		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Francisco Donoso 2020	1.2162	1.1166	10	2.6479	2.8468	12	14.7%	-0.61 [-1.48, 0.25]	1
Mikhil Santosh Kore 2024	237.1	82.279	8	368	185.52	8	14.0%	-0.86 [-1.90, 0.18]	-
Mingyan Wang 2024	158.67	35.27	8	286.62	52.75	8	12.1%	-2.70 [-4.15, -1.24]	+
Mustajab Quraishi 2018	69.867	2.1996	6	129.251	2.1996	6	0.6%	-24.92 [-37.14, -12.70]	

12.7%

12.9%

72 100.0%

7.5%

12

5

6 12.6%

8 13.0%

-1.88 [-3.22, -0.55]

-3.27 [-4.57, -1.98]

-4.18 [-6.84, -1.52]

-1.53 [-2.89, -0.18]

-2.02 [-3.29, -0.75]

-2.12 [-3.10, -1.14]

-50

-25

Ó

Favours [experimental] Favours [control]

6.8445

279.41

86.437

31.33

13,584.5 2,263.9

12

5

6

8

70

1.7234

41.604

2.9471

20.637

73%). In contrast, longer treatment durations (2-4 weeks)							
significantly increased the total distance traveled (SMD = 2.39;	5						
95% CI = $[0.52, 4.25]$ ; p = 0.01; $I^2$ = 85%). In subgroup analyses							
by species, treatment with quercetin significantly increased the total							
distance traveled in rats (SMD = 1.44; 95% CI = [0.46, 2.43]; p = 0.004;	t						
$I^2 = 83\%$ ), whereas no significant effect was observed in inbred mice							
(SMD = -0.06; 95% CI = [-1.19, 1.07]; p = 0.92). Detailed results of the	1						
subgroup analyses are shown in Supplementary Table S1.							

3 897 1 1 488

158.83 28.232

59.737 9.5359

9,864.6 965.63

16.161

Heterogeneity: Tau<sup>2</sup> = 1.52; Chi<sup>2</sup> = 33.67, df = 8 (P < 0.0001); l<sup>2</sup> = 76%

3.5822

Forest plot for the effect of quercetin on BDNF and CORT levels. (A) BDNF; (B) CORT.

## 4 Discussion

Princewill Ikechukwu Ugwu 2022

Test for overall effect: Z = 4.23 (P < 0.0001)

Puneet Rinwa 2013

Tanveer Singh 2017

Total (95% CI)

FIGURE 9

Sameha Merzoug 2014

Tuğçe DemirtaşŞahin 2020

In this meta-analysis, we summarized the evidence from 52 published animal studies, which investigated the effects of quercetin supplementation on antidepressant effects across various behavioral and biochemical parameters. The results indicate that quercetin significantly affected animal behavior measures, including immobility time and swimming time in the FST, total distance traveled, time spent in the central area, and the number of entries into the central area in the OFT, immobility time in the TST, sucrose preference in the SPT, the number of entries into the open arms, time spent in the open arms, and time spent in the closed arms in the EPM, as well as biochemical markers such as GSH, SOD, CAT, MDA, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , BDNF, and CORT. However, no significant effect was found on the number of standing episodes in the OFT.

This study shows that, compared to the control group, quercetin significantly increased sucrose preference in the sucrose preference test, reduced immobility time in the forced swimming test (FST) and tail suspension test (TST), and decreased time spent in the closed arms in the elevated plus maze (EPM). Additionally, quercetin increased total distance traveled and had significant effects on central area time and the number of entries into the open arms in the open field test (OFT) and EPM, showing the great effciency of quercetin for relieving depressive symptoms in animal studies. Depressive behavior test indicators are crucial for assessing the progression and therapeutic response of depression. Typically, the more severe the depression, the longer the immobility time, the shorter the distance traveled, and the less time spent in the central area and open arms, with lower sucrose preference (Tong et al., 2023; Ma et al., 2024). As reported by Anggreini, mice under stress showed a reduction in the time spent in open arms and the number of open-arm entries, indicating reduced exploratory activity, which is characteristic of higher anxiety in mice (Anggreini et al., 2019). Ma et al. found that chronic quercetin supplementation enhanced sucrose preference in mice subjected to chronic unpredictable mild alleviating one of the key factors of depressive stress, behavior-anhedonia (Ma et al., 2021). Furthermore, Samad et al. reported that quercetin can prevent stress-induced anxiety and depressive-like behaviors, as well as improve memory in male mice (Samad et al., 2018). In addition, Anjaneyu Lu et al.'s research on the antidepressant activity of quercetin in diabetic rats showed that quercetin reduced immobility time in a dose-dependent manner,

50

25

Category	Outcome	Specific measure	NO. of studies	Heterogeneity		neity SMD		%CI	P Value
				I² (%)	P Value				
Behavioral tests	FST	Immobility time	29	74	< 0.001	-2.65	-3.22	-2.08	<0.001
		Swimming time	6	56	0.04	3.83	2.51	5.15	< 0.001
	OFT	Total distance traveled	11	81	< 0.001	1.12	0.30	1.94	0.008
		Time spent in central area	13	79	< 0.001	1.88	1.14	2.63	<0.001
		Number of entries into central area	6	58	0.04	1.18	0.44	1.92	0.002
		Number of standing episodes	10	85	< 0.001	0.98	-0.01	1.98	0.05
	TST	Immobility time	20	76	< 0.001	-2.19	-2.82	-1.56	<0.001
	SPT	Sucrose preference	21	75	< 0.001	1.91	1.40	2.42	<0.001
	EPM	Number of entries into open arms	9	78	< 0.001	1.58	0.72	2.44	< 0.001
		Time spent in open arms	15	76	< 0.001	1.53	0.91	2.15	<0.001
		Time spent in closed arms	5	84	< 0.001	-1.99	-3.39	-0.58	0.006
Biochemical assay	Oxidative stress	GSH	16	79	< 0.001	2.85	2.02	3.67	<0.001
		MDA	14	67	< 0.001	-2.42	-3.08	-1.76	<0.001
		CAT	12	82	< 0.001	2.36	1.32	3.40	<0.001
		SOD	14	82	< 0.001	2.57	1.63	3.50	<0.001
	Inflammatory cytokines	IL-6	11	76	< 0.001	-2.49	-3.48	-1.50	<0.001
		TNF-α	14	82	< 0.001	-4.16	-5.39	-2.93	<0.001
		IL-1β	10	77	< 0.001	-2.17	-3.09	-1.24	<0.001
	Neurofactor	BDNF	11	66	0.001	1.46	0.67	2.26	<0.001
		CORT	9	76	< 0.001	-2.12	-3.10	-1.14	<0.001

TABLE 4 Summary of the effects of quercetin vs. control on all behavioral and biochemical endpoints.

Abbreviations: CI, credibility interval; SMD, standardized mean difference; FST, forced swimming test; TST, tail suspension test; SPT, sucrose preference test; OFT, open field test; EPM, elevated plus maze; CORT, corticosterone; BDNF, brain-derived neurotrophic factor; CAT, catalase; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, glutathione; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

which was similar to the effect of the antipsychotic drug fluoxetine and imipramine (Anjaneyulu et al., 2003). Moreover, the antidepressant and anxiolytic-like effects observed in quercetin-treated animals in our study are consistent with the findings of Sameha Merzoug, who reported that quercetin alleviates doxorubicin-induced anxiety-like behaviors and motor dysfunction in the open field and elevated plus maze tests, except for vertical exploration (i.e., the number of standing episodes) (Merzoug et al., 2014).

This study shows that quercetin significantly increases the levels of GSH, SOD, and CAT in animals, and decreases the levels of MDA, TNF- $\alpha$ , IL-6, and IL-1 $\beta$ . The anti-inflammatory and antioxidant effects of quercetin may be one of the important mechanisms underlying its antidepressant effects. Many studies suggest that the anti-inflammatory effects of quercetin may help alleviate neuropsychiatric symptoms. Sah et al. demonstrated that quercetin significantly reduced the levels of IL-1 $\beta$  and IL-6 in rats treated with lipopolysaccharide (LPS), thereby improving anxiety-like symptoms (Sah et al., 2011). These results were also verified in mice subjected to chronic unpredictable stress (CUS) (Mehta et al., 2017; Du et al., 2024). Due to the presence of both catechol and hydroxyl functional groups in its molecular structure, quercetin can directly exert antioxidant effects (Qi et al., 2022). Previously, Şahin et al.

showed that quercetin, when administered via intraperitoneal injection, increased the SOD activity in the striatum of rats in the CUMS model (Ahin et al., 2020). One study found that quercetin had a significant effect on the perimenopausal depression rat model, as quercetin treatment significantly increased GSH levels in the brain and reduced the level of the oxidative stress marker MDA (Hou et al., 2025). Another study showed that quercetin alleviated oxidative stress and inflammation in rats by upregulating antioxidant mechanisms and downregulating the expression of COX2 and NF- $\kappa$ B (Bahar et al., 2017).

This study demonstrates that quercetin significantly increases BDNF levels and decreases CORT levels in animals, further supporting the biological basis of its antidepressant action. BDNF is a protein abundantly present in the human brain, which plays a critical role in protecting dendrites and axons, promoting synaptic plasticity, and regulating neuronal survival and intracellular signaling pathways (Kowiański et al., 2018). Clinical studies have shown that BDNF levels are significantly reduced in patients diagnosed with major depressive disorder (Kishi et al., 2017; Shi et al., 2020). CORT is an important glucocorticoid that regulates the body's response to various stressors, such as psychological and physiological stress. A large body of evidence indicates that patients with depression or those who are chronically stressed typically exhibit overactivation of the hypothalamic-pituitaryadrenal (HPA) axis and elevated cortisol levels (Cubała and Landowski, 2014; Fischer et al., 2017; Druzhkova et al., 2022). Furthermore, existing studies have demonstrated that quercetin and its derivatives may exert neuroprotective effects by interacting with NMDA receptors, thereby reducing neuronal hyperexcitability and damage (Subramanian et al., 2023). Additionally, the modulation of NMDA receptors by quercetin could help restore neurotransmitter balance and ameliorate depressive-like behaviors (Wang et al., 2024c).

The findings of this study may provide multifaceted reference information for the future design of clinical trials of quercetin, which could facilitate the development of quercetin as a potential antidepressant and offer more therapeutic options for patients with depression. First, regarding the selection of subjects, the animal models included in this study cover a variety of methods for inducing depression, suggesting that future clinical trials may consider including patient groups with different etiologies or clinical manifestations of depression to more comprehensively evaluate the efficacy of quercetin. Second, in terms of dosing regimen design, this study has a wide range of quercetin doses and diverse routes of administration. Future clinical trials can refer to this information and, in combination with human pharmacokinetic characteristics, design rational human dosing regimens and routes of administration. Finally, regarding the evaluation of efficacy, this study involves multiple behavioral tests and biochemical indicators as outcome measures. Future clinical trials can draw on these indicators and, in combination with clinical practice, select more sensitive and specific assessment tools to measure the symptom improvement of patients with depression.

## 5 Strengths

To our knowledge, the strength of this study lies in its being the first systematic review and meta-analysis of quercetin's antidepressant effects in preclinical research. Through a comprehensive analysis of multiple behavioral tests and biochemical indicators, the ameliorative effects of quercetin on depressive-like symptoms in animal experiments were evaluated. Our findings provide practical value for translating animal data to clinical evidence.

## 6 Limitations

However, there are several limitations in our systematic review and meta-analysis. First, the number of studies included is limited, and the total sample size is relatively small. Second, the included studies lacked standardized protocols regarding animal species, depression modeling methods, treatment interventions, and outcome assessment methods, which led to higher heterogeneity. Third, most of the studies included did not implement effective allocation concealment measures, nor did they blind the researchers or outcome assessors, which may have introduced selection, performance, and detection biases. Finally, although the sensitivity analysis indicated that the results were relatively stable, the significant risk of bias remains a concern. Therefore, further high-quality studies are urgently needed to validate the results presented in this study. Subgroup analyses revealed that the effects of quercetin on the total distance traveled in the open field test were significantly influenced by dose, treatment duration, and animal species. Specifically, high doses ( $\geq 60 \text{ mg/kg}$ ) and prolonged treatment durations (2–4 weeks) significantly increased the total distance traveled in rats. However, no significant effects were observed in mice or under conditions of low doses and short treatment durations. Collectively, these findings indicate that treatment duration, dosage, and animal species significantly influence the therapeutic efficacy of quercetin. Therefore, future studies should further standardize experimental protocols.

## 7 Conclusion

In this study, we conducted a Meta-analysis for the first time to demonstrate that quercetin exhibits significant antidepressant effects in animal studies. The underlying mechanisms may involve the regulation of oxidative stress, inflammatory responses, neurotrophic factors, and HPA axis function. Although the results are limited by the heterogeneity of animal models and the risk of bias, the multitarget properties of quercetin provide a theoretical basis for its potential as an antidepressant agent. Future research should focus on standardized preclinical studies and explore its clinical translation, including dose optimization, sex differences, and combination therapy strategies.

## Data availability statement

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

## Author contributions

YY: Data curation, Software, Formal Analysis, Writing - original draft, Visualization, Conceptualization. YZ: Writing - original draft, Methodology, Software, Data curation, Visualization, Formal Analysis. LC: Software, Visualization, Writing - original draft, Methodology, Formal Analysis. ZL: Formal Analysis, Writing - original draft, Methodology, Data curation. QZ: Validation, Supervision, Conceptualization, Software, Writing - review and editing.

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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.

## Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1598053/ full#supplementary-material

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