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The increasing relevance of traditional medicine systems for the primary health care sector and general practice: global research perspectives

Edited by
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The increasing relevance of traditional medicine systems for the primary health care sector and general practice: global research perspectives

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Editorial: The increasing relevance of traditional medicine systems for the primary health care sector and general practice: global research perspectives

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traditional medicine, complementary medicine, integrative medicine, primary healthcare, family medicine

Editorial on the Research Topic
The increasing relevance of traditional medicine systems for the primary health care sector and general practice: global research perspectives

Introduction

In the context of global health care challenges, traditional, complementary and integrative medicine (TCIM) systems have gained increasing attention due to their potential to improve primary health care and beyond (1). This editorial addresses the importance of TCIM in addressing unmet health care needs, particularly in the primary care setting. As traditional medicine gains greater recognition worldwide, initiatives such as the recent WHO Summit on Traditional Medicine—culminating in the Gujarat Declaration (2)—highlight the value of integrating TCIM approaches on a global scale. These summits advocate for an evidence-informed and culturally sensitive incorporation of TCIM to improve health outcomes and at the same time recognize the long-standing role of traditional practices in health care and for wellbeing across diverse populations (3).

The body of research presented in this Research Topic highlights the role of TCIM in addressing diverse health issues. Studies range from analyzing the efficacy of traditional herbal medicines to exploring TCIM approaches that support holistic health, providing global perspectives that shape our understanding of the potential of TCIM in modern healthcare settings.

Overview of featured research articles

1. *Exploring the association between phytopharmaceutical use and antibiotic prescriptions in upper respiratory infections: results from a German cohort study evaluating the impact of naturopathy qualifications of general practitioners using routine data* (Wetzel et al.) investigates the influence of phytopharmaceutical prescriptions on antibiotic use. This German study found that general practitioners with TCIM qualifications prescribed fewer antibiotics, illustrating the potential of TCIM to support antibiotic stewardship in primary care settings.
2. *Efficacy and safety of Lianhua Qingwen granule in the treatment of non-influenza viral pneumonia: a randomized, double-blind, placebo-controlled, multicenter clinical study* (Ma et al.) presents results of a clinical trial that suggests efficacy and safety of Lianhua Qingwen in relieving symptoms of viral pneumonia. This study highlights the potential role of traditional Chinese medicine (TCM) in managing infectious respiratory conditions, an area with heightened relevance post COVID-19.
3. *Associations of traditional Chinese medicine body constitution and all-cause mortality in patients with type 2 diabetes mellitus: a prospective cohort study of a Taiwanese medical center* (Lee et al.) examines associations between TCM body constitution types and mortality in diabetic patients, suggesting that Yin deficiency correlates with higher mortality risk. This work suggests that TCM could inform tailored diabetes management strategies.
4. *Efficacy and safety of the Ayurvedic herbal preparation Maharishi Amrit Kalash: a systematic review of randomized controlled trials* (Koch et al.) systematically reviews MAK, an Ayurvedic supplement, in supporting chemotherapy side effects and cognitive function, encouraging further research into Ayurveda's potential therapeutic roles within integrative oncology.
5. *Can acupuncture increase microcirculation in peripheral artery disease and diabetic foot syndrome? – a pilot study* (Valentini et al.) shows promising results of acupuncture in enhancing microcirculation for diabetic patients, underscoring TCIM's potential role in managing common chronic complications of diabetes mellitus and improving quality of life.
6. *Use and acceptance of traditional, complementary and integrative medicine in Germany—an online representative cross-sectional study* (Jeitler et al.) provides an overview of TCIM's widespread use in Germany, with a significant percentage of the population endorsing it as relevant to their health. These findings stress the need for health policies that recognize TCIM's role in meeting patient needs.
7. *Development of the Korean Medicine Core Outcome Set for Facial Palsy: herbal medicine treatment of patients with facial palsy in primary clinics* (Kim, Kim et al.) contributes a core outcome set for herbal treatment of facial palsy, aligning TCIM evaluation methodologies with mainstream medical standards.
8. *A review of the WHO strategy on traditional, complementary, and integrative medicine from the perspective of academic consortia for integrative medicine and health* (Hoenders et al.) looks at the WHO's TCIM strategies from the lens of academic consortias, arguing for an enhanced integrative approach that builds on both biomedical and TCIM practices for improved healthcare outcomes.
9. *Wellness or medicine? Use and perception of Ayurveda in Germany: data from an online-representative cross-sectional study* (Schiele et al.) examines the use and perception of Ayurveda in Germany. The survey results suggest a growing interest in its medical application, with acceptance being limited by cultural differences and a lack of scientific evidence.
10. *Exploring the gap: attitudes, knowledge, and training needs in complementary and integrative medicine among healthcare professionals at German university hospitals* (Hesmert et al.) underscores the importance of training for healthcare professionals to effectively integrate TCIM into patient care, addressing a gap that is essential for integrative patient management.
11. *Protocol for a scoping review of traditional medicine research methods, methodologies, frameworks and strategies* (Ijaz et al.) lays out a scoping review protocol to explore methodologies suited to TCIM research, advocating for an approach to bridge both indigenous and biomedical knowledge systems.
12. *Comprehensive review of Korean Medicine registries 2015–2023* (Kim, Choi et al.) highlights the role of registries in capturing real-world TCIM data, suggesting that registries could inform policy and practice on TCIM's effectiveness and safety in chronic disease management.
13. *Effect of the health and wellness Kneipp concept on health promotion and reduction of sick days for kindergarten children: a cluster randomized controlled trial protocol* (Gerganova et al.) outlines a study protocol evaluating the Kneipp health concept in children, a TCIM intervention with potential to improve child health through lifestyle-based therapies.
14. *Integrative nursing interventions: knowledge, attitudes and practice in home nursing services in Germany—a quantitative and qualitative online survey* (Stolz et al.) explores how integrative nursing interventions, like aromatherapy and herbal teas, are applied in home care settings, reinforcing the importance of TCIM in chronic care.
15. *Effectiveness and safety of acupuncture modalities for overweight and obesity treatment: a systematic review and network meta-analysis of RCTs* (Kim Y. et al.) presents a systematic review and meta-analysis on acupuncture's efficacy in managing obesity, pointing at its role as a complementary approach to weight management in TCIM.

The global relevance of TCIM in healthcare

The works presented highlight the multiple potential applications and benefits of TCIM and underscore its value as a patient-centered approach (4). The WHO summit on TCIM has accelerated efforts to systematically integrate evidence-informed TCIM into global healthcare systems, recognizing its cultural relevance and its cost-effective contribution to health outcomes, particularly in underserved areas. In Germany, for example, acceptance of TCIM is high, indicating a cultural need and readiness for integrative health policies that include both biomedicine and TCIM practices (Jeitler et al.). Continued research, education, and policy integration of TCIM are critical

to promoting a health paradigm that values both traditional and scientific knowledge systems (Hoenders et al.). These efforts support the vision of the WHO Gujarat Declaration on TCIM, which advocates for an integrative approach to health care that respects traditional wisdom while at the same time advancing modern health practices (2).

Conclusion

As TCIM obviously gains momentum globally, its integration into primary health care could address critical gaps in healthcare delivery, particularly in the areas of chronic disease management, preventive care and health promotion. The studies presented here support the growing role of TCIM in global health, and future research will be critical to its further development and scientific validation in healthcare systems. This Research Topic is a testament to the potential of TCIM to improve health care accessibility, promote sustainable practices, and enrich the diversity of health care knowledge. The papers in this Research Topic not only highlight the therapeutic potential of TCIM, but also emphasize the need for robust scientific methods to validate and integrate these practices into modern healthcare, in line with the sustainable development goals of the WHO (5).

Author contributions

CK: Writing – original draft, Writing – review & editing. PP: Writing – review & editing. RP: Writing – review & editing. AD: Writing – review & editing.

Conflict of interest

CK is a member of the scientific advisory board of the company Bruno Zimmer, board member of the German Medical Doctors' Association for Ayurveda-Medicine (DÄGAM e.V.) and receives honoraria for lecturing Ayurveda at Sonne und Mond, Berlin.

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

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Associations of traditional Chinese medicine body constitution and all-cause mortality in patients with type 2 diabetes mellitus: a prospective cohort study of a Taiwanese medical center

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Introduction: The objective of this study was to investigate associations between baseline body constitutions (BCs) in traditional Chinese Medicine (TCM) and all-cause mortality in Chinese individuals with type 2 diabetes.

Methods: A total of 887 individuals with type 2 diabetes who were enrolled in managed care in 2010 were included. These individuals were followed up until 2015, and their mortality status was determined through the use of Taiwan National Death Datasets. At baseline, BC status of participants, including Yin deficiency, Yang deficiency, and phlegm stasis, was assessed using a well-developed Body Constitutions Questionnaire. Hazard ratios (HR) were calculated using a multivariate Cox proportional hazards model.

Results: During 6807.2 person-years of follow-up of 887 participants, with an average follow-up period of 7.7 years, a total of 190 individuals died, resulting in an incidence density of 0.0279 person-years. Yin deficiency was associated with all-cause mortality (HR, 95% CI: 1.39, 1.02–1.90). This study indicates that individuals diagnosed with Yin deficiency in TCM, characterized by symptoms such as thirst, reduced urine volume, hard stool, and hot flushes, had a 39% higher risk of all-cause mortality.

Discussion: The findings may provide information for TCM practitioners on tailoring treatment plans for persons with type 2 diabetes. No conclusive statements can be made on the basis of the preliminary data presented here. Controlled prospective studies are warranted.

KEYWORDS

traditional Chinese medicine, body constitution, all-cause mortality, type 2 diabetes, glucose control

Introduction

Background of body constitution in tradition Chinese medicine

Traditional Chinese medicine (TCM) is a popular form of complementary and integrative medicine both in China and worldwide. In Taiwan, it is covered by the National Health Insurance Program. TCM is based on the theory of body constitution (BC), which involves individualized medicine. An individual's BC is determined by the balance of Yin and Yang within their body. Yang relates to the energy that maintains bodily functions, which can be assessed by regulating interstitial fluid, body temperature, and organ systems' physiological functions. Yin refers to the delivery of materials to cells through interstitial fluid and blood (1). When external factors or environmental stimuli disrupt the balance, physical symptoms such as loose stool, fatigue, chills, shortness of breath, and increased urine output may indicate Yang deficiency or energy deficiency (2, 3). On the other hand, symptoms such as thirst, reduced urine volume, hard stool, and hot flushes may indicate Yin deficiency or a deficiency in essential materials like body fluids, and blood (2, 3). Additionally, symptoms like numbness in the limbs, dizziness, and chest tightness may indicate phlegm stasis or an imbalance in the dynamic harmony state (4). Studies have shown that individuals with different BC are associated with disease and disease progression (4, 5). TCM practitioners employ varied treatment approaches for patients who share the same disease diagnosis, tailoring their treatments to the individual's body constitution. This concept, known as "tong bing yi zhi" in Chinese, similar to the concept of individualized medicine, entails prescribing specific herbal treatments based on the patient's signs and symptoms to achieve the most optimal treatment outcome (5, 6).

Importance of all-cause mortality as an outcome measure

Infant and young adult mortality rates have decreased over the past two decades due to improvements in public health and medical care (7). In the general population, young adults have a lower mortality risk compared to middle-aged and elderly adults, particularly due to chronic diseases like diabetes and cardiovascular diseases (8). As the population continues to age, it is important to identify the factors that influence mortality in middle-aged and older adults for clinical practice and public health policy. With the rising costs of medical care and healthcare systems driven by demographic changes, preventive services targeting mortality need to be prioritized in order to reduce costs.

What has not been done in this line of research question

The prevalence and incidence rates of type 2 diabetes have been steadily increasing worldwide, making it a significant public health concern associated with significant clinical and socioeconomic burdens (9). Diabetes is a leading cause of mortality and is linked to both macrovascular and microvascular complications that contribute to premature death. The identification of the factors associated with mortality can be helpful in addressing premature mortality and improving the accuracy of mortality risk estimates. Studies on diabetes care have explored an association between body constitution (BC) and various clinical outcomes, such as health-related quality of life (10), diabetic retinopathy (11), and incident albuminuria (12). However, no previous studies have investigated an association between BC and mortality. Therefore, the objective of this study was to examine associations between baseline BC measured by body constitution questionnaires (BCQs) and risks of all-cause mortality among Chinese individuals with type 2 diabetes.

Methods

Study design and participants

The Taichung Diabetic Body Constitution Study (TDBCS) is a hospital-based prospective cohort study that recruited participants with type 2 diabetes aged 18 years and older from the Department of Endocrinology and Metabolism outpatient clinics at Taichung Veterans General Hospital in Taichung, Taiwan. The recruitment period was from February 2010 to February 2011. The patients were selected from the Diabetes Shared Care Network of Taichung Veterans General Hospital. Baseline data collection was conducted during the period from February 2010 to February 2011, and the endpoint for the study was set at September 20, 2015. Type 2 diabetes was diagnosed based on the criteria of the American Diabetes Association, including fasting plasma glucose levels >126 mg/dL, random plasma glucose levels >200 mg/dL with symptoms (such as polydipsia, polyuria, and unexplained weight loss), and 2-h plasma glucose levels >200 mg/dL during an oral glucose tolerance test on two separate occasions. After excluding participants from the original TDBCS who had missing data in the BCQs (with missing items ≥10%), a total of 887 participants diagnosed with type 2 diabetes were included in the study.

Data collection approach and measurements

All clinical variables and biomarkers of the participants in TDBCS were assessed during a comprehensive health check-up at baseline. These variables included body measurements such as waist circumference and body mass index (BMI), blood pressure measurements including systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as various blood and urinary tests. Additionally, the participants' diabetes history, history of comorbidities and complications, and medication use were also recorded. Blood and urinary samples were collected from the participants' antecubital vein in the morning after a 12-h overnight fast. These samples were then sent for analysis within 4 h. The biomarkers analyzed included HbA1c and fasting plasma glucose (FPG) to assess glucose levels, creatinine to measure kidney function, and lipid profiles including low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG). A standardized questionnaire was used to collect self-reported data, which included the BCQ assessing previous or current disease history, medication use, and lifestyle behaviors.

Measurements for BCQ

The BCQ, developed by Su et al. (3), consists of 44 five-point Likert-type items. The questionnaire measures the physiological state of patients' BC in terms of Yang deficiency (19 items), Yin deficiency (19 items), and phlegm stasis (16 items). There is some overlap in the items between these three scales. The responses to the five-point questions range from 1 (no occurrence) to 5 (always occurring). The multi-item summative scales for the BCQ, representing Yang deficiency, Yin deficiency, and phlegm stasis, have ranges of 19–95, 19–95, and 16–80, respectively. Higher scores on the BCQ scales indicate a greater deviation from the specific BC being measured. The cut-off points for defining Yang deficiency, Yin deficiency, and phlegm stasis are set at 30.5, 29.5, and 26.5, respectively (2, 13). The BCQ was administered to all participants as a self-report questionnaire by trained interviewers. The interviewers were trained to identify and address any ambiguity, discrepancy, or omission in order to minimize potential error. BCQ has a good factorial validity (2) and internal consistency with Cronbach's alpha above 0.88 for all three BCQ variables (2).

Outcome ascertainment

The main outcome variable was all-cause mortality, which was determined from the annual record linkage with the Taiwan National Death Datasets provided by the Taiwan Ministry of Health and Welfare. The linkage was based on basic information such as the personal identification number and date of birth. All patients included in the study were followed up from their index date until August 2021 or until the occurrence of death. The index date refers to the date of entry into the present study.

Measurements for covariates

The covariates in the study included sociodemographic factors such as age and sex, anthropometric measurements of waist circumference and BMI, blood pressure measurements of SBP and DBP, lifestyle behaviors such as smoking history, alcohol consumption, and physical activity habits, and diabetes-related variables including duration of diabetes and type of anti-hyperglycemia medication. These covariates were obtained through personal interviews and physical check-ups. Biochemical markers, including HbA1c, FPG, creatinine, blood urea nitrogen (BUN), serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), uric acid, total cholesterol, HDL-C, TG, and LDL-C were analyzed using a biochemical autoanalyzer (Hitachi Labospect 008, LST008, Hitachi High-Technologies Corporation, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the formula suggested by the Chronic Kidney Disease Epidemiology Collaboration (14). The anti-diabetes medication included two main categories, namely, oral medication agents and insulin injection.

Statistical analysis

Descriptive statistics were used to report the mean and standard deviation for continuous variables. Two-sample *t*-tests were conducted to compare variables between groups. Frequencies and percentages were reported for categorical variables, and the chi-square test was used to assess differences in categorical variables between groups. Bivariate survival analyses were performed using the Kaplan–Meier method to estimate survival curves, and the log-rank test was used to compare the survival functions among BC subgroups (15). Cox proportional hazard models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). This method allowed for the assessment of an association between the time to an event outcome and a set of explanatory variables (16). Three models were created for the Cox models. Model 1 did not include any covariates. Model 2 included adjustments for sociodemographic characteristics, lifestyle behaviors, BMI, waist, blood pressure, and lipid profile. Model 3 included additional adjustments for diabetes-related factors, such as anti-diabetes medication and diabetic duration, eGFR, albuminuria status, diabetic retinopathy, and cerebrovascular accident. The proportionality assumption was assessed by including an interaction term of BC subgroups and person-time in the Cox models. No statistically significant violation of the assumption was found. Multiple testing was not used in our study because two-group comparisons were made, one outcome variable was considered, and no interim analysis was conducted in the present study. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p values were reported, and statistical significance was considered at $p < 0.05$.

Results

Distributions of baseline characteristics

A total of 887 individuals with type 2 diabetes were included in the present study. The average age at baseline was 63.8 (standard deviation: 13.4) years. During the 6807.2 person-years of follow-up period, with a mean (median) follow-up of 7.7 (8.5) years, 190 individuals died, resulting in an incidence density of 0.0279 person-years. The characteristics of the participants according to their survival status are described in Table 1. In decedents, the mean values of age, waist circumference, HbA1c, diabetes duration, SBP, albumin-to-creatinine ratio, serum creatinine, and eGFR were higher compared to those in patients who were alive. Additionally, the mean value of HDL-C was lower in decedents than in patients who were alive. Male individuals, those with BCs of Yin deficiency and phlegm stasis, no exercise habits, insulin use, albuminuria, diabetic retinopathy, and cerebrovascular accident were found to have a lower probability of survival compared to individuals who did not have these characteristics.

Associations of BCs with all-cause mortality

The Kaplan–Meier method was used to estimate survival probability for all-cause mortality within subgroups of BCs of Yang deficiency, Yin deficiency, and phlegm stasis, as shown in Figure 1. The HRs estimated from the three models of all-cause mortality according to Yang deficiency subgroups are presented in Table 2. Yang deficiency was not significant in the model without adjustment, and

TABLE 1 Sociodemographic characteristics, body constitution, lifestyle behaviors, diabetes-related factors, biomarkers, and comorbidities according to survival status.

	Decedents	Survivors	
Variables	(n = 190)	(n = 697)	p value
Sociodemographic factors			
Age (years)	73.6 (10.7)	61.1 (12.8)	<0.001
Gender			
Female	57 (15.0%)	324 (85.0%)	<0.001
Male	133 (26.3%)	373 (73.7%)	
BMI (kg/m^2)	25.5 (3.5)	25.7 (4.0)	0.42
Waist (cm)	91.0 (10.3)	88.8 (10.9)	0.01
Body constitution			
Yang deficiency			
No	164 (21.0%)	618 (79.0%)	0.37
Yes	26 (24.8%)	79 (75.2%)	
Yin deficiency			
No	120 (18.5%)	527 (81.5%)	<0.001
Yes	70 (29.2%)	170 (70.8%)	
Phlegm stasis			
No	154 (20.1%)	614 (79.9%)	0.01
Yes	36 (30.3%)	83 (69.7%)	
Lifestyle behaviors			
Smoke history			
No	184 (21.8%)	659 (78.2%)	0.20
Yes	6 (13.6%)	38 (86.4%)	
Alcohol history			
No	187 (21.8%)	672 (78.2%)	0.16
Yes	3 (10.7%)	25 (89.3%)	
Exercise habits			
No	52 (27.5%)	137 (72.5%)	0.02
Yes	138 (19.8%)	559 (80.2%)	
Diabetes-related factors			
FPG (mg/dL)	150.6 (52.9)	143.2 (46.2)	0.08
HbA1c (%)	7.9 (1.7)	7.6 (1.5)	0.03
Diabetes duration (years)	11.4 (9.3)	8.6 (7.7)	<0.001
OHA			
No	9 (22.0%)	32 (78.0%)	0.93
Yes	181 (21.4%)	665 (78.6%)	
Insulin usage			
No	130 (19.3%)	544 (80.7%)	0.006
Yes	60 (28.2%)	153 (71.8%)	
Lipid profile			
TC (mg/dL)	172.6 (40.5)	174.1 (34.5)	0.63
TG (mg/dL)	144.7 (108.5)	148.0 (125.2)	0.723
HDL (mg/dL)	50.5 (13.3)	52.9 (15.0)	0.05
LDL (mg/dL)	105.9 (37.1)	106.0 (30.3)	0.98

(Continued)

TABLE 1 (Continued)

	Decedents	Survivors	
Blood pressure			
SBP (mmHg)	133.5 (15.3)	131.1 (14.3)	0.04
DBP (mmHg)	77.0 (10.9)	77.8 (8.7)	0.35
Renal parameters			
Albumin-to-creatinine ratio (mg/g)	46.0 (91.4)	15.2 (58.4)	<0.001
Creatinine (mg/dL)	1.5 (0.8)	1.1 (0.5)	<0.001
eGFR (mL/min/1.73m^2)	54.5 (20.4)	71.4 (21.4)	<0.001
Albuminuria			
No (<30 mg/g)	58 (12.2%)	419 (87.8%)	<0.001
Yes (≥30 mg/g)	120 (32.1%)	254 (67.9%)	
Diabetic retinopathy			
No	94 (17.7%)	438 (82.3%)	<0.001
Yes	96 (27.0%)	259 (73.0%)	
Cerebrovascular accident			
No	174 (20.4%)	680 (79.6%)	0.001
Yes	16 (48.5%)	17 (51.5%)	

Data were presented in terms of the mean (SD) for continuous variables or number (%) for categorical variables. *p* values were calculated using Chi-square test for categorical variables and *t*-test for continuous variables.
BMI, body mass index; FPG, fasting plasma glucose; OHA, oral hypoglycemic agent; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

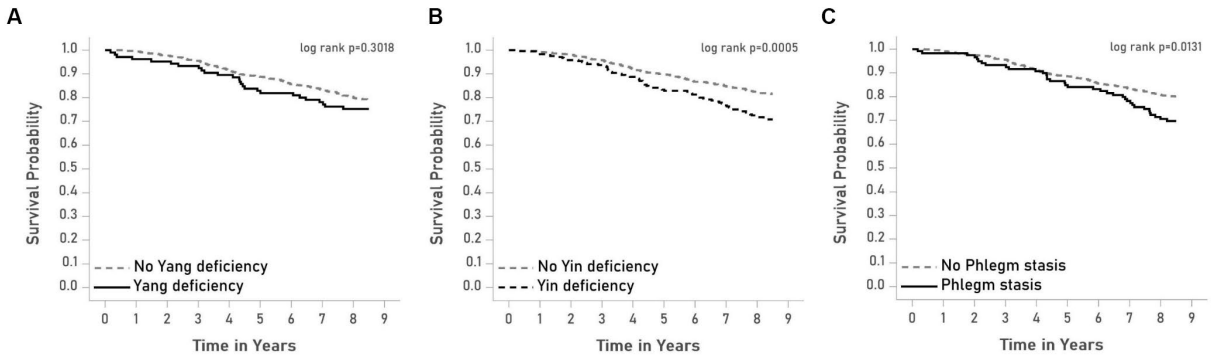

FIGURE 1
Survival curves of all-cause mortality according to the subgroups of **(A)** Yang deficiency, **(B)** Yin deficiency, and **(C)** Phlegm stasis.

this remained non-significant even after considering sociodemographic characteristics, lifestyle behaviors, waist circumference, blood pressure, and lipid profiles (model 2), as well as diabetes-related factors, eGFR, albuminuria, diabetic retinopathy, and cerebrovascular accident (model 3). Yin deficiency showed a significant association with all-cause mortality in the model without adjustment (HR, 95% CI: 1.68, 1.25–2.26). This association remained significant after further considering factors related to all-cause mortality, although its effect was attenuated when lifestyle behaviors and diabetes-related factors were included in the multivariate model (HR, 95% CI: 1.39, 1.02–1.90, Table 3). Phlegm stasis was significantly associated with all-cause mortality in the model without adjustment (HR, 95% CI: 1.58, 1.10–2.27), and this association remained significant after further considering sociodemographic factors, lifestyle behaviors, and blood pressure and lipid profiles (HR, 95% CI: 1.39, 1.02–1.90). However, its effect became borderline after multivariate adjustment (HR, 95% CI: 1.43, 0.95–2.15, Table 4). Other significant factors associated with all-cause mortality were age (HR, 95% CI: 1.08, 1.06–1.10), gender (HR, 95% CI: 1.95, 1.35–2.81), exercise habits (HR, 95% CI: 0.65, 0.46–0.93), HbA1c (HR, 95% CI: 1.14, 1.01–1.29), eGFR (HR, 95% CI: 0.99, 0.98–0.99), and albuminuria (HR, 95% CI:1.58, 1.12–2.24). We conducted a sensitivity analysis by excluding individuals with stroke ($n = 33$) and end-stage renal disease ($n = 10$) in order to improve the homogeneity of the study subjects and test the robustness of our findings. The results of the sensitivity analysis showed that the findings of the study remained similar to those of the original analysis, indicating the robustness of our results. The HRs for Yang deficiency and phlegm stasis were not

TABLE 2 Cox's proportional hazards model: Yang deficiency.

Variables	HR (95%CI)		
	Model 1	Model 2	Model 3
Body constitution			
Yang deficiency	1.24 (0.82–1.88)	1.44(0.93–2.20)	1.31 (0.83–2.07)
Sociodemographic factors			
Age (years)	1.09 (1.07–1.10)***	1.09 (1.07–1.11)***	1.08 (1.06–1.10)***
Male	1.88 (1.38–2.56)***	1.71 (1.19–2.45)**	1.95 (1.34–2.83)***
Lifestyle behaviors			
Smoke history	0.60 (0.27–1.35)	1.15 (0.49–2.68)	0.87 (0.34–2.22)
Alcohol history	0.46 (0.15–1.45)	0.41 (0.12–1.37)	0.66 (0.20–2.23)
Exercise habits	0.67 (0.49–0.92)*	0.54 (0.38–0.75)***	0.64 (0.45–0.90)*
BMI (kg/m^2)	0.99 (0.95–1.02)	1.00 (0.94–1.07)	1.00 (0.93–1.07)
Waist (cm)	1.02 (1.00–1.03)*	1.00 (0.98–1.03)	1.00 (0.98–1.02)
Blood pressure			
SBP (mmHg)	1.01 (1.00–1.02)*	1.00 (0.99–1.02)	1.01 (0.99–1.02)
DBP (mmHg)	0.99 (0.98–1.01)	1.01 (0.99–1.03)	1.00 (0.98–1.03)
Lipid profile			
TC (mg/dL)	1.00 (0.99–1.00)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
TG (mg/dL)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
HDL (mg/dL)	0.99 (0.98–1.00)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
LDL (mg/dL)	1.00 (1.00–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Diabetic factors			
FPG (mg/dL)	1.00 (1.00–1.01)		1.00 (1.00–1.00)
HbA1c (%)	1.10 (1.01–1.19)*		1.15 (1.01–1.30)*
Diabetes duration (years)	1.04 (1.02–1.05)***		1.00 (0.98–1.02)
OHA	0.94 (0.48–1.83)		0.79 (0.34–1.83)
Insulin usage	1.58 (1.17–2.15)**		1.49 (1.03–2.17)*
Renal parameters			
eGFR (mL/min/1.73m^2)	0.97 (0.96–0.97)***		0.99 (0.98–0.99)**
Albuminuria ≥ 30	2.97 (2.17–4.07)***		1.60 (1.13–2.27)**
Diabetic retinopathy	1.68 (1.27–2.24)***		1.13 (0.83–1.55)
Cerebrovascular accident	2.71 (1.62–4.53)***		1.29 (0.73–2.29)

Model 1 is unadjusted.
Model 2 is adjusted for sociodemographic characteristics, lifestyle behaviors, BMI, waist, blood pressure and lipid profile.
Model 3 is further adjusted for diabetic factors, renal parameters, and diabetic retinopathy and cerebrovascular accident.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, fasting plasma glucose; OHA, oral hypoglycemic agent; eGFR, estimated glomerular filtration rate.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

significantly associated with all-cause mortality, while Yin deficiency remained significantly associated with all-cause mortality (HR, 95% CI: 1.48 [1.07–2.06], $p < 0.05$).

Assessing interactions of covariates on associations between BCs and all-cause mortality

The effects of BCs were stratified by gender, age, duration of DM, and glucose control status. No significant interactions of gender, age, and duration of DM with any BCs were observed (all p for interactions > 0.05). Considering the limited sample size, significant associations of Yin deficiency were observed with mortality in persons aged 55 years and older (HR, 95% CI: 1.45, 1.04–2.00) and of phlegm stasis with mortality in persons aged 55 and younger (HR, 95% CI: 0.003, 0.00–0.82). We observed significant interactions of glucose control status with Yang and Yin deficiency (p for interaction = 0.0363 and 0.0379, respectively) and borderline significant interaction of glucose control status with phlegm stasis (p for interaction = 0.0641) (Figure 2). Yang deficiency, Yin deficiency, and phlegm stasis had no significant interactions with mortality in persons with good glucose

TABLE 3 Cox's proportional hazards model: Yin deficiency.

Variables	HR (95%CI)		
	Model 1	Model 2	Model 3
Body constitution			
Yin deficiency	1.68 (1.25–2.26)***	1.50 (1.11–2.03)**	1.39 (1.02–1.90)*
Sociodemographic factors			
Age (years)	1.09 (1.07–1.10)***	1.09 (1.07–1.10)***	1.08 (1.06–1.10)***
Male	1.88 (1.38–2.56)***	1.69 (1.18–2.40)**	1.92 (1.33–2.77)***
Lifestyle behaviors			
Smoke history	0.60 (0.27–1.35)	1.16 (0.50–2.69)	0.90 (0.35–2.30)
Alcohol history	0.46 (0.15–1.45)	0.41 (0.12–1.36)	0.66 (0.20–2.24)
Exercise habits	0.67 (0.49–0.92)*	0.54 (0.38–0.75)***	0.64 (0.45–0.92)*
BMI (kg/m^2)	0.99 (0.95–1.02)	1.00 (0.93–1.07)	0.99 (0.93–1.07)
Waist (cm)	1.02 (1.00–1.03)*	1.00 (0.98–1.03)	1.00 (0.98–1.02)
Blood pressure			
SBP (mmHg)	1.01 (1.00–1.02)*	1.00 (0.99–1.02)	1.01 (1.00–1.02)
DBP (mmHg)	0.99 (0.98–1.01)	1.01 (0.99–1.03)	1.01 (0.98–1.03)
Lipid profile			
TC (mg/dL)	1.00 (0.99–1.00)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
TG (mg/dL)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
HDL (mg/dL)	0.99 (0.98–1.00)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
LDL (mg/dL)	1.00 (1.00–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Diabetic factors			
FPG (mg/dL)	1.00 (1.00–1.01)		1.00 (1.00–1.00)
HbA1c (%)	1.10 (1.01–1.19)*		1.14 (1.01–1.29)*
Diabetes duration (years)	1.04 (1.02–1.05)***		1.00 (0.99–1.02)
OHA	0.94 (0.48–1.83)		0.74 (0.32–1.70)
Insulin usage	1.58 (1.17–2.15)**		1.46 (1.01–2.11)*
Renal parameters			
eGFR (mL/min/1.73m^2)	0.97 (0.96–0.97)***		0.99 (0.98–0.99)**
Albuminuria ≥ 30	2.97 (2.17–4.07)***		1.63 (1.16–2.30)**
Diabetic retinopathy	1.68 (1.27–2.24)***		1.09 (0.80–1.49)
Cerebrovascular accident	2.71 (1.62–4.53)***		1.27 (0.72–2.27)

Model 1 is unadjusted.
Model 2 is adjusted for sociodemographic characteristics, lifestyle behaviors, BMI, waist, blood pressure and lipid profile.
Model 3 is further adjusted for diabetic factors, renal parameters, and diabetic retinopathy and cerebrovascular accident.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, fasting plasma glucose; OHA, oral hypoglycemic agent; eGFR, estimated glomerular filtration rate.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

control, while Yang deficiency, Yin deficiency, and phlegm stasis had a significant positive association with mortality in persons with poor glucose control (HRs, 95% CI: 1.75, 1.06–2.90; 1.88, 1.27–2.77; and 1.85, 1.16–2.95, respectively).

Discussion

Overall, this study suggests that BCs of Yang deficiency, Yin deficiency, and phlegm stasis are associated with increased mortality in individuals with diabetes, particularly in those with poor glucose control. These BCs may serve as potential prognostic indicators in diabetes management, and further research is needed to understand the underlying mechanisms and develop targeted interventions. The other significant factors associated with mortality were age, gender, physical activity, HbA1c, insulin use, eGFR, and albuminuria. In addition, the study suggests that associations between BCs of Yang deficiency, Yin deficiency, and phlegm stasis with mortality were only significant in individuals with poor glucose control. In persons with poor glucose control, BCs of Yang deficiency, Yin deficiency, or phlegm stasis were associated with 75–88% increase in mortality. On the contrary, in

TABLE 4 Cox's proportional hazards model: Phlegm stasis.

Variables	HR (95%CI)		
	Model 1	Model 2	Model 3
Body constitution			
Phlegm deficiency	1.58 (1.10–2.27)*	1.59 (1.07–2.37)*	1.43 (0.95–2.16)
Sociodemographic factors			
Age (years)	1.09 (1.07–1.10)***	1.09 (1.07–1.11)***	1.08 (1.06–1.10)***
Male	1.88 (1.38–2.56)***	1.73 (1.21–2.48)**	1.95 (1.35–2.81)***
Lifestyle behaviors			
Smoke history	0.60 (0.27–1.35)	1.12 (0.48–2.62)	0.87 (0.34–2.21)
Alcohol history	0.46 (0.15–1.45)	0.41 (0.12–1.37)	0.68 (0.20–2.28)
Exercise habits	0.67 (0.49–0.92)*	0.55 (0.39–0.78)***	0.65 (0.46–0.93)*
BMI (kg/m^2)	0.99 (0.95–1.02)	1.01 (0.94–1.08)	1.00 (0.93–1.07)
Waist (cm)	1.02 (1.00–1.03)*	1.00 (0.98–1.02)	0.99 (0.97–1.02)
Blood pressure			
SBP (mmHg)	1.01 (1.00–1.02)*	1.00 (0.99–1.02)	1.01 (0.99–1.02)
DBP (mmHg)	0.99 (0.98–1.01)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
Lipid profile			
TC (mg/dL)	1.00 (0.99–1.00)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
TG (mg/dL)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
HDL (mg/dL)	0.99 (0.98–1.00)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
LDL (mg/dL)	1.00 (1.00–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Diabetic factors			
FPG (mg/dL)	1.00 (1.00–1.01)		1.00 (1.00–1.00)
HbA1c (%)	1.10 (1.01–1.19)*		1.14 (1.01–1.29)*
Diabetes duration (years)	1.04 (1.02–1.05)***		1.00 (0.99–1.02)
OHA	0.94 (0.48–1.83)		0.77 (0.34–1.78)
Insulin usage	1.58 (1.17–2.15)**		1.44 (0.99–2.09)
Renal parameters			
eGFR ($mL/min/1.73m^2$)	0.97 (0.96–0.97)***		0.99 (0.98–0.99)**
Albuminuria ≥ 30	2.97 (2.17–4.07)***		1.58 (1.12–2.24)**
Diabetic retinopathy	1.68 (1.27–2.24)***		1.14 (0.83–1.55)
Cerebrovascular accident	2.71 (1.62–4.53)***		1.35 (0.76–2.41)

Model 1 is unadjusted.
Model 2 is adjusted for sociodemographic characteristics, lifestyle behaviors, BMI, waist, blood pressure and lipid profile.
Model 3 is further adjusted for diabetic factors, renal parameters, and diabetic retinopathy and cerebrovascular accident.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, fasting plasma glucose; OHA, oral hypoglycemic agent; eGFR, estimated glomerular filtration rate.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

individuals with good glucose control, these BCs were not associated with increased mortality.

In the present study, it was observed that an association between phlegm stasis and all-cause mortality was influenced by diabetes-related variables, renal-related variables such as eGFR and albuminuria, and comorbidities. Among individuals with poor glucose control, there was a significant association between phlegm stasis and all-cause mortality, and this association had a borderline significant interaction with poor glucose control. According to TCM theory, BC is defined as the essential component that makes up a human being and encompasses physiological, psychological, and pathological aspects that characterize an individual's health. BC is also influenced by both nature and nurture (17). Phlegm stasis arises due to the stagnation of energy flow, leading to the development of watery phlegm or static blood, as explained by TCM theory (1). A previous cross-sectional study has shown that individuals with type 2 diabetes with phlegm stasis BC are more likely to develop albuminuria (11). A prospective cohort study has demonstrated that the interaction between phlegm stasis and glucose control status may affect the development of new-onset albuminuria in individuals with type 2 diabetes. These findings from epidemiologic studies can be explained using TCM theory, as stagnation arises due to difficulties in the

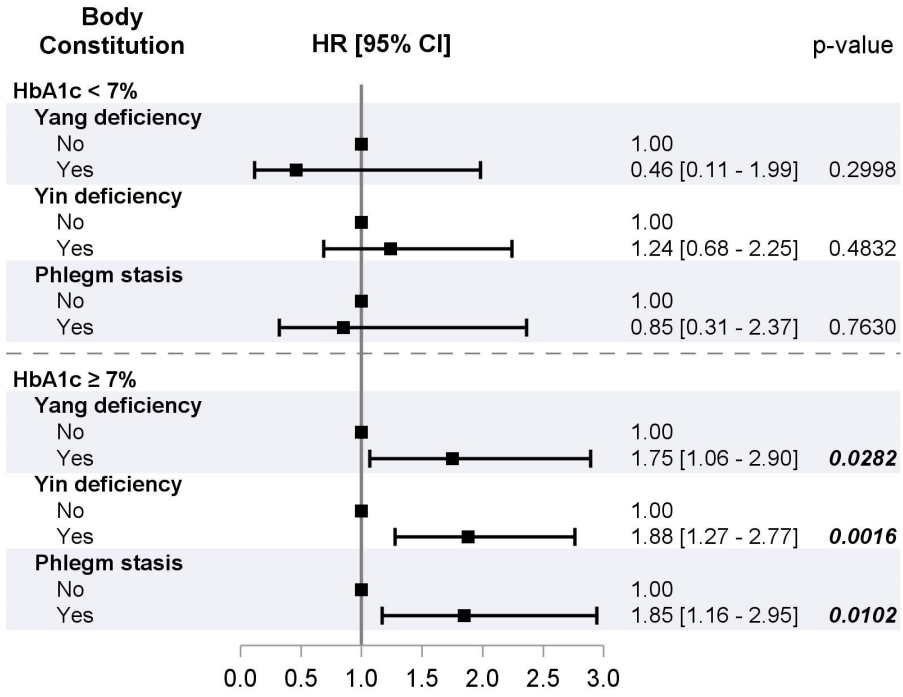

FIGURE 2
HRs of all-cause mortality for Yang deficiency, Yin deficiency, and phlegm stasis stratified by glucose control status from multivariate Cox proportional hazard models.

transportation of sugar (Yin) by the energy (Yang) among individuals with type 2 diabetes who have poor glucose control. This phenomenon can be understood through the biological mechanisms of vessel obstructions (18) and vascular endothelial dysfunction (19), which hinder the flow of energy. The occurrence of phlegm stasis BC leads to diabetes complications such as renal dysfunction and albuminuria. Therefore, the effect of phlegm stasis is mediated by diabetes-related factors such as FPG and HbA1c, as well as renal-related factors such as eGFR and albuminuria.

The findings of this study have important implications for healthcare providers, as they provide information on potential effects of BCs and their interaction with glucose control status on all-cause mortality. TCM practitioners can consider to tailor treatment plans based on an individual's body constitution, such as Yang deficiency, Yin deficiency, or phlegm stasis, particularly in patients with poor glucose control. This information can be used to design targeted TCM BC-based education interventions and identify individuals at high risk who could benefit from such interventions to reduce mortality. For example, individuals with Yin deficiency BC may be advised to avoid grilled, fried, and spicy foods, consume less dessert drinks, increase water intake, and include more yin-nourishing foods in their diet, such as pears, yams, water chestnuts, lotus seeds, lilies, fungus, white fungus, wolfberry, and honey.

The strengths of this prospective cohort study include being the first of its kind to examine associations between BCs and all-cause mortality in individuals with type 2 diabetes. Additionally, the study assessed the mediating effect of traditional risk factors, using a hierarchical model approach in TCM research. The findings from the study suggest potential associations between Yin deficiency and all-cause mortality, as well as between phlegm stasis and mortality through diabetes-related factors. Finally, the study utilized a standardized and well-validated instrument to measure BC status, reducing potential measurement error.

It is important to acknowledge the limitations of this study. First, the participants were recruited from a specific population in a medical center in central Taiwan. This may limit the generalizability of the findings to individuals with type 2 diabetes in other clinical settings. The characteristics of the study population, such as higher prevalence of comorbidities and longer diabetes duration, may not be representative of other populations with type 2 diabetes. Therefore, caution should be exercised when applying the results to different populations. Moreover, our prospective cohort study is an observational study, which means that it cannot eliminate the influence of unknown or unmeasured factors due to the absence of randomization. Even though we have made efforts to control for potential confounding variables through covariate adjustment, there may still be residual confounding that could affect the observed associations.

Conclusion

This study suggests an association between Yin deficiency and all-cause mortality in individuals with type 2 diabetes. These findings can inform TCM practitioners in tailoring treatment plans based on an individual's body constitution, developing targeted TCM body constitution-based education interventions, and identifying high-risk individuals who could benefit from such interventions to reduce mortality in individuals with type 2 diabetes. No conclusive statements

can be made on the basis of the preliminary data presented here. Controlled prospective studies are warranted.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Taichung Veterans General Hospital IRB (approved number: C10007). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

C-HL: Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. Y-CS: Methodology, Project administration, Writing – review & editing. S-YL: Data curation, Writing – review & editing. I-TL: Data curation, Writing – review & editing. C-IT: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. T-CL: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & 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.

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Glossary

TCM	Traditional Chinese medicine
BC	Body constitution
BCQs	Body constitution questionnaires
TDBCS	Taichung diabetic body constitution study
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
LDL-C	Low-density lipoprotein-cholesterol
HDL-C	High-density lipoprotein-cholesterol
TG	Triglycerides
BUN	Blood urea nitrogen
SGPT	Serum glutamic-pyruvic transaminase
SGOT	Serum glutamic-oxaloacetic transaminase
eGFR	Estimated glomerular filtration rate
HRs	Hazard ratios
CIs	Confidence intervals

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Efficacy and safety of Lianhua Qingwen granule in the treatment of non-influenza viral pneumonia: a randomized, double-blind, placebo-controlled, multicenter clinical study

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Objective: To observe the effectiveness and safety of Lianhua Qingwen granule in the treatment of non-influenza viral pneumonia.

Methods: This study was a multicenter, randomized, double-blind, placebo-controlled trial. Subjects who met the inclusion and exclusion criteria and were clinically diagnosed with viral pneumonia (negative for influenza virus) were randomly divided into the Lianhua Qingwen granule trial group and placebo control group. Patients in the trial group was given Lianhua Qingwen granule, 2 bags at a time, 3 times a day, and the controls were given placebo, with a treatment course of 7 days. Patients' clinical symptoms and signs, and treatment-associated adverse events were observed. Subjects should be included in the full analysis set (FAS) as long as they were all given the medication and had an effectiveness test performed after randomization. Subjects should be included in the Per Protocol Set (PPS),a subset of the total analysis set, which should contain those with strong compliance, no protocol violations, and complete baseline values for the primary indicators.

Results: A total of 169 subjects were enrolled in 12 subcenters, including 151 (76 in the trial group and 75 in the control group) in the FAS and 140 (68 in the trial group and 72 in the control group) in the PPS. After 7 days of treatment, the clinical symptom relief rates were 82.98% (FAS) and 87.12% (PPS) in the trial group, and 75.11% (FAS) and 76.02% (PPS) in the control group, respectively. The clinical symptom relief rates in the trial group were significantly higher than those in the control group ($p < 0.001$). Significant improvements in single symptoms of cough and expectoration in the trial group were observed compared with the control group ($p < 0.05$). There were no statistical differences in fever, sputum color change, chest pain, muscle pain, dyspnea, chills, and thirst between the two groups ($p > 0.05$).

Safety: There were no significant differences in body weight, vital signs, blood routine, urine routine, stool routine, and blood biochemical indicators (CK, AST, ALT, Cr, and Bun) between the two groups before and after treatment ($p > 0.05$). During treatment, there were no significant differences in the incidence of adverse events and serious adverse events between the two groups ($p > 0.05$).

Conclusion: Lianhua Qingwen granules improved the clinical symptoms of patients with non-influenza virus pneumonia, especially ameliorating cough and expectoration. Lianhua Qingwen granules were associated with good safety.

KEYWORDS

non-influenza virus pneumonia, Lianhua clear blast particles, Chinese medicine treatment, clinical trials, RCT – randomized controlled trial

Introduction

Pneumonia is a leading cause of death in children and the elderly (1). Among the pathogens that cause community-acquired pneumonia (CAP), the disease burden of viral pneumonia is severely underestimated. In recent years, with the development of molecular biological detection technology, more and more attention has been paid to respiratory virus in CAP (2, 3).

As a common and frequently-occurring disease, the diagnosis and treatment of viral pneumonia are not standard. Influenza virus is the most common respiratory virus, easy to cause lung inflammation, especially influenza A H1N1, H3N2, avian influenza H5N1, H7N9 epidemic, making influenza has become the focus of attention of the medical community, there are more drugs to choose, such as amantadine, rimantadine, oseltamivir, zanamivir, peramivir, etc. There is good evidence of evidence-based medicine for clinical efficacy. There are few studies on the standardized treatment of other respiratory viruses except influenza related viruses. For example, respiratory syncytial virus is also the cause of common viral pneumonia, and for patients with more severe illness, the existing evidence recommends the use of ribazole treatment, and palivizumab/Synagis can also be used. Parainfluenza virus does not have a good treatment drug, some experts recommend the use of ribavirin treatment. The treatment of adenovirus mainly uses cidofovir, *in vitro* data show that cidofovir has a good effect against 14 subtypes of adenovirus, but currently it is mainly used in patients with low immunity, especially in patients with hematopoietic stem cell transplantation. Severe Acute Respiratory Syndromes (SARS) and Middle East Respiratory Syndrome (MERS) are both caused by coronaviruses. Although they account for a small proportion in the whole respiratory tract, they have been the focus of medical attention due to their greater public health hazards. The protease inhibitors lopinavir and ritonavir showed anti-SARS-CoV activity. It can be seen that no matter respiratory syncytial virus, parainfluenza virus, adenovirus or coronavirus, the clinical treatment drugs for pneumonia caused by these non-influenza viruses are mostly empirical drugs, which have a long market time, large side effects, lack of high-level evidence-based medicine support, and clinical efficacy is not accurate. Therefore, it is of practical clinical significance to explore new therapeutic means and develop new drugs. With the development of nucleic acid diagnostic technology, pathogen diagnosis can be well distinguished and clarified clinically.

Traditional Chinese medicine (TCM) has a long history, rich experience and exact clinical efficacy in the treatment of infectious diseases, especially respiratory infectious diseases. With the progress of The Times, the clinical experience of traditional Chinese medicine needs to come up with clinical data in line with modern evaluation standards to prove its efficacy. A standard RCT study was conducted by the National Administration of Traditional Chinese Medicine (4). A total of 147 severe influenza patients were collected, 86% of whom had pneumonia. It is analyzed that the traditional Chinese medicine is heat and toxin obstructing the lung, and the treatment is to clear the heat and detoxize the lung and ventilate the pathogens. Other viruses, such as syncytial virus and adenovirus, cause pneumonia. When there are no other complications in the early stage, the pathogenesis of TCM is mainly heat and poison in the lung. Therefore, the basic pathogenesis of virus associated pneumonia in traditional Chinese medicine is the invasion of warm epidemic virus on the lung, and the lung is closed. When the treatment of Qingwen detoxification, Xuan lung heat.

Lianhua Qingwen granule is a Chinese patent medicine for the treatment of common cold and influenza under the guidance of the theory of collateral disease of traditional Chinese medicine. It has been recommended by many diagnosis and treatment plans and guidelines due to its significant clinical therapeutic effect. The treatment method of Lianhua Qingwen is "clearing away the pestilence, detoxifying the lung heat." This study evaluated the efficacy and safety of Lianhua Qingwen granule in the treatment of non-influenza viral pneumonia, aiming to provide evidence-based medical evidence to develop standardized treatment strategy for pneumonia caused by viral infection.

Materials and methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the clinical efficacy of Lianhua Qingwen Granule in the treatment of non-influenza viral pneumonia.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Bun, blood urea nitrogen; CAP, community-acquired pneumonia; CK, creatine kinase; Cr, creatinine; ECG, electrocardiogram; EENT, eyes ears nose and throat; FAS, full analysis set; PCT, procalcitonin; PPS, per protocol set; RICU, respiratory intensive care unit; SAS, statistics analysis system; SS, safe analysis set; WBC, white blood cell.

This study was approved by the Ethics Committee of Beijing Ditan Hospital Capital Medical University, China. (Ethics Approval Number: Jing Di Lun Zi [2015] No. [56] -02). Each subject was informed of the purpose and procedures of the study and the potential benefits and risks of treatment, and signed the informed consent. This study was registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-16007773).

Subject enrollment

Inclusion criteria

The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria according to the Chinese Guidelines for Diagnosis and Treatment of Community-acquired Pneumonia issued by the Chinese Thoracic Society (2015 Edition); (2) Clinical diagnosis of viral pneumonia: fever with respiratory symptoms, with or without dyspnea (respiratory rate > 30 times/min); white blood cell (WBC) count was normal or below normal, with or without thrombocytopenia; only those patients undergo chest CT who were based on the doctor's professional judgment and the doctor's full understanding of the patient's condition, fully understand the benefit risk ratio of using CT from the patient's perspective, and finally obtain the informed consent of the patient before undergoing CT examination, the chest CT examination was consistent with the clinical findings of viral pneumonia; (3) Rapid influenza antigen test result was negative (Shenzhen Miraclean Technology Co., Ltd. Influenza antigen test Real-time RT-PCR. Those with negative results were further screened for respiratory viruses in accordance with the guidelines by the Chinese Center for Disease Control and Prevention (Nanjing Synthgene Medical Technology Co. Ltd. Multiple Respiratory pathogen nucleic acid detection kit PCR-Fluorescent probe method. (4) Patients enrolled within 5 days of disease onset; (5) Patients aged 14 years or older, without gender limitation.

Exclusion criteria

The exclusion criteria were as follows: (1) Without definitive evidence of bacterial infection (PCT > 1ug/L); (2) patients receiving other antiviral drugs within 1 week; (3) Patients who met the diagnosis criteria of severe pneumonia in accordance with the 2015 Chinese Guidelines for Diagnosis and Treatment of Community-acquired Pneumonia; (4) Chest CT confirmed severe interstitial lung disease, bronchiectasis, and other underlying lung diseases; (5) Patients with positive influenza A/B rapid test results and with streptococcus pneumonia, Legionella pneumonia urine antigen, mycoplasma pneumonia, and positive chlamydia antibody testing; (6) Patients with severe liver and kidney dysfunction: ALT /AST values were 3 times higher than the upper limit of normal value, and blood creatinine was 1.5 times higher than the upper limit of normal value; (7) Patients with previous or current diseases that might affect their participation in the trial and the research results, including malignant, autoimmune, liver and kidney, hematological, neurological endocrine diseases; (8) Patients with diseases such as human immunodeficiency virus infection, hematological disorders, or received treatments such as splenectomy and organ transplantation, which seriously affected their immune system; (9) History of seizures, mental illness, drinking alcohol, and illicit drug abuse; (10) Pregnant or lactating women.

Discontinuation and withdrawal criteria

The discontinuation and withdrawal criteria were as follows: (1) Subjects who have an acute exacerbation leading to the progression to severe disease during the trial; (2) Subjects who develop allergic reactions or serious adverse events; (3) Subjects who experience serious complications or specific physiological changes during the trial that are unsuitable to continue the study; (4) Subjects with poor medication adherence (<80% of dose) or who no longer receive dosing and testing are considered unsuitable to continue in the trial. The reasons for their withdrawal should be recorded in detail. (5) For whatever reason, the patient is unwilling or unable to continue the trial and requests withdrawal from the trial.

Usage and detection principle

For those with negative results of the rapid influenza antigen test, the usage is the collected person first rinses his mouth with normal saline, and the sampler puts the swab into sterile normal saline to moisten it (it is forbidden to put the swab into the virus preservation solution to avoid allergies caused by antibiotics), the head of the collected person is slightly tilted, the mouth is wide open, and the "ah" sound is made, exposing the tonsils on both sides, the swab is crossed over the base of the tongue, and the tonsils on both sides of the collected person are wiped back and forth at least 3 times with a little force, and then wiped up and down the posterior pharyngeal wall at least 3 times, and the swab head is immersed in a virus preservation solution containing 2~3ml (isotonic saline solution can also be used, tissue culture solution or phosphate buffer) in the tube, discard the tail and tighten the cap. A throat swab can also be placed in the same tube as a nasopharyngeal swab.Detection principle: The real-time RT-PCR-based method for the detection and identification of influenza viruses includes a series of oligonucleotide primers and dual-labeled Taqman probes for the qualitative identification of influenza viruses in respiratory samples and virus isolated cultures using Real-time RT-PCR assays. Among them, the primers and probes for the detection of influenza A and B viruses are general-purpose detection primers and probes, which can be used for the identification of influenza A and B virus types, respectively. Other primer probes are subtype-specific detection primer probes that can be used to identify seasonal influenza viruses currently circulating in the population as well as avian influenza virus subtypes that can infect humans.

For those rapid influenza antigen test result was negative were further screened for respiratory viruses, the usage is 1. To prepare the reagent, take out the reaction buffer and primer probe Mix in the kit, place it at room temperature, wait for complete thawing, shake and mix, and centrifuge for later use; Take out the detection enzyme solution in the kit, centrifuge and set aside, prepare PCR-Mix according to the number of samples to be prepared N (N = number of samples + 1 tube of positive control + 1 tube of negative control), and divide 20 μL of PCR-Mix per well into the fluorescence quantitative PCR eight-link reaction tube, and immediately put it into cryopreservation below −18°C after the reaction buffer, primer probe Mix and detection enzyme solution are used. 2. Sample processing,

after the sample is received, the water bath is used for inactivation at 56°C for 30 min, the collected throat swab sample should be extracted, and the RNA sample should be guaranteed to meet the number of RNA required by the experiment, and the extracted RNA sample should be detected immediately or stored below −70°C (no more than 7 days); At the same time, the corresponding volume of positive and negative controls was extracted. 3. Add 10 μL of each of the negative control extraction RNA, positive control extraction RNA, and RNA to be tested in step 2 to each set reaction tube, close the tube cap tightly, and centrifuge briefly. 4. Conduct an analysis of the results. Detection principle: A number of respiratory pathogen nucleic acid detection kits (PCR-fluorescent probe method) use Taqman fluorescent probe method to design primer probes for fluorescence detection for highly conserved and specific regions such as influenza A virus, influenza B virus, respiratory syncytial virus, adenovirus, rhinovirus and Mycoplasma pneumoniae, etc., using different fluorophores for labeling, the nucleic acids in the detection process are reverse transcribed into cDNA, and in the amplification process, specific primers and probes are bound to the target sequence. The DNA polymerase activity and 5'-3' exonuclease activity of Taq enzyme were used to achieve complete synchronization between PCR product formation and fluorescence signal accumulation. Qualitative detection of influenza A virus, influenza B virus, respiratory syncytial virus, adenovirus, rhinovirus and Mycoplasma pneumoniae nucleic acid in samples was achieved by detecting different fluorophore signals.

Randomization and masking

We randomly assigned patients (1,1) to receive treatment with Lianhua Qingwen granule or matching placebo (manufactured by Shijiazhuang Yiling Pharmaceutical Co. Ltd., Shijiazhuang, China) based on the randomization numbers generated with the SAS package (SAS Inc., Cary, United States). The block size was 4 with no stratification. With a competitive recruitment scheme, the sub-site investigators allocated patients in an ascending order. The study medications had an identical color, odor and appearance, except that the placebo did not contain any active ingredient of LHQW. Patients, the study investigators and other staff were masked to treatment allocation until database lock.

Research methods

Subjects in the experimental group were given Lianhua Qingwen granule (10 bags per box, 6 g per bag), 2 bags at a time, 3 times a day, which was composed of Chinese herbs (Table 1).

The control group subjects were given placebo, 2 bags at a time, 3 times a day, and the treatment course was 7 days. The placebo of Lianhua Qingwen granules was made of dextrin (59.45%), lactose (39.63%), caramel (39.63%), sunset yellow (0.01%), tartrazine (0.02%), and menthol (0.14%), which did not contain inert substances. All test drugs were provided by Yiling Pharmaceutical. Clinical symptoms and signs were followed up every day for 7 days. Blood samples were collected for routine biochemical tests on the 8th day. Combined administration and adverse events were recorded.

In addition to research drugs, basic conventional treatment drugs refer to the Guidelines for Diagnosis and Treatment of Community-acquired Pneumonia issued by the Chinese Thoracic Society in 2015. Antiviral drugs and Chinese medicines with antiviral effects, such as Xiyanping, Reduning, Tanreqing, Jinhuaqinggan, and Banlangen, were not allowed to be used within one week before participating in this study and after entering the randomization period. The name, dosage, frequency, and treatment time of antibiotics, hormones, antipyretic analgesics, and cough and asthma relief drugs that were used should be recorded in the case report form. Taking medication for other diseases must also be recorded in the case report form. Subjects could take medications to control hypertension, angina, and diabetes.

Assessment

Efficacy assessment

The main end point of efficacy was the decrease of clinical symptom score at day 7, which was the sum of eight symptom scores including fever, cough, phlegm, chest pain, muscle pain, chills, dyspnea, and thirst. Secondary efficacy endpoints included the proportion of patients whose blood oxygen saturation returned to

TABLE 1 Composition of LHQW.

Botanical name	Family	Used part	Weight
Forsythia suspensa (Thunb.) Vahl	Oleaceae	Fructus	255 g
Lonicera japonica Thunb.	Caprifoliaceae	Flower bud	255 g
Gypsum Fibrosum	–	–	255 g
Isatis indigotica Fortune	Brassicaceae	Root	255 g
Dryopteris crassirhizoma Nakai	Dryopteridaceae	Rhizoma	255 g
Houttuynia cordata Thunb.	Saururaceae	Whole plant	255 g
Ephedra sinica Stapf	Ephedraceae	Stem	85 g
Glycyrrhiza uralensis Fisch.	Leguminosae	Rhizoma	85 g
Pogostemon cablin (Blanco) Benth.	Labiatae	Whole plant	85 g
Armeniaca sibirica (L.) Lam.	Rosaceae	Seed	85 g
Rhodiola crenulata	Crassulaceae	Rhizoma	85 g
Rheum palmatum L.	Polygonaceae	Rhizoma	51 g
Mentha haplocalyx Briq.	Mentha	Aerial part	7.5 g

normal; the relief rate of individual symptoms such as fever, cough and expectoration (symptom relief was defined as: when the pre-treatment symptom score was >2 points, less than 2 points was considered symptom relief; when the pre-treatment symptom score was ≤2 points, 0 point was considered symptom relief); length of hospital stay; RICU transfer time; incidence of complications; and antibiotic utilization rate.

According to the specific conditions of the patients, the study doctors decide whether to be hospitalized or treated at home. The patients receiving treatment at home will visit the hospital and complete the relevant efficacy evaluation, laboratory and imaging examinations according to the visit time stipulated in the program. Participants receiving treatment at home filled out a symptom score and medication status on a daily basis, and the investigators assessed the subjects' medication compliance based on the diary cards filled out by the patients and the amount of medication withdrawn.

Safety assessment

Safety endpoints comprised the incidence of adverse events; clinical laboratory indicators including blood routine, urine routine, serum biochemistry examination (CK, ALT, AST, Bun, Cr); 12-lead ECG examination; physical examination: a. complete physical examination: general condition (including height and weight), vital signs (including blood pressure and pulse rate), skin (including hair and nails), EENT, neck/thyroid, chest/lung, cardiovascular system, abdominal/gastrointestinal system, genitourinary system, nervous system, lymph, and skeletal muscle. b. simplified physical examination: general information (including weight), vital signs (including blood pressure and pulse rate), chest/lung, cardiovascular system. c. vital signs: sitting blood pressure, pulse rate, respiratory rate, and heart rate.

Statistical analysis

Sample size estimation

The primary endpoint is the reduction in clinical symptom score. The authors assumed that the efficacy rate of the trial group was 80% and that of the control group was 60% according to the clinical experience. The patients in the trial group and the control group were allocated in the ratio of 1:1 (a = 0.05 [bilateral] and power = 0.80) and the total sample size of this study was finally set to 164, including 82 cases in the trial group and 82 cases in the control group according to Power Analysis and Sample Size (PASS)15.0 calculation.

Clinical data analyses and outputs

Statistical analysis was performed using SAS 9.3 software. p value indicates a statistical difference, $p < 0.05$ indicates a statistically significant difference. Two-sided tests was used for baseline comparison before treatment between the two groups. Group T-test or Wilcoxon rank-sum test was used to compare quantitative data. Chi-square test or exact probability method was used to compare categorical data. Wilcoxon rank-sum test was used to compare grade data.

A covariance model was constructed with clinical symptom remission rate as the dependent variable, and clinical symptom scores, grouping, and baseline characteristics as independent variables. The least-square mean and 95% confidence interval were calculated and compared between the trial and control groups. The treatment in the trial group achieved higher efficacy compared with the control group when H0 was rejected at the significance level of $\alpha = 0.05$, or the lower limit of 95% CI was greater than 0 when comparing the difference in clinical symptom remission rate between the two groups.

Results

Study recruitment and follow-up

From January 2016 to December 2018, a total of 169 subjects meeting the study requirements were enrolled in 12 hospitals.

A total of 296 subjects were screened and 174 subjects were randomly enrolled, including 90 in the trial group and 84 in the control group. There were 151 subjects, including 76 in the trial group and 75 in the control group, in the FAS set. PPS set comprised 140 subjects, including 68 in the trial group, and 72 in the control group. SS set covered 169 subjects, including 87 in the trial group and 82 in the control group. A total of 160 subjects completed the study, including 80 in the trial group and 80 in the control group. Totally, 14 subjects dropped out the trial, including 10 in the trial group, and 4 in the control group (Figure 1).

Subject characteristics

According to FAS set data analysis, the average age of the subjects was 46.83 ± 20.94 years in the trial group, and 43.29 ± 19.72 years in the control group. Subjects in the trial group had a body weight of 63.74 ± 14.55 Kg and a BMI of 22.98 ± 4.17 Kg/m^2, and those in the control group had a body weight of 64.05 ± 13.27 Kg and a BMI of 23.43 ± 3.86 Kg/m^2. The average body temperature of the subjects in the trial and control group was 37.71 ± 1.09 and 37.83 ± 1.09, respectively. There were no significant differences in vital signs (body temperature, respiration and heart rate, pulse, and blood pressure), symptoms and signs of runny nose, sore throat, rales, headache and fatigue, and diarrhea during the screening period between the two groups ($p > 0.05$). There was no significant difference in clinical symptom scores (the sum scores of eight symptoms including fever, cough, phlegm, chest pain, muscle pain, chills, dyspnea, and thirst) between the two groups during the screening period ($p > 0.05$). Patients in both groups were diagnosed with non-influenza viral pneumonia. The baseline data of the two groups were comparable ($p > 0.05$) (Table 2).

Clinical outcomes

After 7 days of treatment, the clinical symptom relief rates of the trial groups were 82.98% (FAS) and 87.12% (PPS), respectively, and the clinical symptom relief rates of the control group were 75.11% (FAS) and 76.02% (PPS), respectively. The trial group achieved a better efficacy compared with the control group ($p < 0.001$). The difference in remission rate between the two groups was 7.87 [95%CI (0.42, 15.32)] (FAS) and 11.10 [95%CI (4.61, 17.58)] (PPS), respectively. ANCOVA showed that the lower limit of 95%CI was greater than 0 when comparing the difference in remission rate of clinical symptoms between the two groups, indicating that the treatment in the trial group was superior to the control group. The results of FAS and PPS analyses were consistent (Tables 3–5).

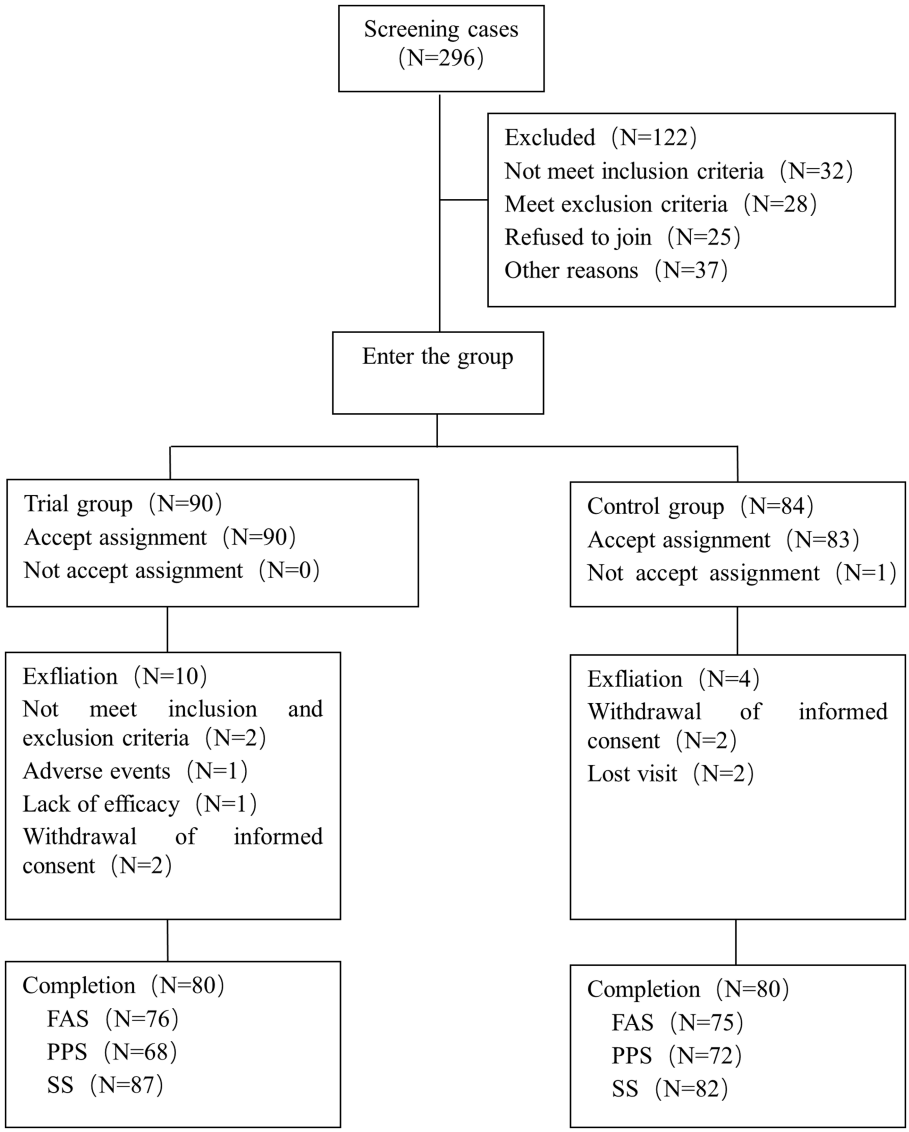

FIGURE 1
Study flow diagram.

On the 7th day of treatment, subjects in the trial group had significant improvements in cough and expectoration compared with those in the control group ($p < 0.05$). There were no statistical differences in fever, sputum color change, chest pain, muscle pain, dyspnea, chills, thirst, and other symptoms ($p > 0.05$) (Tables 3–6).

Some subjects in FAS were dropout (exclusion) and were not included in the PPS, of which 1 patient withdrew informed consent, 3 patients had poor compliance, 1 patient had adverse events, 1 patient lacked efficacy withdrawal, and 5 patients did not come to the hospital on time for a revisit visit (Table 7).

Safety

There were no significant differences in body weight, vital signs, blood routine, urine routine, stool routine, and blood biochemical results (CK, AST, ALT, Bun, and Cr) between the two groups before and after 7 days of treatment ($p > 0.05$). During treatment, there was no significant difference in the incidence of adverse events and serious adverse events between the two groups ($p > 0.05$) (Table 8).

Discussion

Pneumonia is estimated to cause the death of more than 3 million people worldwide each year. In the last decade, with the improvements in sensitivity, availability, and affordability of molecular pathogen detection methods, there has been a new understanding of the structure of pneumonia (3). As one of the pathogens causing community-acquired pneumonia, pneumonia virus has attracted more and more attention. At least 20 viruses, such as influenza A, B, and C viruses, respiratory syncytial viruses, rhinoviruses, parainfluenza viruses, adenoviruses, human metapneumoviruses, human boca viruses, and coronaviruses, have been found to cause pneumonia. The

TABLE 2 Baseline demographic and clinical characteristics of the full-analysis set.

	LHQW group (*N* = 76)	Placebo group (*N* = 75)	Total (*N* = 151)
Age (years), Mean ± SD	46.83 ± 20.94	43.29 ± 19.72	45.07 ± 20.35
Females, n(%)	42 (55.26)	46 (61.33)	88 (58.28)
males, n(%)	34 (44.74)	29 (38.67)	63 (41.72)
Height (cm), Mean ± SD	166.01 ± 7.90	164.93 ± 7.86	165.48 ± 7.87
BMI (kg/m^2), Mean ± SD	22.98 ± 4.17	23.43 ± 3.86	23.20 ± 4.01
Vital signs			
Body temperature (°C), Mean ± SD	37.71 ± 1.09	37.83 ± 1.09	37.77 ± 1.09
Breath (Times/min), Mean ± SD	19.66 ± 2.16	19.84 ± 2.27	19.75 ± 2.21
Heart rate (Times/min), Mean ± SD	87.17 ± 12.06	90.92 ± 14.28	89.03 ± 13.30
Pulse (Times/min), Mean ± SD	87.17 ± 12.06	90.88 ± 14.30	89.01 ± 13.31
Systolic blood pressure (mmHg), Mean ± SD	119.79 ± 14.80	120.99 ± 15.92	120.38 ± 15.33
Diastolic blood pressure (mmHg), Mean ± SD	73.25 ± 9.82	74.09 ± 8.96	73.67 ± 9.38
Symptoms or signs			
Running nose, yes, n (%)	12 (15.79)	11 (14.67)	23 (15.23)
Running nose, no, n (%)	64 (84.21)	64 (85.33)	128 (84.77)
Angina, yes, n (%)	28 (36.84)	25 (33.33)	53 (35.10)
Angina, no, n (%)	48 (63.16)	50 (66.67)	98 (64.90)
Nasal obstruction, yes, n (%)	9 (11.84)	15 (20.00)	24 (15.89)
Nasal obstruction, no, n (%)	67 (88.16)	60 (80.00)	127 (84.11)
Rale, yes, n (%)	25 (32.89)	27 (36.00)	52 (34.44)
rale, no, n (%)	51 (67.11)	48 (64.00)	99 (65.56)
Headache and fatigue, yes, n (%)	39 (51.32)	38 (50.67)	77 (50.99)
Headache and fatigue, no, n (%)	37 (48.68)	37 (49.33)	74 (49.01)
diarrhea, yes, n (%)	3 (3.95)	7 (9.33)	10 (6.62)
diarrhea, no, n (%)	73 (96.05)	68 (90.67)	141 (93.38)
Self-medication before visit, yes, n (%)	43 (56.58)	46 (61.33)	89 (58.94)
Self-medication before visit, no, n (%)	33 (43.42)	29 (38.67)	62 (41.06)

TABLE 3 Comparison of clinical symptom relief rate between the two groups after 7 days of treatment.

		FAS		PPS	
Indicator		Trial group	Control group	Trial group	Control group
Clinical symptom remission rate (%)	Mean (SD)	82.98 (24.00)	75.11 (22.28)	87.12 (18.01)	76.02 (20.62)
	P*	0.004		<0.001	

Clinical symptom remission rate (%) = (clinical symptom score before treatment – clinical symptom score after treatment)/score before treatment X100. *Wilcoxon rank sum test.

TABLE 4 Optimal test of 7-day clinical symptom relief rate between the two groups.

		FAS		PPS	
Indicator	Control	Remission rate	95%CI	Remission rate	95%CI
Clinical symptom remission rate (%)	control group	7.87	0.42,15.32	11.10	4.61,17.58

The optimal threshold is 0.00%.

normal lower respiratory tract is not colonized by viruses. Viral pneumonia is mainly caused by virus infection, usually affecting the upper respiratory tract down to the respiratory tract. Viral pneumonia is often highly seasonal and contagious, with a high incidence in winter and spring, and is easy to spread. Some special populations, such as the elderly, children and those with chronic underlying diseases, are

TABLE 5 The corrected mean difference in 7-day clinical symptom remission rate between the two groups.

	FAS		PPS	
	Trial group	Control group	Trial group	Control group
Fixed mean	85.53	77.48	88.39	77.01
Standard error	2.98	2.95	2.59	2.48
Test statistic t	2.116		3.467	
P	0.036		<0.001	
Corrected mean difference	8.05		11.38	
95%CI	0.53,15.57		4.88,17.88	

Baseline clinical symptom score before treatment was a covariate, and there was no interaction between the centers and the subgroups.

TABLE 6 Comparison of single symptom relief between the two groups.

Symptoms	FAS			PPS		
	Trial group	Control group	*p*-value	Trial group	Control group	*p*-value
Fever	68/69 (98.55%)	71/72 (98.61%)	0.949	66/67 (98.51%)	70/71 (98.59%)	0.949
Cough	64/69 (92.75%)	58/72 (80.56%)	0.018	62/67 (92.54%)	57/71 (80.28%)	0.019
Expectoration	52/69 (75.36%)	41/72 (56.94%)	0.019	51/67 (76.12%)	40/71 (56.34%)	0.010
Chest pain	69/69 (100.00%)	70/72 (97.22%)	0.144	67/67 (100.00%)	69/71 (97.18%)	0.144
Muscle soreness	69/69 (100.00%)	70/72 (97.22%)	0.151	67/67 (100.00%)	69/71 (97.18%)	0.151
Chills	68/69 (98.55%)	71/72 (98.61%)	0.942	66/67 (98.51%)	70/71 (98.59%)	0.942
Difficulty breathing	69/69 (100.00%)	69/72 (95.83%)	0.070	67/67 (100.00%)	68/71 (95.77%)	0.057
Thirst	69/69 (100.00%)	71/72 (98.61%)	0.317	67/67 (100.00%)	70/71 (98.59%)	0.317

TABLE 7 List of dropout/exclusion subjects.

						Analysis dataset		
No	Group	Enrollment time	Dropout/ Exclusion	Date of last visit	Cause of dropout/ exclusion	PPS	FAS	SS
1	Trial group	2016-12-13	Dropout	2016-12-16	Withdrew informed consent	No	Yes	Yes
2	Trial group	2018-02-24	Exclusion	2018-03-05	Poor compliance	No	Yes	Yes
3	Trial group	2017-01-16	Dropout	2017-01-17	The patient did not come to the hospital on time for a revisit visit	No	Yes	Yes
4	Trial group	2018-01-26	Dropout	2018-01-30	Adverse events	No	Yes	Yes
5	Trial group	2017-09-08	Exclusion	2017-09-12	Poor compliance	No	Yes	Yes
6	Control group	2018-05-01	Exclusion	2018-05-08	Poor compliance	No	Yes	Yes
7	Trial group	2017-11-11-	Dropout	2017-11-14	The patient did not come to the hospital on time for a revisit visit	No	Yes	Yes
8	Trial group	2017-07-26	Dropout	2017-07-30	Lack of efficacy and withdrawal	No	Yes	Yes
9	Control group	2017-11-12	Dropout	2017-11-19	The patient did not come to the hospital on time for a revisit visit	No	Yes	Yes
10	Trial group	2017-12-12	Dropout	2017-12-15	The patient did not come to the hospital on time for a revisit visit	No	Yes	Yes
11	Control group	2017-12-28	Dropout	2017-12-31	The patient did not come to the hospital on time for a revisit visit	No	Yes	Yes

TABLE 8 The incidence of adverse events between the two groups.

	Trial group			Control group			
	Times	Number of people	Percentage	Times	Number of people	Percentage	*p*-value
Adverse events	30	23	26.44%	51	30	36.59%	0.185
Adverse reactions	4	4	4.60%	3	2	2.44%	0.683
Severe adverse events	0	0	0.00%	0	0	0.00%	–
Severe adverse reaction	0	0	0.00%	0	0	0.00%	–
Adverse event leading to abscission	1	1	1.15%	0	0	0.00%	1.000

Adverse reactions refer that the relationship with the study drug is positive, possible, and cannot be determined. Serious adverse events refer that occur at any dose of the investigational drug or at any time during the observation period. Serious adverse reactions refer that cause death, cancer, teratogenesis, birth defects, life-threatening or permanent or significant damage to the human body or organ.

susceptible to severe pneumonia triggered by bacterial or fungal infection, resulting in multiple organ dysfunction (7, 8).

For the treatment of pathogen-induced pneumonia, currently, only antiviral drugs against influenza virus have been proved to be effective. No definitive effects of other antiviral drugs for treating viral pneumonia have been reported. Traditional Chinese Medicine has a rich historical record in the treatment of viral infectious respiratory diseases and has the advantages of a short course of disease, less relapse after antipyretic, and quick elimination of systemic symptoms.

Lianhua Qingwen granule is a pure Chinese medicine preparation, and its components include lianqiao, jinyinhua, zhimahuang, chaokuxingren, shigao, banlangen, mianmaguanzhong, yuxingcao, guanghuoxiang, dahuang, hongjingtian, bohenao, and gancao. Jinyinhua and lianqiao have the effect of clearing away heat, relieving the toxin, and further dispelling wind and heat from the body. Banlangen, guanzhong, and yuxingcao can also clear heat and detoxify, and are important antiviral drugs in Traditional Chinese Medicine. Lianhua Qingwen granules are effective in treating influenza virus, and also have an antiviral effect on common respiratory viruses. At the same time, they have antibacterial, antipyretic, analgesic, anti-inflammatory functions, thereby relieving cough, reducing phlegm, and adjusting immune responses (2, 9, 10).

Some possible shortcomings of this trial are that patients were treated with antibiotics, which are not recommended in any current guidelines for uncomplicated viral pneumonia. About viral pneumonia, it is correct that various guidelines do not recommend the use of antibiotics. The use of antibiotics in viral pneumonia is mainly based on doctors' experience and the habit of fearing secondary bacterial infections after viral infections (11). This is especially common in developing countries, including China (12). Regardless of whether it is pneumonia caused by influenza viruses (13) or pneumonia caused by covid-19 (14) infection, the misuse of antibiotics still exists. There has even been a situation of antibiotic overuse, which is a public health issue that we need to address. In this study, considering the practical situation in clinical settings, there was no specific agreement on the types of antibiotics used. The choice of antibiotics was mainly based on physicians' prescribing habits and the availability of antibiotics. The antibiotics primarily used in this project include Moxifloxacin, Piperacillin Tazobactam, Levofloxacin, Minocycline, Ceftriaxone, Azithromycin, Ceftazidime, and others. There were some differences in the antibiotics used by different research centers, but there was no statistically significant difference in the use of antibiotic types between the two groups, and it did not have a specific impact on the evaluation of the efficacy of Lianhua Qingwen Capsules. Of course, in future research, efforts should be made to further strengthen the management of antibiotic use.

Our results showed that after 7 days of treatment, for both FAS and PPS sets, the remission rate of clinical symptoms and the total score of clinical symptoms in the trial group were improved compared with the control group, with statistical significance. Moreover, there were no significant differences in safety evaluation indexes, such as body weight, vital signs, blood routine, urine routine, stool routine, creatine kinase, alanine aminotransferase, aspartate aminotransferase, creatinine and urea nitrogen, between the two groups. There were no significant differences in the incidence of adverse events and serious adverse events between the two groups, suggesting that Lianhua Qingwen granules were well tolerated and safe.

Conclusion

Lianhua Qingwen granule treatment improved the clinical symptoms of patients with non-influenza virus pneumonia, especially the symptoms of cough and expectoration, and was associated with good safety.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing Ditan Hospital Capital Medical University, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CM: Writing – original draft, Writing – review & editing. BC: Writing – original draft, Writing – review & editing. YL: Writing – original draft, Writing – review & editing. LG: Writing – original draft, Writing – review & editing. JD: Project administration, Writing – original draft. ZX: Project administration, Writing – original draft. LW: Project administration, Writing – original draft. ZH: Project administration, Writing – original draft. XN: Project administration, Writing – original draft. SF: Project administration, Writing – original draft. BC: Project administration, Writing – original draft. LS: Project administration, Writing – original draft. LY: Project administration, Writing – original draft. XL: Conceptualization, Supervision, Writing – original draft. RJ: Conceptualization, Supervision, Writing – original draft.

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Conflict of interest

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

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Can acupuncture increase microcirculation in peripheral artery disease and diabetic foot syndrome? – a pilot study

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Background: Globally, diabetes mellitus (DM) and peripheral artery disease (PAD) have an increasing incidence and a high prevalence and are both associated with high morbidity and complication rates, e.g., as chronic non-healing peripheral ulcers. Impaired macro- and microcirculation and peripheral neuropathy lead to an increased risk of foot ulcers and infections. These complications are difficult to treat, have a high risk of becoming chronic and often lead to lower limb amputation. The aim of this planned study was to investigate the potential effects of acupuncture on improving microcirculation in patients with Diabetic Foot Syndrome (DFS) and PAD.

Materials and methods: In 18 patients with chronic non-healing peripheral ulcers and diagnosed DM or PAD, data on 8 microcirculatory parameters were collected simultaneously on intact skin close to the wound margin. Microcirculation was assessed using an O2C device combining laser Doppler shift and white light spectroscopy (LEA Medizintechnik GmbH, Giessen, Germany). Unilateral and bilateral acupuncture was performed on the connecting line between acupuncture points Stomach 14 and Stomach 15.

Results: After unilateral acupuncture (ipsilateral to the wound side), a statistically significant improvement in 7 out of 8 microcirculatory parameters was demonstrated compared to baseline measurements before acupuncture. After bilateral acupuncture, there was an additional improvement and statistical significance in all parameters in both DFS and PAD patients.

Discussion: These results show an improvement in the microcirculation and peripheral blood flow at the edges of the wound. As impaired micro- and macrocirculation is considered to be a critical prognostic factor for the healing of a peripheral lesion, the intervention could have a positive impact on the healing of (chronic) peripheral wounds.

KEYWORDS

peripheral artery disease (PAD), diabetes mellitus, acupuncture, chronic wounds, microcirculation, diabetic foot syndrome (DFS)

1 Introduction

Diabetes mellitus (DM) and peripheral artery disease (PAD) have an increasing incidence and a high prevalence worldwide. While around half a billion people currently suffer from diabetes, this figure is estimated to rise to more than three-quarters of a billion by 2045 (1). The situation is similar for PAD, the prevalence grew between 2000 and 2010 by 24% (2). In the meantime, far more than 200 million individuals are affected worldwide. The prevalence increases continuously with age. In high-income countries, it is estimated to be under 4% for men and women aged 40 to 44 years and over 20% for those over 80 years. The PAD prevalence is expected to continue to rise (3–5).

DM and PAD are both associated with high morbidity. Chronic non-healing peripheral ulcers, eventually combined with wound infections, are common in both patients with DM and patients with PAD. Diabetic foot syndrome (DFS) is one of the most clinically significant complications in patients with DM. Impaired blood flow and peripheral neuropathy increase the risk for foot ulcers and infections (6). People with diabetes mellitus have an estimated lifetime incidence of foot ulcers of up to 34% with frequent recurrences (7).

This is associated with a high economic burden. In the US, the treatment of diabetic foot syndrome is as expensive as that of carcinomas, with a comparable 5-year mortality rate (8). Recently, a large-scale study in Southeast Asia showed that coordinated care of patients with DFS from primary to tertiary care effectively reduces amputation rates (9). The data support the demand for a multi-disciplinary and interprofessional team approach in the management of DFS and lower extremity amputation prevention, as recommended by both the National Institute for Health and Care Excellence (NICE) and International Working Group on Diabetic Foot (IWGDF) guidelines (10, 11).

A common basic principle for the healing of a peripheral lesion is the restoration of impaired macro- and microcirculation, as this is considered to be a critical prognostic factor for wound healing (12–14). However, despite successful restoration of the macrocirculation, chronic wounds fail to heal in many cases. In a systematic review, wound healing was not achieved in 40% within 1 year in patients with DFS and PAD treated by endovascular or surgical therapy, and the major amputation rate was up to 10% (15). In addition, new treatment strategies are urgently needed for extremities at risk of amputation which cannot be revascularized for various reasons (16). In recent years, the crucial importance of microcirculation for limb preservation in both DFS and PAD has been emphasized. There is clear evidence that the microvascular function is altered first in the presence of risk factors associated with atherosclerosis (17). Even at the stage of intermittent claudication, microcirculation plays an important pathophysiological role (18). Patients with either diabetes or PAD demonstrate deteriorated cutaneous oxygen saturation at the plantar foot (19). Impaired microcirculation increases the risk of amputation in individuals with PAD by more than 20 times compared to those who neither have PAD nor microvascular disease (20). Therefore, interventions to improve cutaneous tissue oxygenation may be considered valuable therapy approaches to avoid complications and to promote the healing of chronic, non-healing peripheral ulcers.

One approach that might meet these criteria is acupuncture. It is a therapy from Traditional Chinese Medicine (TCM) and can be understood as reflex zone therapy, where certain areas of the body are stimulated with acupuncture needles (21, 22). Although the mechanisms of action of acupuncture have not yet been fully scientifically clarified, there are numerous publications that prove the effectiveness and efficacy of acupuncture (23–28). According to current studies, acupuncture can be used to increase peripheral microcirculation and skin blood perfusion (29–33). This effect may be useful in the therapy of DM and PAD patients with chronic ulcers. The aim of the study therefore was to investigate potential effects of acupuncture on microcirculation close to the wound margin in patients with DM or PAD.

2 Methods

2.1 Study design

We conducted a prospective, non-controlled pilot study to assess changes in microcirculation before and after intervention in patients with DM and PAD following unilateral or ipsilateral acupuncture.

The study was reviewed and approved by the Medical Ethics Committee II of the Mannheim Medical Faculty under the numbers 2013–546 N-MA and 2013–547 N-MA for the study in patients with PAD and DFS, respectively.

2.2 Study population

Inpatients from the Department of Angiology and Diabetes-related Diseases at the Diakonissenkrankenhaus Mannheim, Germany, were selected according to the following inclusion and exclusion criteria.

2.2.1 Inclusion criteria

Patients with peripheral lesions of the lower limbs and diagnosed PAD Fontaine stages III-IV (34, 35) or DFS, Wagner-Armstrong classification stages 1–4 A-D (36) were included in the study. All study participants provided written informed consent in German language.

2.2.2 Exclusion criteria

Exclusion criteria were angiological intervention (e.g., percutaneous transluminal angioplasty or bypass surgery) within the previous 2 months, acute ischemia, vasoactive therapy within the previous 48 h, body temperature > 37.8°C or systemic signs of infection. Other exclusion criteria were skin disease in the area of the acupuncture point, oral anticoagulation therapy and women of childbearing age.

2.3 Intervention

The intervention is reported according to the STRICTA guidelines (37). Acupuncture was provided by two physicians with an additional specialization in acupuncture from the Medical Chamber Baden-Württemberg, Germany, or an equivalent of at least 200 teaching hours. Each acupuncturist had more than 10 years' experience in acupuncture and TCM. The acupuncture treatment

TABLE 1 Sociodemographic data: description of the study population.

Characteristics		$n = 18$	[%]
Disease	PAD	9	50
	DFS	9	50
Gender	Male	12	66.7
	Female	6	33.3
Acupuncture	Ipsilateral	8	44.4
	Ipsi- and contralateral	10	56.6
Age [mean (SD)]		76.94 (9.5), min 55, max 92	

SD, Standard Deviation.

consisted of a single acupuncture session of approximately 5 minutes' duration. The acupuncture was performed on the connecting line between the acupuncture points Stomach 14 (ST 14, 库房, kù fáng) and Stomach 15 (ST 15, 屋 翳, wū yì) (22). These points are located at the front of the chest in the first and second intercostal space respectively, on the mamillary line. The selected points were chosen based on principles of Chinese medical theory and supported by available evidence, as follows: (i) According to Chinese medical theory, points are selected based on their location along the same meridian (38). Acupuncture points on the Stomach meridian were chosen to target the back of the foot, where many chronic wounds in PAD and DFS are located. The Stomach meridian starts at the lateral side of the nose, runs through the chest and abdomen, extends to the front of the upper and lower leg, and ends at the back of the foot on the second toe (22). (ii) Additionally, a fundamental principle of acupuncture emphasizes the combination of local and distal points. Due to a relative contraindication for needling close to open wounds, only distal points were chosen for needling (22). (iii) The decision to use the region between these two points on the chest was further supported by clinical experience and observations within the author group, as understood in terms of internal evidence. Acupuncture was applied either unilaterally (ipsilateral to the wound side) or bilaterally (first ipsi- then contralateral) to the other half of the participants. A so-called sparrow-picking or blood-letting technique was used with standardized needles (Becton Dickinson B-D Micro Fine ™ + Demi insulin syringes 0.3 × 5 mm, 31 G) (32, 39, 40). The needles were inserted to their full length of 5 mm, no needle retention was used in this technique. No specific response (e.g., de qi) was sought. No other interventions (e.g., moxibustion, cupping, lifestyle advice) were given to the participants.

2.4 Micro-lightguide spectrophotometer (O2C)

Microcirculation was assessed using an Micro-lightguide Spectrophotometer (O2C device), which combines a laser Doppler shift and white light spectroscopy system (LEA Medizintechnik GmbH, Giessen, Germany) (41). A flat probe placed horizontally on the tissue collects data simultaneously from the tissue as a multi-channel system. Data collection was performed on the intact skin at the distance of 1 cm from the wound edge of the damaged tissue and covered a time interval from 3 min before acupuncture (= baseline measurement) until 10 min after acupuncture. Due to potential movement artifacts, data recorded 30 s each before and after the acupuncture treatment were excluded from data analysis. Microcirculation was assessed using the following microperfusion parameters: oxygen saturation of hemoglobin (SO2), relative amount of hemoglobin (rHb), relative blood flow (Flow) and blood flow velocity (Velo). SO2 was expressed as a percentage, rHb, Flow and Velo in arbitrary units (AU). These four parameters were measured at 3 mm (S) and 8 mm (D) depth, resulting in a total of 8 parameters (e.g., Velo S (superficial 3 mm) and Velo D (deep 8 mm)). In cases of diabetic microangiopathy, the O2C device has been shown to provide reliable data and valid non-invasive measurements of tissue oxygenation and microvascular blood flow (42, 43).

2.5 Statistical analysis

Linear mixed models were used to assess the influence of acupuncture on the eight microcirculatory parameters. These models included each measured parameter as a dependent variable, acupuncture (baseline/unilateral acupuncture/ bilateral acupuncture) and disease (PAD/DFS) as fixed factors, and patient as a random factor. The inclusion of patient as a random factor ensures that the clustered data structure is considered in the statistical model (measurements clustered within patients). An additional linear mixed model explored the difference in the effects of acupuncture between PAD and DFS patients by including an interaction term between acupuncture and disease. Restricted maximum likelihood was used to fit all models. Effect estimates were calculated along with *p*-values and 95% confidence intervals of the profile likelihood type. Due to the exploratory nature of the study, no adjustment for multiple testing was made. *P*-values less than 0.05 were considered statistically significant. R version 3.4.2[1] with the packages 'lme4' and 'lmerTest' was used for statistical analysis.

3 Results

3.1 Patient characteristics: sociodemographic and clinical characteristics

A total of $n = 18$ patients were included in the pilot study, thereof $n = 9$ with DFS and $n = 9$ with PAD. Two thirds of the participants were male ($n = 12$) and one third female ($n = 6$). Age of the participants ranged from 55 to 92 years, with a mean of 77 years (SD 9.5). Additional clinical characteristics of the study population are shown in Table 1.

3.2 Unilateral and bilateral acupuncture in pre-post comparison in patients with DFS and PAD

After unilateral acupuncture (ipsilateral to the wound side), a statistically significant improvement in seven out of eight

1 http://r-project.org

microcirculatory parameters (superficial and deep Flow, Velo and rHb as well as in deep S02) could be demonstrated in both patients with PAD and DFS with chronic non-healing peripheral ulcers compared to baseline measurements before acupuncture. With unilateral acupuncture alone, superficial SO2 measurements did not show a statistically significant improvement. However, bilateral acupuncture (first ipsi-, then contralateral) led to statistically significant improvements in all eight microcirculatory parameters s compared to baseline measurements. When comparing unilateral versus bilateral acupuncture in patients with both DFS and PAD, an additional improvement in all parameters was observed after bilateral acupuncture. Further details are shown in Tables 2, 3.

3.3 Acupuncture in patients with DFS versus PAD

Table 4 shows the different results of the acupuncture intervention in patients with PAD compared to patients with DFS for unilateral and bilateral acupuncture compared to baseline measurements before acupuncture. For all superficial measurements (3 mm depth), better results could be shown for single and bilateral acupuncture in patients with DFS compared to patients with PAD (values marked with ∞ in Table 4). For the deep measurements (8 mm depth), an inverse trend could be found. After unilateral acupuncture, SO2 and Velo measurements were better in patients with DFS compared to PAD. On the contrary, Flow and rHb measurements were better in PAD compared to DFS (values marked with Δ in Table 4). Measurements of blood flow showed the most distinct differences between patients with DFS and PAD. In addition, with bilateral acupuncture, all deep measurements showed better results in PAD than in DFS. Although there were some trends, not every difference shown between patients with DFS and PAD reached statistical significance. Figure 1 shows the mean values for the differences in treatment effect along with 95% confidence intervals in the acupuncture intervention between patients with PAD and DFS in unilateral acupuncture and bilateral acupuncture when compared to baseline measurements before acupuncture.

4 Discussion

After unilateral acupuncture (ipsilateral to the wound side), a statistically significant improvement in seven out of eight microcirculatory parameters (SO2, rHb, Flow and Velo) was demonstrated at 3 mm and 8 mm depths compared to baseline measurements before acupuncture. These results correspond to an increase in microcirculation around the wound margin. Impaired micro- and macrocirculation is considered a critical prognostic factor for the healing of a peripheral lesion (12–14). Beside arterial revascularization as main therapeutic option, there is limited evidence for non-revascularization interventions including, e.g., Prostanoids (16). Although recommended to accelerate ulcer healing, pain reduction and amputation prevention in PAD (44, 45), Alprostadil (prostaglandin E1) failed to show superiority over placebo in a placebo-controlled randomized multicenter trial (46). Therefore, the results of this study must be interpreted with great caution when considering their clinical implications in wound healing. Nevertheless, acupuncture may have a positive influence on wound healing in (chronic) peripheral wounds. As numerous studies have explored acupuncture's impact on microcirculation, including

TABLE 2 Difference between baseline measurements (Base), unilateral acupuncture (Acu 1) and bilateral acupuncture (Acu 2).

Parameter			Estimate	Std. Error	value of p	95% Confidence Interval	
						Lower bound	Upper bound
Flow	Flow S	Acu 1 vs. Base	12.08	1.12	**< 0.001**	9.89	14.27
		Acu 2 vs. Base	18.16	1.36	**< 0.001**	15.49	20.83
	Flow D	Acu 1 vs. Base	9.33	1.10	**< 0.001**	7.18	11.48
		Acu 2 vs. Base	20.92	1.34	**< 0.001**	18.29	23.54
SO2	SO2 S	Acu 1 vs. Base	0.34	0.26	0.186*	−0.16	0.85
		Acu 2 vs. Base	1.67	0.32	**< 0.001**	1.05	2.29
	SO2 D	Acu 1 vs. Base	1.57	0.23	**< 0.001**	1.12	2.03
		Acu 2 vs. Base.	3.65	0.28	**< 0.001**	3.10	4.21
Velo	Velo S	Acu 1 vs. Base	1.11	0.15	**< 0.001**	0.82	1.40
		Acu 2 vs. Base	1.71	0.18	**< 0.001**	1.36	2.07
	Velo D	Acu 1 vs. Base	1.14	0.16	**< 0.001**	0.83	1.45
		Acu 2 vs. Base	2.74	0.19	**< 0.001**	2.36	3.12
rHb	rHb S	Acu 1 vs. Base	0.44	0.22	**0.0456**	0.01	0.88
		Acu 2 vs. Base	1.90	0.27	**< 0.001**	1.37	2.42
	rHb D	Acu 1 vs. Base	3.02	0.37	**< 0.001**	2.29	3.74
		Acu 2 vs. Base	5.78	0.45	**< 0.001**	4.89	6.66

Acu 1, unilateral acupuncture; Acu 2, bilateral acupuncture; Base, baseline readings before acupuncture; *p* value: <0.05 statistical significance showed in bold.
* = not statistically significant.

TABLE 3 Difference between unilateral acupuncture (Acu 1) and bilateral acupuncture (Acu 2).

Parameter			Estimate	Std. Error	value of p	95% Confidence Interval	
						Lower bound	Upper bound
Flow	Flow S	Acu 2 vs. Acu 1	6.08	1.36	< **0.001**	3.41	8.75
	Flow D	Acu 2 vs. Acu 1	11.59	1.34	< **0.001**	8.96	14.21
SO2	SO2 S	Acu 2 vs. Acu 1	1.32	0.32	< **0.001**	0.70	1.94
	SO2 D	Acu 2 vs. Acu 1	2.08	0.28	< **0.001**	1.53	2.63
Velo	Velo S	Acu 2 vs. Acu 1	0.61	0.18	< **0.001**	0.25	0.96
	Velo D	Acu 2 vs. Acu 1	1.59	0.19	< **0.001**	1.22	1.97
rHb	rHb S	Acu 2 vs. Acu 1	1.45	0.27	< **0.001**	0.93	1.98
	rHb D	Acu 2 vs. Acu 1	2.76	0.45	< **0.001**	1.87	3.64

Acu 1, unilateral acupuncture, Acu 2, bilateral acupuncture, *p* value: <0.05 statistical significance showed in bold.

TABLE 4 Difference in acupuncture intervention for patients with DFS versus PAD in unilateral acupuncture (Acu 1) and bilateral acupuncture (Acu 2) when compared to baseline measurements before acupuncture.

Parameter				Estimate	Std. Error	*p*-value	95% Confidence Interval	
							Lower bound	Upper bound
Flow	Flow S	Acu 1	DFS vs. PAD	13.86$^{\infty}$	2.20	< **0.001**	9.55	18.17
		Acu 2		1.26$^{\infty}$	2.71	0.642*	−4.04	6.56
	Flow D	Acu 1	DFS vs. PAD	−0.25$^{\Delta}$	2.13	0.907*	−4.42	3.92
		Acu 2		−21.80$^{\Delta}$	2.62	< **0.001**	−26.93	−16.69
SO2	SO2 S	Acu 1	DFS vs. PAD	2.94$^{\infty}$	0.51	< **0.001**	1.94	3.94
		Acu 2		2.96$^{\infty}$	0.63	< **0.001**	1.73	4.19
	SO2 D	Acu 1	DFS vs. PAD	0.712$^{\infty}$	0.46	0.122*	−0.19	1.61
		Acu 2		−1.87$^{\Delta}$	0.57	**0.001**	−2.98	−0.76
Velo	Velo S	Acu 1	DFS vs. PAD	1.95$^{\infty}$	0.29	< **0.001**	1.38	2.52
		Acu 2		0.53$^{\infty}$	0.36	0.139*	−0.17	1.23
	Velo D	Acu 1	DFS vs. PAD	0.21$^{\infty}$	0.31	0.499*	−0.40	0.83
		Acu 2		−1.97$^{\Delta}$	0.39	< **0.001**	−2.73	−1.22
rHb	rHb S	Acu 1	DFS vs. PAD	3.03$^{\infty}$	0.43	< **0.001**	2.18	3.88
		Acu 2		1.94$^{\infty}$	0.53	< **0.001**	0.89	2.98
	rHb D	Acu 1	DFS vs. PAD	−0.20$^{\Delta}$	0.74	0.784*	−1.66	1.25
		Acu 2		−1.69$^{\Delta}$	0.91	0.064*	−3.47	0.10

Acu 1, unilateral acupuncture, Acu 2, bilateral acupuncture.
$^{\infty}$ values = DFS better than PAD.
$^{\Delta}$ values = PAD better than DFS.
p value: <0.05 statistical significance showed in bold.
*not statistically significant.

capillary blood flow, indicating potential improvements under specific conditions (47–49). However, the precise mechanisms underlying acupuncture's effects on microcirculation remain under investigation. Some research proposes various mechanisms, including the release of neurotransmitters (e.g., nitric oxide), activation of mast cells and regulation of the autonomic nervous system among others (50–55). When comparing the results of the acupuncture intervention between patients with DFS and PAD, better results could be shown for superficial measurements in patients with DFS. However, for deep measurements, a more pronounced improvement was seen in patients with PAD compared to DFS. Although these differences are only a trend, as they did not reach statistical significance for every microcirculatory parameter measured, the reason for these differences is not clear. Our findings in patients with DFS are consistent with those recently published by Sang et al., who showed that diabetic patients with arteriosclerotic wounds of the lower extremity had a significant reduction in lesion size after 8 weeks of treatment with electroacupuncture (56). An exact explanation of the precise acupuncture mechanisms of our observed effects can only be hypothesized. We would suggest that the observed results could be mainly due to regulatory effects of the autonomic nervous system, which is known to regulate, e.g., perfusion and vasodilation (57). On

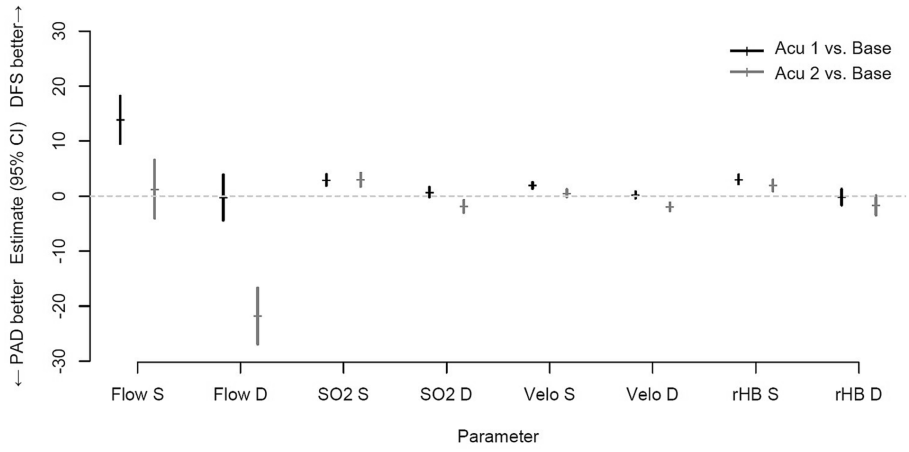

FIGURE 1
Mean outcome differences with 95% confidence intervals in acupuncture intervention between patients with PAD and DFS in unilateral acupuncture (Acu 1) and bilateral acupuncture (Acu 2).

the other hand we would rather rule out that the effects are mainly due to effects on segmental innervation, as the needle insertion point was in the at the cervicothoracic region, whereas the observed effects on microcirculation were in the lumbar or pelvic innervation region. Further studies should address these issues.

4.1 Strengths and limitations

Owing to the exploratory design of this pilot study, there are several limitations that need to be considered when interpreting the results. Due to the small sample size, this study did not include a control group (e.g., sham acupuncture or a control group). This also led to a lack of randomization and blinding of patients. However, as the data recorded before the acupuncture intervention were considered as the baseline measurement, a comparison of the microcirculatory parameters before and after the acupuncture intervention could be implemented in the data analysis. As there was no follow-up in this study, only an immediate acupuncture effect could be demonstrated. As the study used a specific needling technique, it's important to note that the results may not necessarily be applicable to other types of needling or the use of different stimulation methods. Therefore, it is not possible to say how long the effects of acupuncture may last. Whether the measured statistically significant improvement in microcirculatory parameters leads to a clinically significant improvement, resulting in faster healing of chronic peripheral wounds, remains uncertain. Further studies should include a larger sample size, a control group, different needling techniques and ideally, assessments of clinical parameters of wound healing (e.g., wound size with length and width) over a longer period of time, due to the chronicity of lower limb ulcers.

The strength of this study is the investigation of a pragmatic acupuncture approach with a comparatively feasible acupuncture intervention for a worldwide relevant problem of non-healing chronic peripheral wounds in patients with DFS or PAD. As no prior diagnosis according to TCM criteria is required before the acupuncture intervention, it may be a quick and effective method that could potentially be easily implemented and performed during routine medical consultations for both inpatients and outpatients. As no adverse events were reported during the trial, this acupuncture intervention can be considered safe, despite the small sample size. Based on the extensive data available, the overall risk of complications from acupuncture is considered to be very low. No adverse events (e.g., pneumothorax) have been reported in the literature for the acupuncture points used, Stomach 14 and Stomach 15 (58, 59).

These results show an improvement in the microcirculation and peripheral blood flow at the edges of the wound. As impaired micro- and macrocirculation is considered to be the most important prognostic factor for the healing of a peripheral lesion, the intervention may have a positive impact on the healing of (chronic) peripheral wounds.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the author on reasonable request in anonymised form in accordance with the institutional regulations and the General Data Protection Regulation.

Ethics statement

The studies involving humans were approved by Medical Faculty Mannheim, Medical Ethics Commission II (Nr. 2013-546N-MA and 2013-547N-MA). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JV: Conceptualization, Data curation, Investigation, Writing – original draft. MS: Investigation, Writing – review & editing. CD: Investigation, Writing – review & editing. JK: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing

– review & editing. KA: Conceptualization, Resources, Supervision, Validation, Writing – review & editing. HG: Conceptualization, Resources, Supervision, Writing – review & 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.

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Use and acceptance of traditional, complementary and integrative medicine in Germany—an online representative cross-sectional study

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Background: Older representative surveys show that Traditional, Complementary and Integrative Medicine (TCIM) is used by about 60% of the German population. However, no data exists for the current nationwide situation. The main aim of this cross-sectional study is to investigate the current use and acceptance of TCIM in Germany.

Methods: This study is based on a representative sample of the German population aged 18–75 years. Participants were asked about the use and acceptance of TCIM. The survey was conducted online using Computer Assisted Web Interview (CAWI) in 2022 by three renowned German market research institutes on behalf of and in close coordination with the working group. The data set was analyzed descriptively and inferentially.

Results: In total, 4,065 participants (52% female, 48% male, 0.4% diverse) responded completely (response rate: 21.5%). Among participants, 70% stated that they had used TCIM at some point in their lives, with 32% doing so in the last 12 months and 18% currently. The most common reason given (17%) was musculoskeletal pain. For their own health, 39% stated that TCIM is important. Traditional European Medicine was rated as very/mainly effective by 27% of participants and as partly effective by 44% (conventional medicine: 69% very/mainly effective, 19% partly effective). As a complementary treatment strategy to conventional medicine, 35% considered TCIM to be optimal ("Complementary Medicine"), 33% in combination with conventional medicine ("Integrative Medicine") and 5% without conventional medicine ("Alternative Medicine"). The majority of the participants were in favor of more research on TCIM and stated that the costs of TCIM services should be covered by health insurance companies (71% and 69%, respectively).

Conclusion: These results from a representative online-population suggest that the use of TCIM in Germany remains at a high level. The nationwide relevance of TCIM should be given greater consideration in German health care policy making. TCIM should be systematically investigated using appropriate study designs and

methods including high quality randomized clinical trials to investigate their effectiveness, efficacy, therapeutic safety and costs in the future.

KEYWORDS

traditional medicine, traditional European medicine, complementary medicine, integrative medicine, alternative medicine, online-representative, cross-sectional study, Naturheilkunde

1 Introduction

According to the World Health Organization (WHO), Traditional Medicine (TM) "is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (1). In the official WHO strategy paper "Traditional Medicine 2014–2023" and at the 1st WHO Global Summit on TM in August 2023, the WHO also calls for the increased and consistent use of these methods in primary care on a global scale (2, 3). The WHO also uses the term Traditional, Complementary and Integrative Medicine (TCIM) or Traditional, Complementary and Integrative Healthcare (TCIH) (4). We use the term TCIM as a comprehensive umbrella term here.

TM can be used as a complementary, integrative or alternative to conventional medicine (1, 2), represented in terms such as 'Complementary Medicine', 'Integrative Medicine' and 'Alternative Medicine'. The term "Traditional European Medicine" (TEM) stands for German "Naturheilkunde" and refers to a concept of TM especially used in German speaking countries. These terms are often difficult to distinguish from one another in terms of content and the terminology used is sometimes blurred. For this reason, and to make the survey as comprehensive as possible, we decided in a consensus process to use them all while preparing the survey (5) (Table 1).

The lack of clarity is also reflected in the heterogeneity of definitions and differentiations between the various methods. Historically, since the 1980s, the term 'Complementary and Alternative Medicine' (CAM), coined by the *National Institutes of Health* (NIH), has become widely established in the Anglo-American world. It has since been replaced by the modified term 'Complementary and Integrative Medicine' (CIM), which uses the word "integrative" as opposed to "alternative" to focus on the integration of evidence-informed complementary medical procedures into medical treatment as a meaningful extension (7–9). Therapeutic TCIM approaches have alongside conventional therapeutic approaches broad social acceptance in Germany (10, 11). Older surveys (Härtel 2004/Linde 2014) show that TEM was used by approximately 40–60% of the population in Germany in the 12 months prior to the respective survey (11, 12). There is a long tradition of TEM in German-speaking countries (13). In Germany, it is used in particular for health promotion and prevention, in rehabilitation, private clinics, a few inpatient facilities specializing in TEM in public hospitals and, above all, in the outpatient sector, e.g., herbal medicine, Kneipp hydrotherapy, wholefood plant-based nutrition, fasting, among others (6). Since 1988, TEM has been part of the medical licensing regulations as a cross-sectional curricular subject at medical schools (14). In March 2023, 16,118 doctors with the additional qualification of TEM were registered with the medical associations in Germany (15). Moreover, there are currently eleven appointed professors with a focus on TCIM in Germany, focusing on the scientific evaluation of TCIM according to standards of Evidence-Based Medicine (EBM) as well as the meaningful integration of such therapeutic practices into general health care (16). Reimbursement options for TCIM services by statutory health insurers are very limited in Germany. These are currently limited to acupuncture for chronic pain with the diagnosis osteoarthritis of the knee and chronic lower back pain and a very small selection of herbal remedies as well as additional selective offers from single statutory health insurance carriers like osteopathic medicine (17, 18). In the case of private health insurance, reimbursement options depend on the respective company policy. However, they are generally limited. Selected mind–body interventions (e.g., yoga) can be refunded via the so-called prevention paragraph [§20 Sozialgesetzbuch (SGB) Fifth Book (V)] in Germany.

The main aim of this population-representative survey was to update previous study results on the use and acceptance of TCIM in Germany (11, 12) and to examine additional dimensions.

TABLE 1 Definition of the core contextual terms in the field of TCIM.

Traditional European Medicine (TEM, German: Naturheilkunde): Health promotion or treatments with natural healing methods, e.g., with phytotherapy, fasting and a healthy diet, exercise and a healthy lifestyle or Kneipp water treatments (hydrotherapy) (6).
Conventional medicine: the socially established "conventional medicine" taught at medical faculties (7).
Complementary Medicine (CM): traditional diagnostic and therapeutic methods from Western culture that complement conventional medicine, but also, for example, from traditional Chinese or Indian medicine (7).
Integrative Medicine (IM): combination of conventional medicine with evidence based Traditional European Medicine (German: Naturheilkunde) and CM (8).
Alternative medicine: non-scientifically supported healing methods which, by definition, are used as an alternative to conventional medicine, often because conventional methods are rejected (7).

2 Materials and methods

2.1 Study design

The study was conducted by the Charité University Outpatient Clinic for Complementary and Integrative Medicine at the Immanuel Hospital Berlin and the Institute of Social Medicine, Epidemiology and Health Economics of Charité—Universitätsmedizin Berlin. The study was approved by the Charité Ethics Committee and registered with ClinicalTrails.gov (NCT05530720). It was based on an online

cross-sectional survey of the German resident population aged 18–80 years. The collection, processing and storage of all data generated in the study are carried out in accordance with the international guidelines for clinical trials (Declaration of Helsinki, ICH-GCP) and the research ethics framework of the accompanying sociological research.

The questions regarding the use and acceptance of TCIM were created as part of an iterative process by the working group with the involvement of TCIM experts from German-speaking countries (one professor from Switzerland, a total of six professors and four senior researchers from Germany). The final questionnaire covered the following topics: sociodemographics, use of TCIM, attitudes toward TCIM, diagnoses for which TCIM were used, importance and familiarity with terms (Supplementary material 1). This publication covers the aforementioned topics. Further items of the survey were: the role of TCIM in the context of the Covid-19 pandemic, nutrition, Ayurveda, attitude and behavior toward TCIM, Sinus milieu indicator and the EQ-5D-5L quality of life questionnaire (19, 20). Sociological analyses and a qualitative sub study are also part of the research project and will be reported elsewhere, as will other aforementioned topics of the questionnaire used in this study.

As the term TCIM is not (yet) widely used in Germany, the following four terms were used in all items of the questionnaire in German language: Traditional European Medicine (German: Naturheilkunde), Complementary Medicine, Integrative Medicine as well as Alternative Medicine. However, the umbrella term TCIM is used throughout the results section.

The survey was implemented by three renowned German market research institutes (Conversio, Sinus Institute and Respondi Institute) on behalf of and in close coordination with the study management. Conversio advised on the methodology and feasibility of the questionnaire for an online survey and commissioned the other two institutes and supervised the survey process. Sinus contributed the institute's own national milieu indicator, while Respondi carried out the online survey. The respondents were recruited from Respondi's online access panel but remained completely anonymous.

The inclusion criteria for the study included active consent to the informed consent form, a minimum age of 18 years, sufficient German language skills and sufficient cognitive abilities to take part in an online survey lasting approximately 30 min. Exclusion criterion was a lack of consent to participate in the study.

The survey was conducted online using Computer Assisted Web Interview (CAWI). The online panel is certified according to the international standard ISO 26362, which monitors the quality of online sampling. This includes quality procedures that continuously check the response behavior. In general, studies based on probability samples, in which each member of the population has a known and non-zero chance of being included in the sample, are preferred to non-probability samples (21). In order to come as close as possible to the requirements of a representative sample, participation in Respondi requires a double opt-in registration, with a team of experts monitoring and managing the panel. The number of Respondi panelists contains approximately 100,000 participants with good coverage of different age, education and income groups. A key advantage of an online access panel is the experience and motivation of the panel participants, which means that high data quality can be achieved even for complex questions. The online mode also offers the advantage that questions are answered more truthfully, particularly with regard to the sensitive area of health.

The quotas were based on the best4planning (B4P) study, which follows the methodological standard for drawing representative samples (22). With B4P, a structural analysis of the German resident population between the ages of 18 and 80 was carried out to determine the quota specifications for the study population. The B4P study itself is based on a sample of more than 30,000 randomly selected people. Quota control makes it possible to compensate for socio-demographic imbalances in relation to the overall population.

2.2 Statistical analysis

As part of the descriptive analyses, (relative) response frequencies and various measures of position (e.g., mean, median) and dispersion (e.g., standard deviation, variance) were described in the results for the overall sample as well as for various subgroups. Crosstab analysis helped to make informed decisions by identifying patterns, correlations, and trends between the study's parameters. Decision trees were calculated using Exhausted Chi-squared Automatic Interaction Detection (CHAID) or Classification and Regression Trees (CRT). The data were analyzed using R (R Foundation; version 4.3) and IBM SPSS Statistics (vers. 29). Data were unweighted or, if weighted, then based on age, gender, education, federal state and city size. As the weighted and unweighted values differ only in the decimal places, except for the sociodemographic characteristics, we only report the unweighted values in the results. Both the unweighted and weighted values are shown in the sociodemographic characteristics (Table 2).

3 Results

The survey was conducted from September to October 2022; 41,011 invitations were sent out. Of these, 8,821 participants started the survey (response rate 21.5%). Based on the exclusion criteria (mainly due to having read study information but not giving consent, no age information), 453 cases were removed. Additionally, 2,845 participants were excluded because they had already assigned themselves to closed quotas. Exactly 1,000 people dropped out of the survey and were therefore not included in the analysis. A total of 4,505 participants completed the questionnaire. In the quality screening, 18 participants were excluded due to variance check in the Sinus-Milieu indicator. Subsequently, a further 295 participants were removed for quality reasons, including conspicuous open-ended responses and using the quality variable. The final dataset included 4,210 participants. In order not to compromise the online representativeness due to the upper age limit of 80 years, this was reduced to 75 years. As a result, the final population-representative data set for the age group 18–75 years comprises a total of 4,065 participants (nearly 10% of the invited persons; 51.7% female, 47.9% male, 0.4% diverse; average age: 49.3 ± 15.8 years). Further sociodemographic characteristics are listed in Table 2.

3.1 Use of TCIM

The use of TCIM is shown in Figure 1; 69.6% of participants stated that they had used TCIM at some point. At the time of the survey,

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TABLE 2 Sociodemographic characteristics of the study population (n = 4,065).

	Unweighted		Weighted	
	n	%	*n*	%
Gender				
Male	1947	47.9	2026	49.8
Female	2,101	51.7	2018	49.6
Diverse	17	0.4	21	0.5
Age in years				
Under 20	67	1.6	87	2.1
20 to 29	557	13.7	679	16.7
30 to 39	631	15.5	701	17.2
40 to 49	656	16.1	651	16.0
50 to 59	896	22	863	21.2
60 to 75	1,258	30.9	1,084	26.7
Education				
No general school-leaving certificate (yet)	30	0.7	36	0.9
Secondary (elementary, basic) school leaving certificate without completed apprenticeship/vocational training	251	6.2	271	6.7
Secondary school leaving certificate with completed apprenticeship/vocational training	885	21.8	891	21.9
Secondary school without A-levels (German: Realschulabschluss/Mittlere Reife/Oberschule) or equivalent qualification	1,173	28.9	1,288	31.7
A-levels, (technical) university entrance qualification without studies	751	18.5	723	17.8
Studies (university, college, university of applied sciences, polytechnic)	949	23.3	835	20.6
PhD	26	0.6	19	0.5
Federal states				
Baden-Wuerttemberg	417	10.3	537	13.2
Bavaria	604	14.9	630	15.5
Berlin	342	8.4	174	4.3
Brandenburg	98	2.4	122	3
Bremen	40	1	33	0.8
Hamburg	159	3.9	89	2.2
Hesse	293	7.2	305	7.5
Mecklenburg-Western Pomerania	71	1.7	78	1.9
Lower Saxony	341	8.4	403	9.9
North Rhine-Westphalia	868	21.4	878	21.6
Rhineland-Palatinate	179	4.4	203	5
Saarland	43	1.1	49	1.2
Saxony	238	5.9	199	4.9
Saxony-Anhalt	107	2.6	106	2.6
Schleswig-Holstein	152	3.7	146	3.6
Thuringia	113	2.8	114	2.8
Personal monthly net income				
No own income	175	4.3	199	4.9

(Continued)

TABLE 2 (Continued)

	Unweighted		Weighted	
	n	%	*n*	%
Up to 1,000 €	887	21.8	883	21.7
1,000–2000 €	1,549	38.1	1,544	38
2000–3,000 €	959	23.6	952	23.4
3,000–4,000 €	311	7.7	317	7.8
4,000–5,000 €	99	2.4	93	2.3
> 5,000 €	85	2.1	76	1.9
Net monthly household income				
Up to 1,000 €	505	12.4	482	11.9
1,000–2000 €	1,047	25.8	1,023	25.2
2000–3,000 €	1,049	25.8	1,051	25.8
3,000–4,000 €	735	18.1	769	18.9
4,000–5,000 €	424	10.4	443	10.9
> 5,000 €	305	7.5	298	7.3
Location size				
Under 2,000 inhabitants	273	6.7	310	7.6
2,000 to under 5,000 inhabitants	232	5.7	267	6.6
5,000 to under 20,000 inhabitants	603	14.8	1,072	26.4
20,000 to under 50,000 inhabitants	557	13.7	655	16.1
50,000 to under 100,000 inhabitants	401	9.9	470	11.6
100,000 to under 500,000 inhabitants	889	21.9	617	15.2
500,000 inhabitants and more	1,110	27.3	674	16.6
Religious community				
Catholic	853	21.0	894	22.0
Protestant	1,051	25.9	1,096	27.0
Muslim	69	1.7	70	1.7
Buddhist	17	0.4	18	0.4
Hindu	2	0.1	2	0.1
Jewish	12	0.3	8	0.2
Other	72	1.8	68	1.7
No religious affiliation/atheist	1989	48.9	1909	47.0
Party affiliation				
CDU	506	12.4	515	12.7
CSU	177	4.4	184	4.5
FDP	229	5.6	244	6
Bündnis 90/Die Grünen	637	15.7	595	14.6
SPD	650	16	629	15.5
Die Linke	330	8.1	311	7.6
AfD	418	10.3	443	10.9
Other political parties	194	4.8	206	5.1
Not specified	924	22.7	941	23.1
Medical background				
Nursing training/nursing studies	195	4.8	193	4.7
Alternative practitioner examination	39	1	42	1

(Continued)

TABLE 2 (Continued)

	Unweighted		Weighted	
	n	%	*n*	%
Medical studies	51	1.3	57	1.4
Pharmacy studies	29	0.7	32	0.8
Physiotherapy training	39	1	43	1.1
Occupational therapy training	27	0.7	27	0.7
Self-acquisition of basic medical knowledge	670	16.5	670	16.5
Miscellaneous	112	2.8	110	2.7

PhD, Philosophiae Doctor; CDU, Christlich Demokratische Union Deutschlands; CSU, Christlich-Soziale Union; FDP, Freie Demokratische Partei; SPD, Sozialdemokratische Partei Deutschlands; AfD, Alternative für Deutschland.

10.9% of participants used TCIM daily or several times a week (9.3% several times a month, 18% several times a year, 31.4% less frequently and 30.4% never; Figure 1).

In addition, 31.8% of participants had used TCIM in the last 12 months (63.3% had not, 4.9% did not know). At the time of the survey, 17.5% were "currently" (at the time of the survey) using TCIM, with 78.5% not doing so and 4% did not know. Regarding future intentions, 38.1% intended to use TCIM, while 40% did not know and 21.9% had no intention. Additionally, 14.8% stated that other household members were currently using TCIM, with 78.4% unsure and 6.8% who did not know.

Regarding the sociodemographic characteristics of TCIM use in the last 12 months, the parameters gender, age, education, net monthly household income, religious community and party affiliation differed highly significantly in both the unweighted and weighted dataset (each $p = 0.001$; Supplementary Table 1 in Supplementary Material 2). Only the personal monthly net income differed significantly regarding the use of TCIM in the last 12 months in the weighted data set ($p = 0.037$).

TCIM was used more frequently by women in the last 12 months (women 37.3%, men/diverse 25.9%, from the whole sample, $p < 0.001$; Supplementary Figure 1 in Supplementary Material 2). The proportion of TCIM use in the last 12 months was significantly dependent on the level of education. Participants with at least a high school diploma had used TCIM in the last 12 months at a rate of 36.7%; without a high school diploma, TCIM use was at 28.1% ($p < 0.001$). Almost every second woman (46.5%) with at least a high school diploma and a total monthly income of over €2,000 had used TCIM in the last 12 months.

If these women classified themselves as spiritual, the percentage increased to 64.6%. Familiarity with TCIM correlated highly significantly with its use in the last 12 months for women and men ($p < 0.001$), but there are still gender differences: 74.1% of women and 64.0% of men who were very familiar with TCIM had also used TCIM in the last 12 months.

Household income is a significant ($p < 0.001$) predictor for the use of TCIM in the last 12 months. A maximum of 38.2% was found in the group with a monthly household income of 4,000-5,000€. In the group with a household income of up to 500€, the proportion was still 19.6%. Own income, on the other hand, was only significant for men ($p = 0.001$; Supplementary Figure 1 in Supplementary Material 2). In the last 12 months, 36.6% of men with an income of over 4,000€ had used TCIM. For those who earned up to 2,000€ it was 22.8% (Supplementary Figure 1 in Supplementary Material 2).

3.2 Diagnoses for which TCIM was used

TCIM was used most frequently for musculoskeletal pain diseases (17.3%), followed by allergies (12.6%), headache (12.2%), psychological diseases (11.6%) and acute respiratory diseases (10.2%); 41.7% stated that they had not used TCIM at all (for queried diseases) (Figure 2). TCIM predominantly helped or helped the participants a lot with pediatric diseases (91.4% benefit, i.e., 'helped me' or 'helped me a lot'), acute gastrointestinal diseases (85.4% benefit) and acute respiratory diseases (84.5% benefit; Figure 3). TCIM was used with minimal benefit in skin diseases (63.7% benefit), neurological and psychological diseases (66.7 and 66.8% benefit respectively).

When being asked for hypothetical uses, the participants referred that they would use TCIM primarily for headaches, skin diseases, allergies, musculoskeletal pain diseases, acute gastrointestinal diseases, and psychological diseases (Figure 4). For cancer, pediatric diseases, neurological diseases, diabetes mellitus and thyroid diseases, TCIM would be used by fewer participants on average, although the absolute differences are small.

Dietary supplements, vitamin supplements, or herbal remedies were taken daily by 41.9% of respondents. Just over half of the respondents (50.4%) took conventional medication daily.

The majority are in favor (36.7%: definitely, 32.1%: rather yes) of the costs of TCIM services being covered by health insurance (16.4% were undecided, 9.5% stated in individual cases, 5.3% rejected this; Figure 5).

3.3 Importance and familiarity with terminology

For 38.8% of the participants, TCIM was very important or somewhat important for their own health, 16.8% felt that TCIM was somewhat or completely unimportant for their own health (38.6% were neutral, 5.8% did not know; Figure 6).

When asked to what extent the participants were familiar with terms related to TCIM, the terms Traditional European Medicine (German: Naturheilkunde), herbal medicines and Alternative

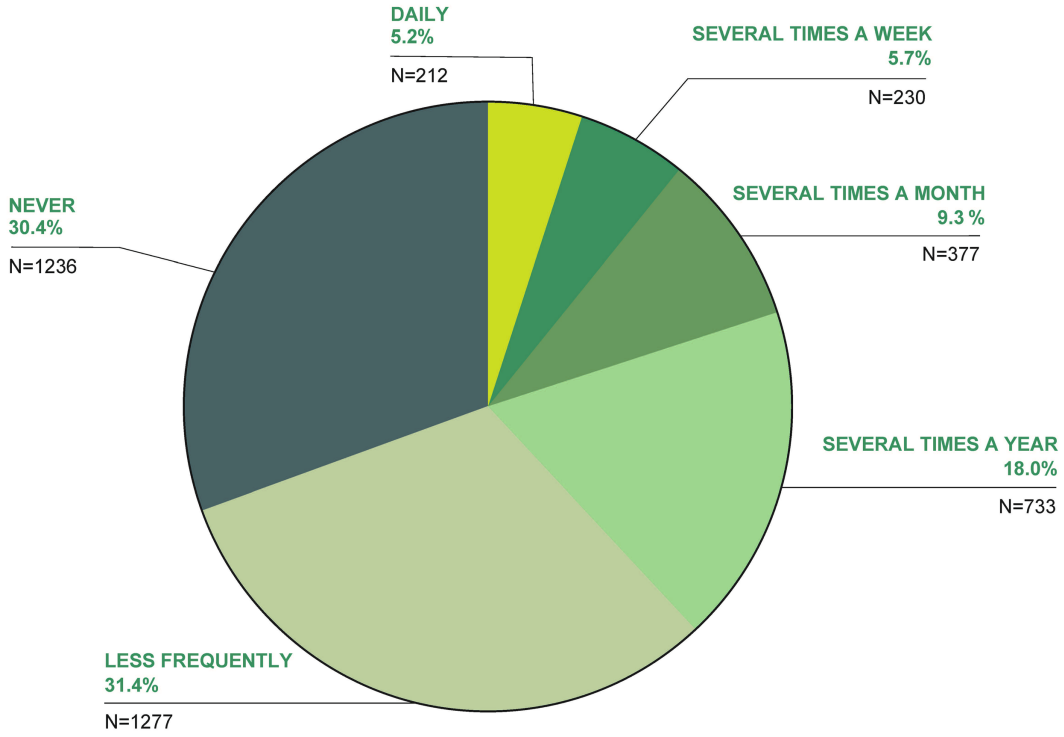

FIGURE 1
How often do you currently use TCIM?

Medicine were particularly familiar (Figure 7). The terms Complementary Medicine and Integrative Medicine, which are mainly used in an academic context in Germany, were less familiar.

In terms of familiarity with TCIM procedures, acupuncture (96.7%), fasting (94.6%), homeopathy (95.1%) and yoga (95.8%) were the best-known procedures (Supplementary Figure 2 in Supplementary Material 2). The better-known methods include various other methods, e.g., Ayurveda, hydrotherapy/water treatments/Kneipp baths, phytotherapy/herbal medicine, manual medicine/osteopathy/chiropractic care, traditional Chinese medicine, whole-food plant-based nutrition, stress management/relaxation methods/meditation (Mind–Body Medicine), movement/dance therapy, art/music therapy. Less well-known methods were anthroposophic medicine, Hijama, traditional African medicine and forest bathing/forest therapy (Supplementary Figure 2 in Supplementary Material 2).

3.4 Attitudes toward TCIM

The attitude toward Traditional European Medicine (German: Naturheilkunde) was very or predominantly positive in 52% of the participants, and 63.1% toward conventional medicine (Figure 8). Integrative Medicine and Complementary Medicine were perceived as very or predominantly positive by 41.1 and 35%, respectively. Alternative Medicine was rated as very or mostly positive by only a quarter (25.1%) of respondents, while 22.4% rated Alternative Medicine as mostly or very negative (Figure 8).

Conventional medicine was rated as very or mostly effective by over two thirds of the participants, while Traditional European Medicine, Complementary Medicine and Integrative Medicine were rated as very or mostly effective by around a quarter, and Alternative Medicine by around a fifth of the respondents (Figure 9).

When asked to what extent the participants considered TCIM to be optimal (in terms of integration into the healthcare system), 34.7% stated that they used it as a supplement to conventional medicine (in the sense of Complementary Medicine), 33.4% in combination with conventional medicine (in the sense of Integrative Medicine; Figure 10).

Stated opinions varied: 7.6% stated TCIM to be only optimal in exceptional medical situations or individual cases, 4.5% alone, without conventional medicine (in the sense of Alternative Medicine).

Another 3.3% believed TCIM should not be used at all, with 16.5% undecided or having no opinion. Regarding its scientific credibility, 9.2% agreed TCIM is unscientific, with 32.8% partially agreeing, 33.7% undecided, 17.2% rather no and 7% not at all (Figure 11). Around a third of the respondents (32.8% partly, 33.7% undecided) agreed with this statement to some extent or were undecided. 17.2% of the participants voted rather no and 7% strongly disagreed with the statement. Over two thirds (70.7%) were in favor of more TCIM research (Figure 12). The main reasons for research in the field of TCIM for 34.5% were that there should be more evidence and for 34.3% to find new healing methods (Figure 13).

The greatest expertise in TCIM, according to 41.6% of respondents, was stated to be held by medical doctors, followed by alternative practitioners (German: Heilpraktiker; 35.4%; Figure 14).

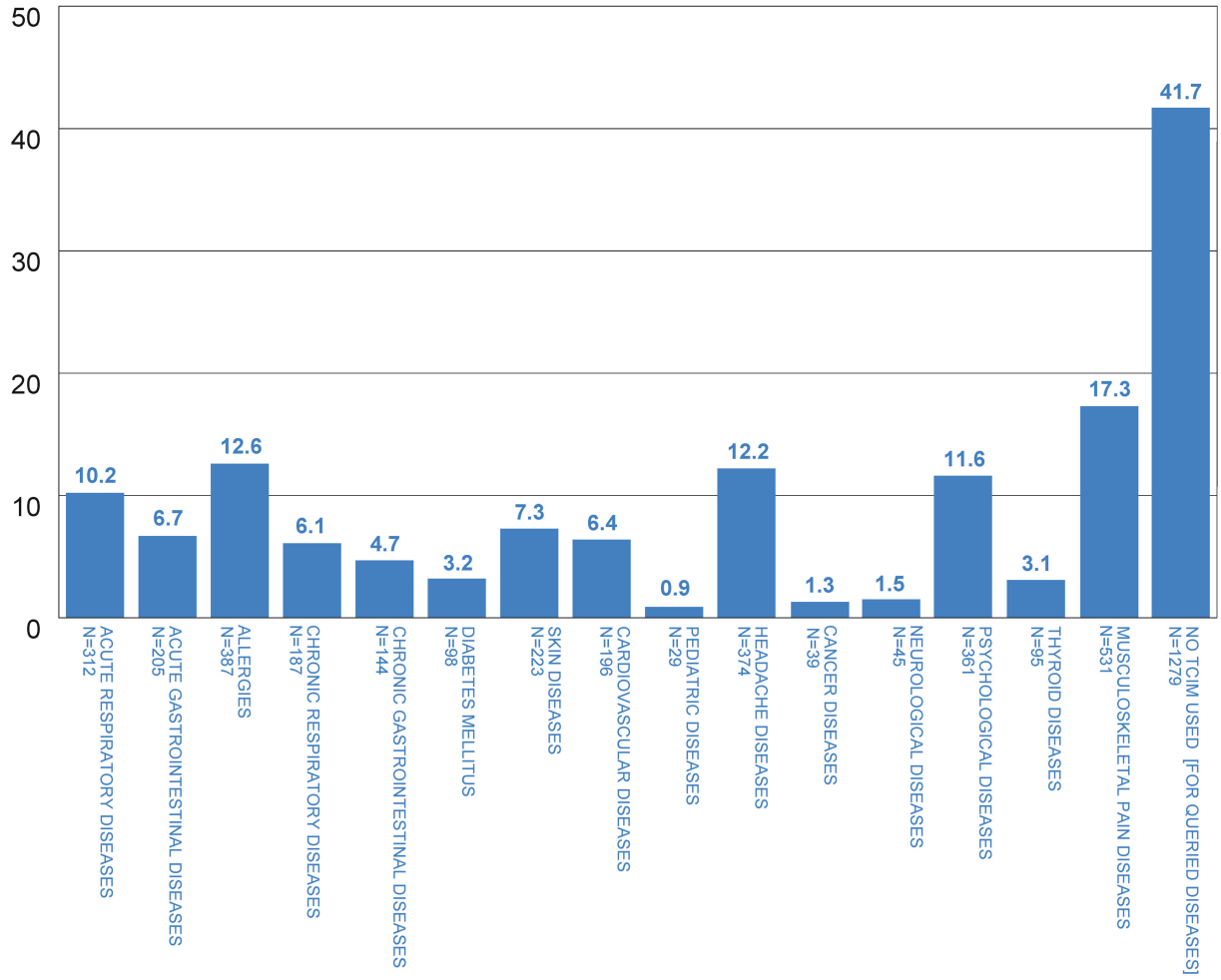

FIGURE 2
For which illnesses have you already used TCIM? (in %).

From the selection of 12 reasons given for using TCIM, the main reasons given were to have fewer side effects than with conventional medicine (very important: 14.3%), reduction of side effects of conventional medicine (very important: 12.3%), former own positive experiences (very important: 12.6%) and the advice of the treating doctor (very important: 12.7%; Figure 15).

In particular, medical recommendations and previous personal experience influenced the decision to choose a treatment method, followed by the results of scientific studies, experiences of family, friends and acquaintances as well as personal recommendations (Supplementary Figure 3 in Supplementary Material 2).

4 Discussion

More than 10 years after the last representative survey on this topic, this study provides a population-representative online-survey update on the use and acceptance of TCIM in Germany. Out of the 4,065 participants, almost 70% stated that they had used TCIM at some point in their lives, with 32% doing so in the last 12 months and 18% currently. The results suggest that TCIM is known about, valued and socially anchored nationwide across all socio-structural characteristics surveyed. It is interesting to note a "base phenomenon," i.e.,—depending on the question—approx. 25–35% make use of TCIM in Germany. Only a small proportion of participants considered these medical procedures to be ineffective, while most respondents would like the costs of TCIM services to be paid by health insurance providers. A large proportion of respondents were in favor of more intensive research in the field of TCIM. Regarding individual procedures, there are considerable differences in the population, e.g., yoga and fasting as more familiar procedures and forest therapy and anthroposophic medicine as more unknown procedures.

4.1 Strengths and limitations

Limitations include a low response rate of 21.5%, which may call into question the generalizability of the results. To increase generalizability, the data used for the analysis was weighted according to age, gender, education, federal state and city size. However, the weighted and unweighted data hardly differed from each other, which suggests a sufficient quota system. The study is based on a survey that was conducted using an online access panel. The basis for this decision on data collection was the high-quality standard that is guaranteed in

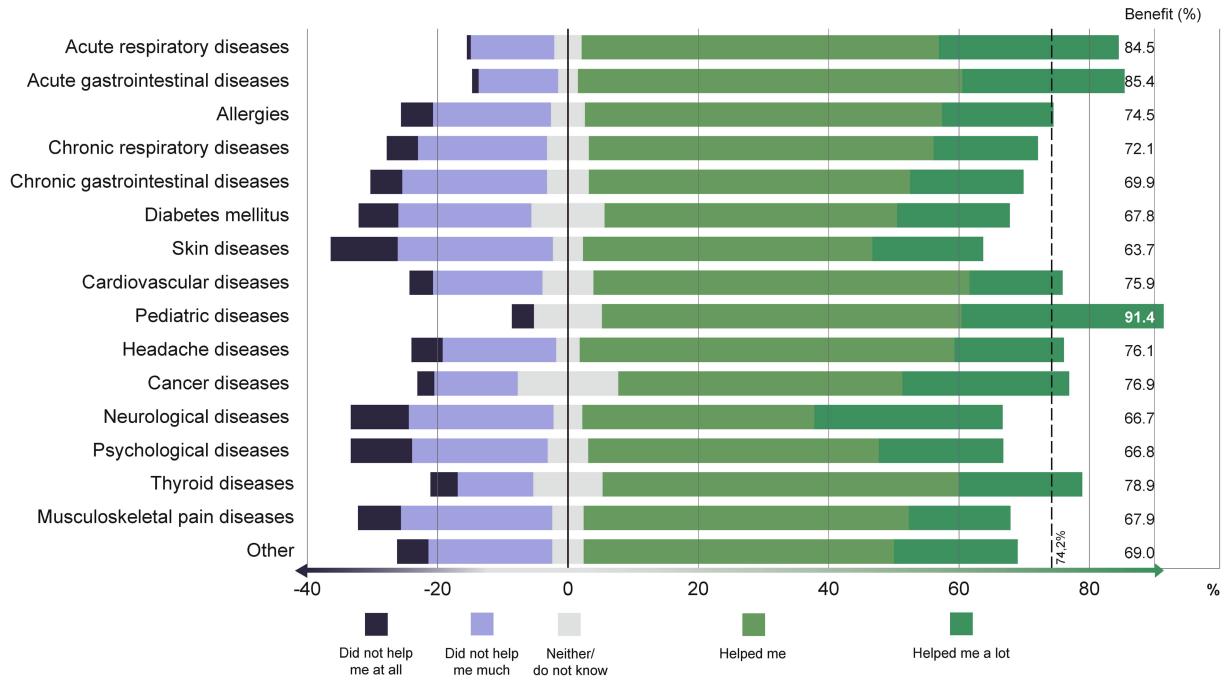

FIGURE 3
To what extent has TCIM helped you with the following illnesses? (in %).

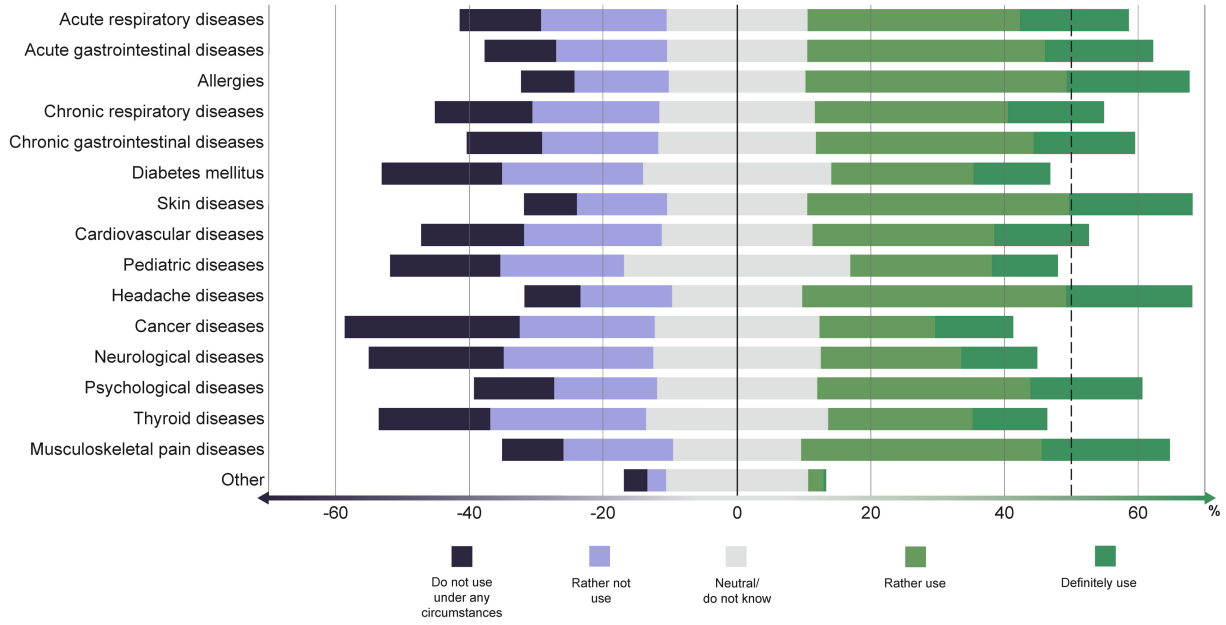

FIGURE 4
To what extent would you use TCIM for the following illnesses? (in %).

the selection and maintenance of the participants of the access panel used, as well as the use of a quota system (21). These aspects facilitate the articulation of population-represetative statements about the use and acceptance of TCIM within the German population. The online mode proofed to be particularly suitable for this research, for it offered a space of discretion and sesitivity regarding questions on personal health. It should be noted, however, that the use of an access panel meant that special populations, such as those without online access and with a low online affinity, were excluded. However, the exclusion of special populations is not a specific problem of access panels or online surveys in general. Telephone surveys and written surveys also exclude people without a telephone connection or home address. An

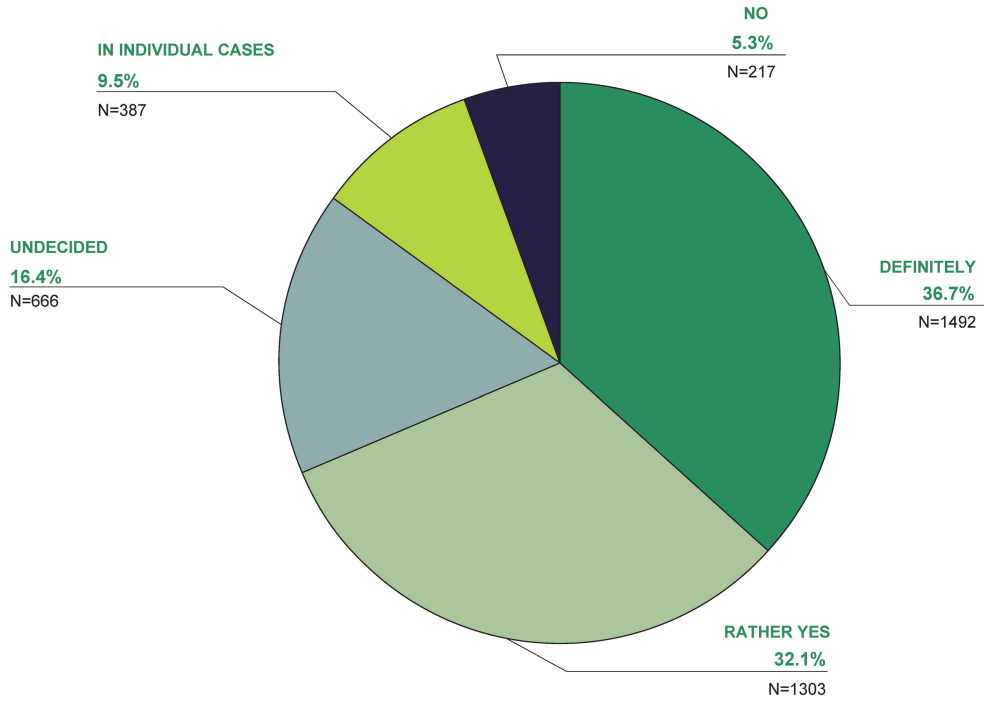

FIGURE 5
In your opinion, which of the following answers is correct? The costs of TCIM services should be covered by health insurance.

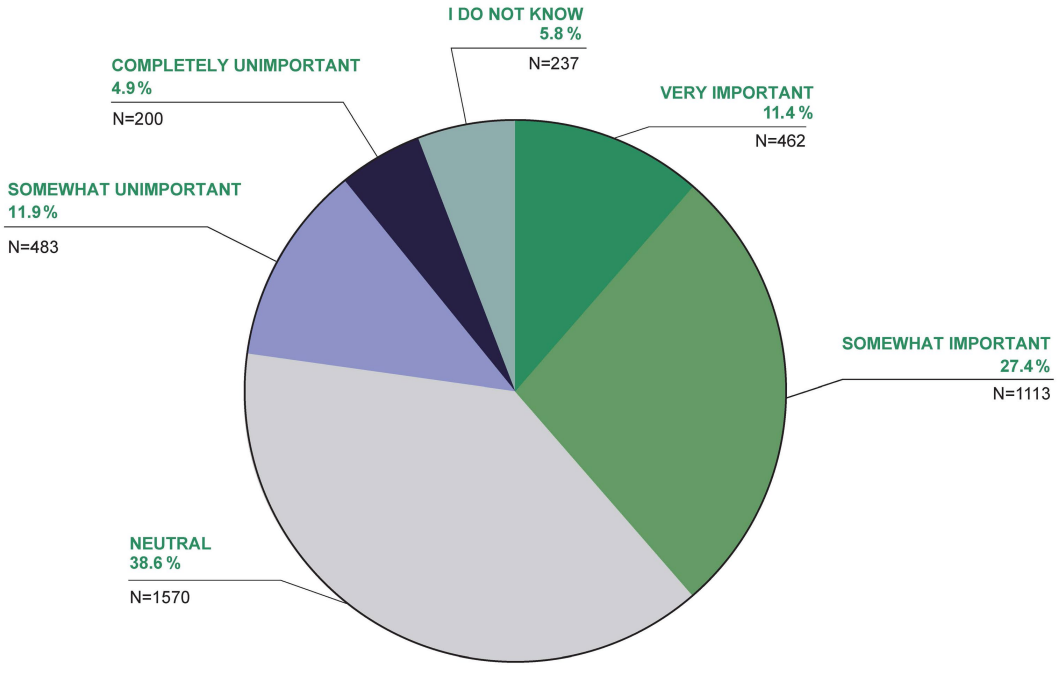

FIGURE 6
How important is TCIM for your health?

additional difficulty with telephone and written surveys is that they are tied to the time and place of the survey, which is largely not the case with online surveys. The limitation of the very elderly possibly not being represented in this study, as they are less likely to have internet access, had little impact, as this age group was excluded from our analysis sample.

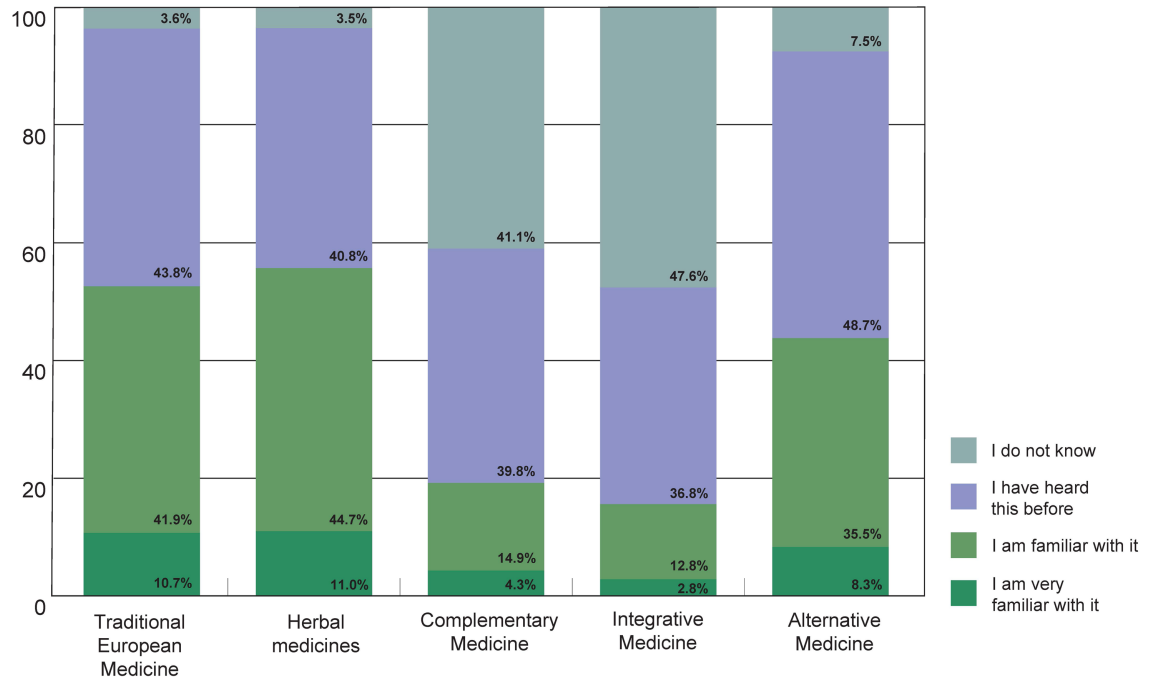

FIGURE 7
To what extent are you familiar with the following terms?

4.2 Comparison with other trials

Due to very heterogeneous survey methods in previous surveys on the topic and a great variety in terms of definitions and terminology of unconventional healing methods as well as traditional medical systems such as Chinese medicine and Ayurveda, it is problematic to compare the results directly with each other (11, 12). In one of the few representative survey studies of 1,100 participants published in peer-reviewed journals in 2004 by Härtel/Volger, approximately 62% had used at least one TCIM intervention in the 12 months prior to the survey (11). In a population-representative online panel survey in Switzerland of 6,375 people aged 16 and above, almost two-thirds of the population had used TCIM at least once (23). For almost half of the respondents, this experience was not longer than three years ago (47%; so-called current users); just under a fifth (19%) had undergone TCIM treatment several times during this period or had treated themselves. In this context, it is important to mention that in Switzerland Complementary Medicine is the dominant term for unconventional therapies. It should also be pointed out that within the given context, comparisons between societies of Germany and Switzerland can only be made to a limited extent due to different health policies and medical law regulations. In the present study, 70% stated that they had used TCIM at some point in their lives and 32% had made use of TCIM in the last 12 months. However, in Härtel/Volger 2004, exercise therapy (e.g., endurance training, targeted muscle training and physiotherapy were listed in the questionnaire) and massage were also asked about as TCIM interventions. This may explain the higher 12-month prevalence rates (11). This shows another general terminological problem in the field of TCIM—namely which interventions (in this country) are to be defined as TCIM interventions at all and which, for example, are already considered part of conventional medicine in Germany or are socially perceived as such, which can be very challenging, especially for participants in surveys. As diverse as the key terms in the spectrum of unconventional forms of diagnosis and therapy are in the German context (see introduction), a system for clearly defining and differentiating these methods is just as inconsistent in this country.

At the same time, certain therapeutic procedures that were considered questionable or dubious not so long ago are now often part of everyday practice in established medical settings (e.g., mindfulness techniques). This processual integration of individual TCIM procedures depends on the respective evidence base, including the increasing inclusion in medical guidelines; but probably also depends on reporting in leading German-language media (24).

There is also limited comparability with previous studies regarding indication based TCIM applications. The most common health problems for which TCIM was used in Härtel/Volger 2004 were back pain (57% of users), colds (29%), headaches (19%), fatigue (15%) and gastrointestinal complaints (12%)—where the question was asked for which complaints/diseases the most recently used TCIM treatment was (11). In this study, the participants had mainly used TCIM for musculoskeletal pain, followed by allergies, headaches, and mental illnesses. Musculoskeletal disorders were also mentioned in the first place in other previous studies (25, 26).

A high popularity of so-called, but not clearly defined herbal medicines (i.e., phytotherapeutics) can be assumed based on data from six German representative Allensbach surveys conducted between 1970 and 2010, with unified and standardized items (10). In 2010, almost three quarters of all Germans over the age of 16 had experience with herbal medicines (70%), a significantly higher proportion compared to 1970,

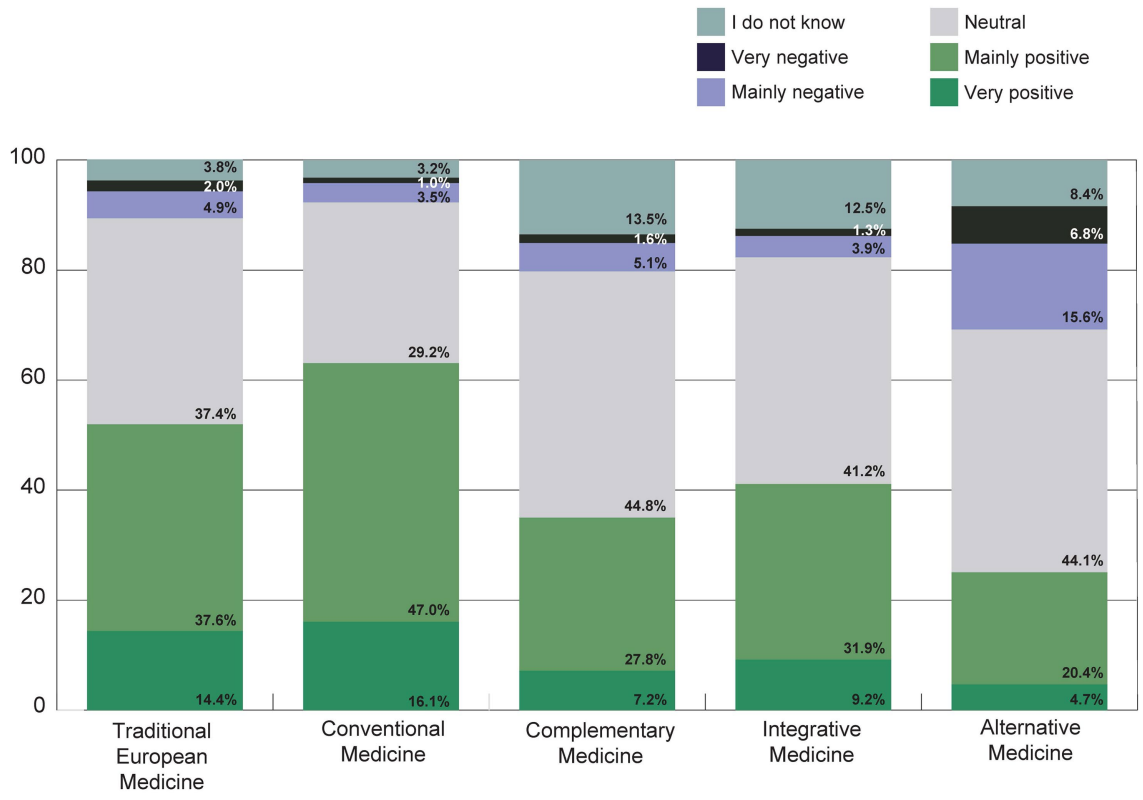

FIGURE 8
How is your general attitude toward Traditional European Medicine (German: Naturheilkunde), conventional medicine, Complementary Medicine, Integrative Medicine or Alternative Medicine? The terms were explained directly with this question (see Table 1).

when this only applied to half of the respondents (52%). Also, most recently (2010), 70% of respondents (1,882 people aged 16 and over) stated that they had used natural remedies at least once (10). In the present study, 42% took dietary supplements, vitamins or herbal remedies daily at the time of the survey. Due to the different wording of the questions, this aspect is only comparable to a very limited extent and represents a limitation of this survey.

In summary, it should be noted that most of the above-mentioned previous studies have not been published in peer-reviewed journals and were not conducted in cooperation with scientific university working groups. This means that the surveys carried out to date on this topic have only limited informative value. The present study is the first to provide up-to-date and reliable data on the use and acceptance of TCIM in Germany.

In Germany, the terms Complementary Medicine and Integrative Medicine are now established in the scientific medical community, but, above all, also in academic and tertial education contexts. However, this data set suggests that in contrast to this, the terms TEM and Alternative Medicine are used much more frequently in the German population for the same subject area. While this phenomenon should be subject of further transdisciplinary research, we see the most important need for action in closing the gap existing in social discourse regarding the generic terms used to ensure a standardized terminological basis for all those involved in the subject area (27). In view of the results, it should be questioned whether it would not be more meaningful to prefer the German term Naturheilkunde or the WHO term Traditional Medicine in academic medical work as well, instead of academically developed constructs that are considerably less well known among patients and users and are hardly used in society as a whole in Germany. Other representative surveys from other countries use a variety of other abbreviations for TCIM, e.g., traditional, complementary, and alternative medicine (TC&AM) or complementary and integrative health (CIH) (28–30). Standardization would be desirable here, e.g., as part of a Delphi method (31).

4.3 Future research

TCIM is attracting great interest internationally. A systematic review conducted as part of the EU FP7 CAMbrella project showed the use of TCIM varying between 0.3 and 86% in different EU countries, although the quality of the 87 studies included in this review varied considerably (25). However, the importance of TCIM in Europe is shown by the fact that, according to another CAMbrella study, there are around 305,000 registered doctors and therapists in Europe who offer these procedures, with more than half of these providers (approximately 160,000) being alternative practitioners (32). Due to the poor evidence base for most TCIM therapies, the CAMbrella Research Roadmap recommends a research strategy with sufficient funding.

The majority of Europeans want TCIM interventions as part of healthcare, but access is difficult in many countries, e.g., due to a lack of cost coverage by health insurance providers, a lack of services or insufficiently regulated qualifications of providers (33).

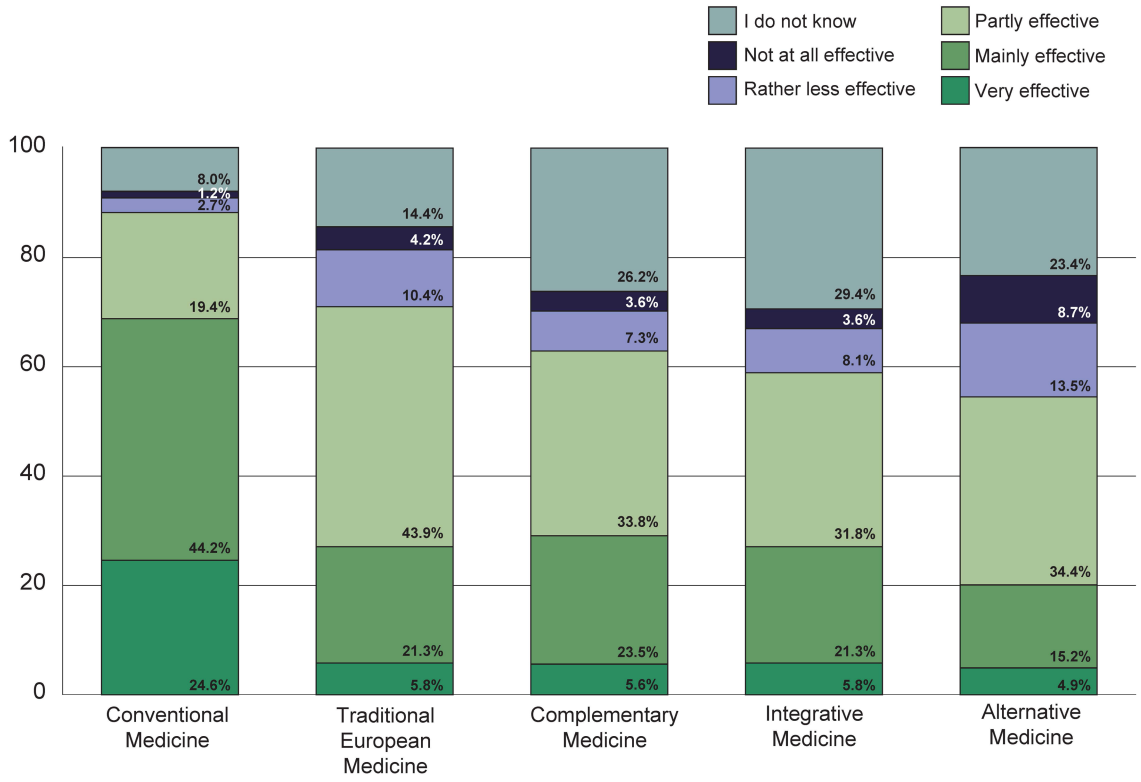

FIGURE 9
How effective do you think the following medical procedures are?

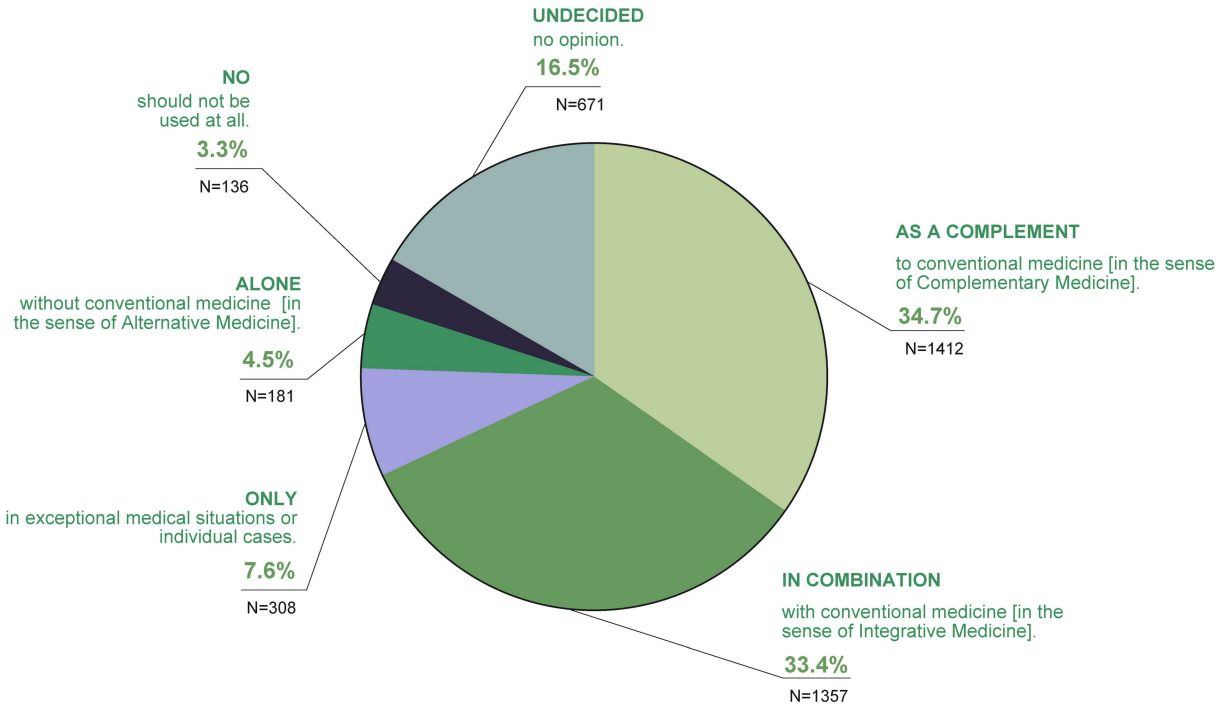

FIGURE 10
To what extent do you consider TCIM to be optimal?

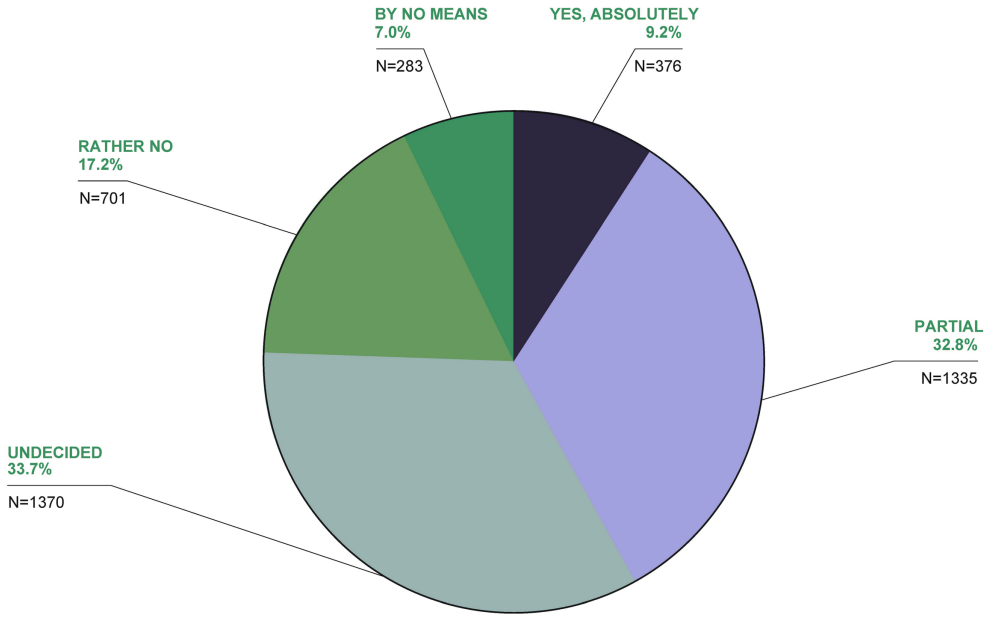

FIGURE 11
TCIM is often described as unscientific. Would you agree with this assessment in principle?

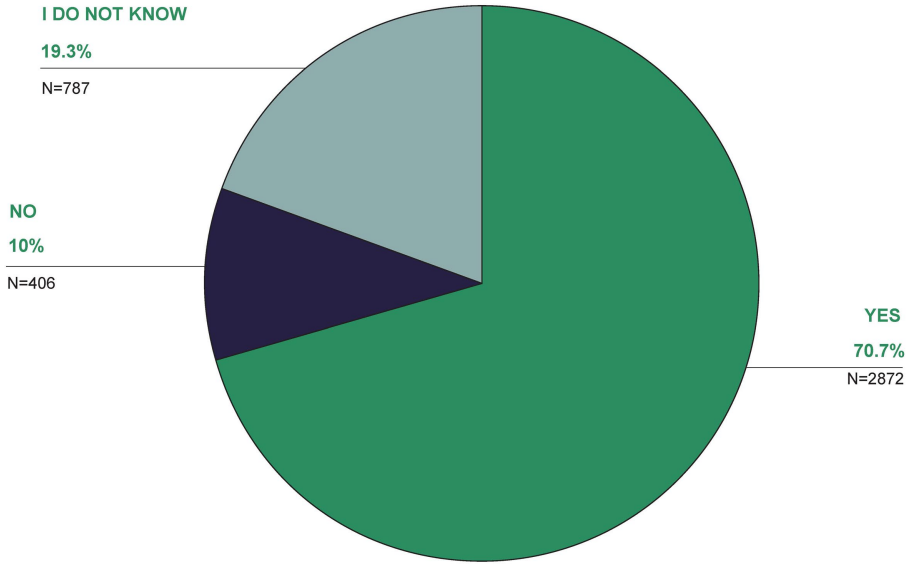

FIGURE 12
In your opinion, should there be more research into TCIM?

The WHO has been interested in TCIM for a long time. The WHO Traditional Medicine Program was launched in the 1970s. Since then, two global strategies on traditional medicine have been developed and a new one is planned for 2025–34 (2). There are several WHO guidelines for herbal remedies as well as for training in Ayurveda and traditional Chinese medicine; similar ones are planned for anthroposophic medicine, cupping and Tibetan medicine (34–36). At least 170 countries worldwide have documented the use of TCIM, and about 100 countries have national policies and programs, implying integration into the health care system, including Germany (3). In the official WHO strategy paper "Traditional Medicine 2014–2023" and at the 1st WHO Global Summit on Traditional Medicine in August 2023, the WHO also calls for the increased and consistent use of these methods in primary care (2–4).

In the last few decades particularly, the US National Institutes of Health (NIH) has systematically promoted research within the framework of the National Center for Complementary and Integrative Health

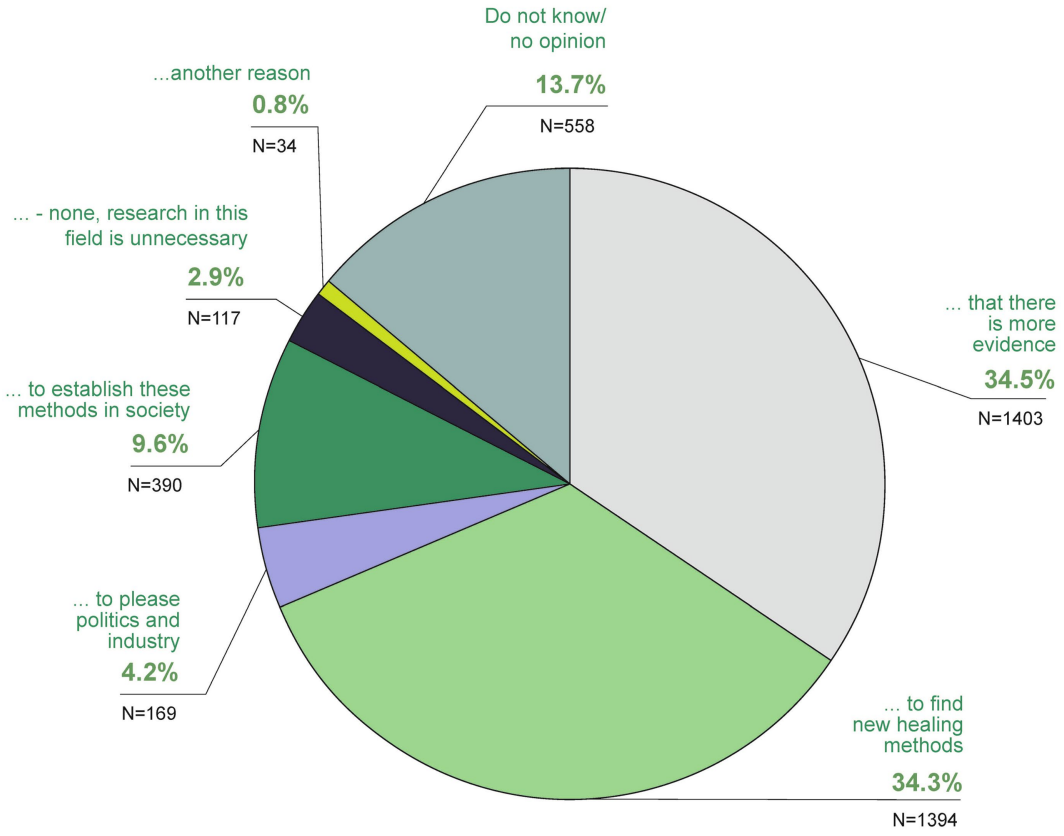

FIGURE 13
In your opinion, which of the following answers is correct? In my opinion, the main reason for research in the field of TCIM is above all.

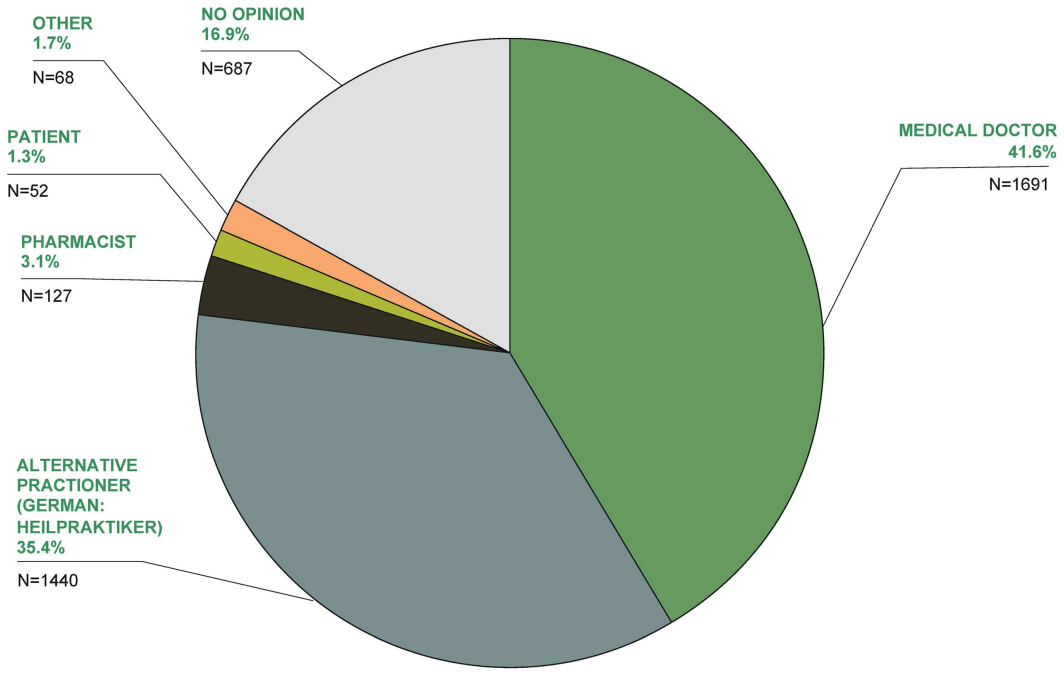

FIGURE 14
In your opinion, who has the greatest expertise in the field of TCIM?

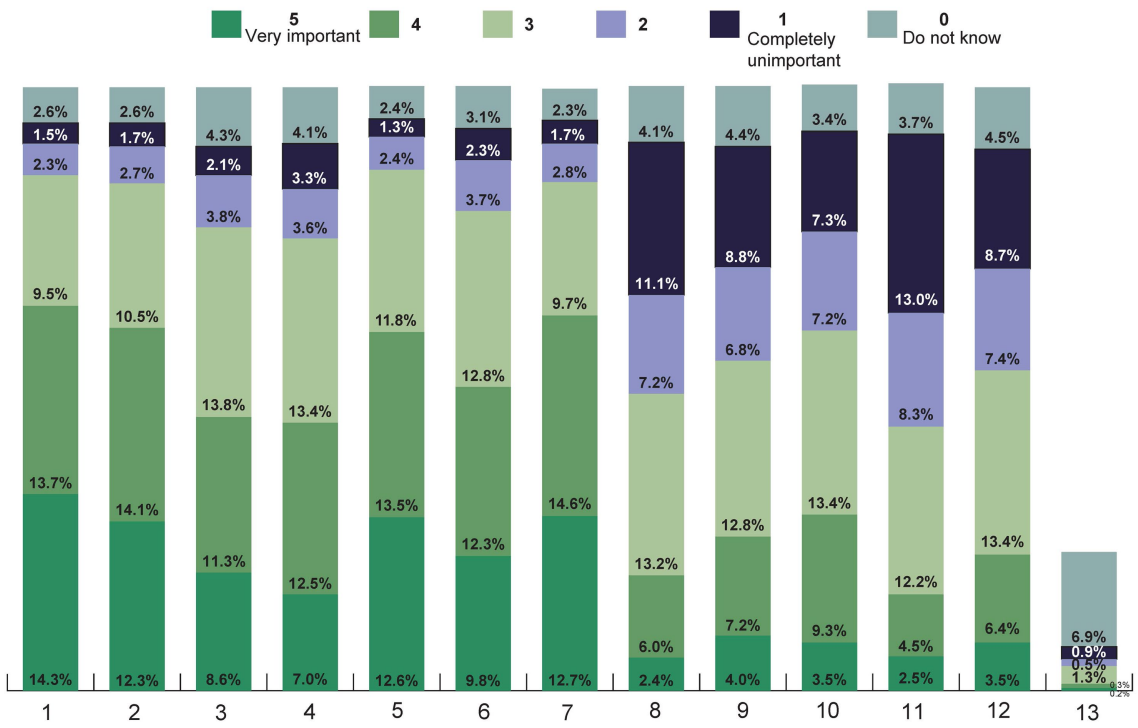

FIGURE 15
How important are the reasons listed for using TCIM to you (Likert scale 1–5 from 1 = completely unimportant to 5 = very important)? Listed reasons were the following: 1 Fewer side effects than with conventional medicine, 2 To reduce the side effects of conventional medicine, 3 Chances of recovery are better, 4 Family, friends or acquaintances have had good experiences, 5 I myself have had good experiences, 6 This strengthens my health competence/self-treatment competence, 7 The advice of my treating doctor, 8 I have heard about it in the media, 9 I am doing it out of health-related desperation, 10 I am doing it out of curiosity about these procedures, 11 I do not think much of conventional medicine, 12 I have had bad experiences with conventional medicine, 13 Other.

(NCCIH) with the aim of generating further evidence for complementary and integrative medical interventions and supplementing existing strategies as part of comprehensive health management (3, 37). Although several larger research projects have been initiated in Germany in the last three decades (38–41), more intensive research often fails due to problematic funding.

TCIM research in Germany is hardly funded by the public sector, which contrasts with the frequent use by the population and the high popularity of TCIM and should therefore be highly relevant for medicine as a whole (33, 42). Currently, many TCIM interventions are not or are not sufficiently scientifically evaluated—this can also pose a potential risk to the population that should not be underestimated.

According to the data from this study, most participants are in favor of comprehensive funding for such projects in Germany as well. In the future, further evaluations of different integrative medical procedures and TCIM interventions should be carried out in the various healthcare sectors (26, 43).

5 Conclusion

Overall, the results of this online survey in a large representative sample indicates a high use and acceptance of TCIM in Germany. Therefore, the importance and relevance of TCIM in the German health care system must be given greater consideration regarding healthcare policy making. Considering the fact that the scientific evidence base of TCIM interventions must be strengthened, these procedures should be scientifically investigated in a systematic and rigorous manner utilizing high quality methodology, investigating their efficacy, effectiveness, therapeutic safety and costs of TCIM interventions.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Charité University ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MJ: Funding acquisition, Investigation, Project administration, Visualization, Writing – original draft. MO: Methodology, Writing

– review & editing. BB: Supervision, Writing – review & editing. MS: Writing – review & editing. RH: Methodology, Project–administration, Supervision, Writing – review & editing. MT: Methodology, Writing – review & editing. AM: Supervision, Writing – review & editing. MW: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – review & editing. CK: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

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In memoriam

The authors dedicate this article to Boike Rehbein (†11.6.2022). Boike Rehbein was involved in the planning and initiation of the project and sadly passed away during the project.

Conflict of interest

MJ reports grants from the Karl and Veronica Carstens Foundation. MO is a board member of the Berlin Brandenburg Medical Doctors' Association for Naturheilkunde (Physiotherapy; ÄN e.V.). AM reports grants from the Karl and Veronica Carstens Foundation and Stifterverband der Deutschen Wissenschaft. He receives honoraria for consulting from the Klosterfrau Foundation. BB and its working group were partly funded by the Kneipp-Bund e.V. MT reports grants from the Karl and Veronica Carstens Foundation. CK reports grants from the Karl and Veronica Carstens Foundation for conducting this study. He is a member of the scientific advisory board of the company Bruno Zimmer, board member of the German Medical Doctors' Association for Ayurveda-Medicine (DÄGAM e.V.) and receives honoraria for lecturing Ayurveda at Sonne und Mond, Berlin.

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1372924/full#supplementary-material

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Efficacy and safety of the Ayurvedic herbal preparation Maharishi Amrit Kalash: a systematic review of randomized controlled trials

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Background: Maharishi Amrit Kalash (MAK) 4 and 5 are Ayurvedic herbal nutritional supplements that are believed to have beneficial effects on overall health and wellbeing. This study aimed to systematically review all available randomized controlled trials (RCTs) investigating the clinical effects and safety of MAK.

Methods: We included RCTs on therapy, health promotion, and prevention for patients and healthy volunteers of all ages. We systematically searched MEDLINE (via PubMed), EMBASE (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), DHARA, Clinicaltrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform, and Google Scholar from inception through 7 May 2023, with no time or language restrictions. The risk of bias was assessed using the Cochrane Risk of Bias Tool version 1. The protocol was registered with PROSPERO before conducting the review (CRD42023421655).

Results: Three RCTs with 418 study participants were included. Two studies were on breast cancer patients and one on healthy adults. The two studies on cancer evaluated the efficacy of MAK in reducing the side effects of chemotherapy in women with breast cancer. The study on healthy adults evaluated whether MAK has an effect on an age-related alertness task as an indicator of cognitive aging. Both studies on breast cancer patients found beneficial effects on performance status, anorexia, vomiting, and body weight. One study reported positive effects regarding stomatitis. Regarding visual alertness, results showed that individuals who received MAK improved in performance. None of the three included studies reported adverse events. The risk of bias was mixed. Due to the small number and heterogeneity of the RCTs, no meta-analysis could be performed.

Conclusion: There is evidence that MAK may have supportive effects in chemotherapeutic treatments for breast cancer patients and for healthy individuals regarding visual discrimination. However, it is difficult to verify treatment effects due to the small number of RCTs and the mixed risk of bias.

Furthermore, none of the included studies recorded adverse events. Therefore, further high-quality studies are warranted to confirm the potential health benefits of MAK and to determine its optimal dosage and duration of use.

Systematic review registration: PROSPERO, CRD42023421655.

KEYWORDS

Ayurveda, systematic review, traditional Indian medicine, herbal medicine, maharishi Amrit Kalash

1 Introduction

Ayurveda is a traditional system of medicine originating in South Asia and has been practiced for more than 2000 years on the Indian subcontinent and elsewhere. It is based on the belief that a person's physical, mental, and spiritual wellbeing is dependent on an individual balance between the body, mind, and soul. It is recognized by the World Health Organization (WHO) and is widely practiced today, including in the Western world (1–3). There are guidelines for the clinical evaluation of Ayurvedic interventions to ensure quality in this area of research (4). Ayurveda includes a wide range of medical practices, such as individualized treatments consisting of manual therapies, purification treatments ("*Pancakarma*"), nutritional therapy and herbs, lifestyle counseling, and yoga exercises (5). Maharishi Ayurveda is a contemporary revival that takes into account these traditional approaches in agreement with the classical texts (6). Since 2014, Ayurveda in India has been regulated by an independent ministry (Ministry of Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa and Homoeopathy; abbreviated as AYUSH Ministry (7)).

Maharishi Amrit Kalash (MAK) 4 and 5 are Ayurvedic herbal preparations that are believed to have beneficial effects on overall health and wellbeing. These preparations are combinations of several herbs and minerals with *rasayana* (rejuvenative and immune boosting) effects and is said to be helpful in supporting the body's natural defenses against disease. MAK 4 is prepared as a paste, whereas MAK 5 is administered as tablet. The ingredients of the two delivery forms differ from each other, a phytochemical standardization of the preparations is being sought (8), see Table 1. The preparations for MAK 4 and MAK 5 are based on the classic Ayurvedic formulation for Brahma Rasayana, as described in traditional texts and the Ayurvedic Pharmacopoeia of India (9, 10). The MAK preparation is complex, with a range of pharmacological activities on various organ systems. In terms of its preparation, it is comparable to the classic Ayurvedic formulation Chyavanprash with regard to numerous ingredients (e.g., *Emblica officinalis*) for which mechanisms have been discussed (11, 12). Studies have shown that Chyavanprash has immunostimulatory effects, enhancing the secretion of cytokines and stimulating macrophage and natural killer cell activity (13). Based on similarities in the preparations and the range of indications, similar mechanisms of action can also be assumed for MAK. Both Chyavanprash and the classic Ayurvedic recipe Brahma Rasayana, on which MAK is based, are classified as *rasayana* in Ayurveda, aimed at maintaining vigor, vitality, and delaying the aging process (14). These mechanisms might contribute to its therapeutic potential for various health conditions. *In vitro* effects for MAK 4 and 5 have been shown in different studies. Inaba et al. (15) evaluated the immunomodulatory effects of MAK 4 and MAK 5 in mice. MAK 4 increased the responsiveness of lymphocytes, and MAK 5 increased not only the responsiveness of lymphocytes but also macrophage function. In this study, it is also suggested that MAK 4 and 5 have mitogenic effects on lymphocytes. Sugiura et al. (16) found that MAK 4 and 5 were found to promote the phagocytic and digestive functions of macrophages in mice compared with control and also had a stimulatory effect on macrophages. Furthermore, Penza et al. (17) found that a MAK-supplemented diet inhibited liver carcinogenesis in urethane-treated mice. Several but fewer studies have also investigated the *in vivo* effects of MAK 4 and 5. Sundaram et al. (18) treated 10 hyperlipidemic patients receiving stable hypolipidemic therapy with MAK 4 and 5 for 18 weeks. Plasma lipoprotein, plasma lipid peroxide, and low-density lipoprotein oxidation studies were evaluated every 6 weeks. The results indicate that MAK 4 and MAK 5 may be useful in the prevention and treatment of atherosclerosis. Zanella et al. (19) put healthy people on diets with or without MAK and found that a MAK-enriched diet reduced oxidative stress parameters and increased antioxidant defenses in both short- and long-term treatment. Accordingly, there is quite some evidence that MAK may have positive effects on various health parameters. However, a systematic review of the available evidence is still lacking.

The preclinical evidence for MAK is already well-reviewed, but the necessary clinical evidence still largely lacking. To date, there has been no systematic review that assesses and compares the efficacy and safety of MAK for the prevention and treatment of various health conditions and in healthy individuals. The aim of this review is to summarize the existing randomized controlled trials (RCTs) on the efficacy and safety of MAK, to provide a comprehensive overview of the existing clinical evidence on MAK and to identify areas where further prospective clinical research is required.

2 Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20, 21). The protocol was registered with PROSPERO before conducting the review (CRD42023421655).

2.1 Eligibility assessment

Randomized controlled, randomized crossover, and cluster randomized trials were eligible. Studies of individuals of any age, sex, and origin were included. We included trials of therapeutic, health-promoting, or preventive use of MAK. Studies that compared MAK with (1) no specific intervention, (2) placebo, (3) other medicine treatment, or (4) other Ayurvedic preparations were eligible. Studies that examined MAK in combination with other

TABLE 1 Preparation of Maharishi Amrit Kalash Paste (MAK 4) (9, 10).

Name of ingredient		Part used	Composition in mg /20 gm
Latin	English		
Saccharum officinarum	Sugarcane	Sugar	12,400,00
Aqua	Water		3,850,00
	Ghee		500,00
Emblica officinalis (Organic)	Indian gooseberry	Fruit	910,00
Mel	Honey		800,00
Terminalia chebula (Organic)	Chebulic myrobalan	Fruit	455,00
Centella asiatica (Organic)	Indian penny wort	Whole plant	78,00
Cinnamomum zeylanicum (Organic)	Cinnamon	Bark	78,00
Convolvulus pluricaulis (Organic)	Aloeweed	Whole plant	78,00
Curcuma longa (Organic)	Turmeric	Rhizome	78,00
Cyperus rotundus (Organic)	Nutgrass	Root	78,00
Cyperus scariosus (Organic)	Nutgrass	Tuberous root	78,00
Elettaria cardamomum (Organic)	Lesser cardamom	Fruit	78,00
Embelia ribes (Organic)	Butterfly pea	Fruit	78,00
Glycyrrhiza glabra (Organic)	Liquorice	Root	78,00
Mesua ferrea (Organic)	Cobra's saffron	Flower	78,00
Piper longum (Organic)	Long pepper	Fruit	78,00
Santalum album	Sandalwood White	Heartwood	78,00
Polygonatum verticillatum (Aqueous Extract)	-	Root	31,00
Asparagus racemosus (Organic) (Aqueous Extract)	Indian asparagus	Root	21,40
Boerhavia diffusa (Organic) (Aqueous Extract)	Spreading hogweed	Whole plant	12,60
Oroxylum indicum (Organic) (Aqueous Extract)	Indian trumpet tree	Bark	7,60
Solanum xanthocarpum (Organic) (Aqueous Extract)	Yellow berried nightshade	Whole plant	7,20
Gmelina arborea (Organic) (Aqueous Extract)	Cashmere tree	Bark	6,80
Pueraria tuberosa (Organic) (Aqueous Extract)	Indian kudzu	Tuberous root	5,80
Teramnus labialis (Organic) (Aqueous Extract)	-	Whole plant	5,80
Tribulus terrestris (Organic) (Aqueous Extract)	Small caltrops	Fruit	5,80
Ipomoea digitata (Organic) (Aqueous Extract)	Giant potato	Tuberous root	5,40
Uraria picta (Organic) (Aqueous Extract)	-	Whole plant	5,40
Clerodendrum phlomidis (Organic) (Aqueous Extract)	-	Whole plant	4,40
Sida cordifolia (Organic) (Aqueous Extract)	Country mallow	Whole plant	4,40
Solanum indicum (Organic) (Aqueous Extract)	Indian nightshade	Whole plant	3,60
Leptadenia reticulata (Organic) (Aqueous Extract)	-	Whole plant	3,20
Phaseolus trilobus (Organic) (Aqueous Extract)	Wild gram	Whole plant	3,20
Stereospermum suaveolens (Organic) (Aqueous Extract)	Yellow snake tree	Bark	3,20
Desmodium gangeticum (Organic) (Aqueous Extract)	Tick trefoil	Whole plant	2,80
Pedalium murex (Organic) (Aqueous Extract)	Large caltrops	Fruit	2,80
Saccharum spontaneum (Aqueous Extract)	Thatch grass	Root	2,20
Eragrostis cynosuroides (Aqueous Extract)	Feather grass	Root	1,80
Saccharum officinarum (Aqueous Extract)	Sugarcane	Root	1,40
Aegle marmelos (Organic) (Aqueous Extract)	Bael	Bark	1,20

procedures were included only if the concurrent intervention was comparable between all groups. There were no restrictions on the type of outcomes.

2.2 Search strategy and databases

MEDLINE (via PubMed), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), DHARA, Clinicaltrials.gov, the WHO International Clinical Trials Registry Platform were searched without time and language restrictions from inception through 7 May 2023. In order to include gray literature (e.g., reports, government documents, dissertations, theses, and conference abstracts), Google Scholar was also searched. The complete search strategy for PubMed is shown in Table 2. Search strategies for the other databases were identical in content except for the fact that we did not filter for RCTs for Google Scholar but included all hits for "Maharishi Amrit Kalash" for a maximum sensitive gray literature search.

2.3 Study selection and data extraction

Search results were checked for duplicates using the open-source software rayyan.ai. Two authors (AKK and RW) independently screened abstracts and full texts for eligibility using rayyan.ai. Disagreements were resolved in discussion with a third author (CK) until a consensus was reached. Study characteristics were extracted using a pre-developed data extraction form independently by two authors (AKK and RW). Data on publication type, design and funding, participants, intervention arms, dosage and pharmaceutical form, outcomes, and safety were extracted from the included full texts.

TABLE 2 Search strategy for MEDLINE (via PubMed) using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format (22).

#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	drug therapy [sh]
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	animals [mh] NOT humans [mh]
#11	#9 NOT #10
#12	"Maharishi Amrit Kalash" or "MAK 5" or "MAK5" or "MAK 4" or "MAK4"
#13	#11 AND #12

2.4 Risk of bias of individual studies

Two authors (AKK and RW) independently assessed the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases using the Cochrane Risk of Bias tool version 1 (23). Disagreements were resolved in discussion with a third author (CK) until a consensus was reached.

2.5 Data synthesis

If at least two studies assessing this specific outcome are available, meta-analyses were planned to be conducted using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, release 29.0; IBM Corporation, Armonk, NY) by a random effects model. Mean differences (MDs) between groups and their 95% confidence intervals (CIs) would have been calculated. The effects of MAK compared with different control interventions were planned to be analyzed separately. In case of data missing, attempts would have been made to obtain the missing data from the trial authors by email. Ultimately, pairwise meta-analyses could not be performed because of the small number of included studies.

2.6 Assessment of statistical heterogeneity

Statistical heterogeneity was planned to be evaluated using chi-square (χ^2) statistics with a p-value of ≤ 0.10, indicating significant heterogeneity. The extent of heterogeneity was categorized using I^2, with $I^2 > 25\%$ representing moderate, $I^2 > 50\%$ representing substantial, and $I^2 > 75\%$ representing considerable heterogeneity (24). Ultimately, the assessment of statistical heterogeneity could not be performed because of the small number and poor reporting of included studies.

2.7 Subgroup analyses

The following subgroup analyses were planned *a priori*: If studies on both (1) MAK 4 and MAK 5 or (2) participants older and younger than 18 years were found, they would be considered separately. Due to the small number of included studies, none of the planned subgroup analyses could be performed.

3 Results

3.1 Literature search

The literature search revealed 575 records; the identification of studies on other methods yielded 12 additional records (Figure 1). After excluding duplicates and irrelevant abstracts, 20 full texts were identified to be assessed for eligibility. For six of those studies, no full text could be retrieved at the time of analysis: Two study registries (25, 26), of which one has been published in the mean time (25) three conference abstracts (27–29), and one dissertation (30). Eight full texts were excluded because there were no RCT (18, 31–37), and three

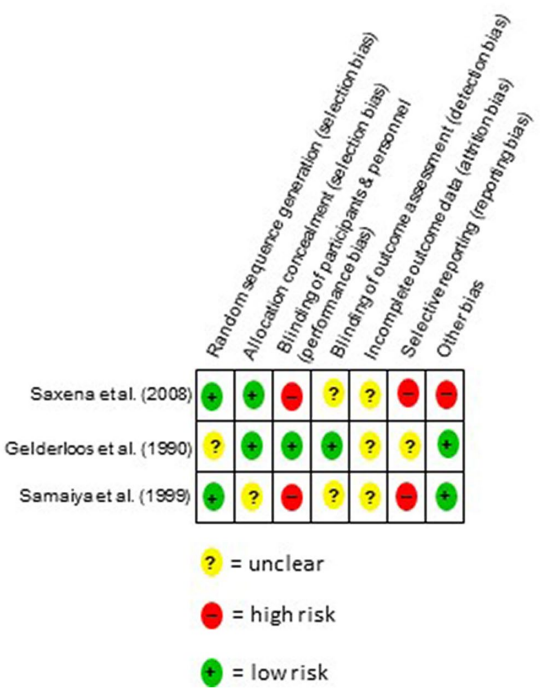

FIGURE 1
Flow chart of the study selection process.

because it was the wrong intervention (37–39). Hence, three RCTs ($N = 418$) were included in the systematic review (40–42).

3.2 Study characteristics

Study characteristics are presented in detail in Table 3. Two studies examined breast cancer patients (41, 42), and one focused on healthy adults (40). The two studies on cancer evaluated the efficacy of MAK in reducing the side effects of chemotherapy in women with breast cancer. The underlying hypothesis was that since MAK is rich in antioxidants, a reduction in the toxicity of chemotherapy can be achieved. The study on healthy adults evaluated whether MAK has an effect on an age-related alertness task. The underlying hypothesis was that MAK positively affects attentional capacity or alertness and thus can reverse the cognitive effects of aging. The studies were carried out in India (41, 42) and the USA (40). All studies were published between 1990 and 2008 and used a randomized study design. One study compared MAK to placebo (40), and the other two studies compared chemotherapy plus MAK to chemotherapy alone (41, 42). The sample size varied between $n = 60$ and $n = 214$ participants.

3.3 Study findings

3.3.1 MAK dosage and pharmaceutical form

Gelderloos et al. (40) administered one MAK tablet twice daily for 6 weeks. Samaiya et al. (41) administered 1 tablespoon (10gm) MAK 4 paste twice daily with milk and one tablet MAK 5 twice daily with water during the entire period of chemotherapy. Saxena et al. (42) administered 2 tablespoons MAK 4 paste twice daily with a glass of milk and two tablets MAK 5 twice daily with lukewarm water half an hour after MAK 4, for approximately 18 weeks.

3.3.2 MAK as a supplement to chemotherapy in breast cancer

Both studies on breast cancer patients (41, 42) assessed outcomes at baseline and at each of the 6 cycles of chemotherapy. Both studies found a positive effect of MAK on *performance status* as measured with the Karnofsky performance scale (43). Samaiya et al. (41) after the fourth chemotherapy cycle, and Saxena et al. (42) after the fifth cycle in favor of MAK. Saxena et al. (42) found positive effects of MAK in *anorexia* in all cycles; however, differences were only clearly reported in the fourth cycle in favor of MAK. Samaiya et al. (41) reported positive effects on *anorexia* after the third cycle in favor of MAK. Regarding *vomiting*, both studies found positive effects of MAK after the third and fourth cycles. Both studies found positive effects on *body weight*. Furthermore, Samaiya et al. (41) reported positive effects regarding *stomatitis* after the fourth cycle in favor of MAK.

3.3.3 MAK for reversing cognitive effects of aging

Gelderloos, Ahlstrom, Orme-Johnson, Robinson, Wallace, and Glaser (40) used a *visual alertness task* as an indicator of cognitive aging. Outcomes were assessed at three time points: before treatment with MAK, after 3 weeks of treatment, and after 6 weeks of treatment. Results showed that individuals who received MAK improved in performance on two of four measured fields at weeks 3 and 6.

3.3.4 Safety

None of the included studies recorded adverse events.

3.4 Assessment of the scope of unpublished data

During the literature search, 181 studies were identified via clinicaltrials.gov and the WHO International Clinical Trials Registry Platform. Of these, two were potentially suitable (25, 26). The study titled "Effects of Herbal Antioxidants on Cardiovascular Disease in Older Blacks" was updated as "completed" with a final update in 2010 (26). However, results were not filed and could not be identified during the literature search, so a final assessment was not possible. The study titled "Role of MAK, Ayurvedic herbal medicine on Breast Cancer" was registered in 2019, and results are not yet available (25). In addition, the literature search identified three conference abstracts (27–29) and one dissertation (30) that could potentially be considered. However, no full-text publication could be found or retrieved for these. No further information could be obtained by writing to the authors either. Thus, there is a restriction with respect to the conclusion due to the scope of unpublished data.

3.5 Risk of bias of individual studies

The risk of bias was highly variable across both studies and domains (Figure 2). The risk of selection bias was low for Saxena et al. (42) and mixed for Samaiya et al. (41) and Gelderloos, Ahlstrom,

TABLE 3 Study characteristics.

Study	Publication type	Design and funding	Participants	Intervention arms	MAK dosage and pharmaceutical form	Outcomes	Significant group differences	Safety
Gelderloos et al. (1990)	Journal article	- RCT - Origin: USA - Funding: n.a.	- Healthy adults older than 35 years - Randomized: $N = 60$ - Analyzed: $n = 48$ ($n = 22$ experimental, $n = 26$ control) - Gender: 100% male - Mean age ± SD: 39.9 ± 2.86 experimental; 39.4 ± 3.99 control	- Experimental: MAK - Control: Placebo; after the study the control group also received MAK	One MAK tablet twice daily for 6 weeks	Performance as measured by visual discrimination: Whole field and three subfields (A, B, C) at three time points: (T1) before treatment, (T2) after 3 weeks of treatment, (T3) after 6 weeks of treatment	Whole field and field A at weeks 3 and 6 in favor of MAK	n.a.
Samaiya et al. (1999)	Journal article	- RCT - Origin: India - Funding: Maharshi Ayurveda Products	- Breast cancer patients receiving chemotherapy - Randomized: $N = 129$ ($n = 61$ experimental, $n = 68$ control) - Analyzed: $n = 112$ ($n = 53$ experimental, $n = 59$ control) - Gender: n.a. - Mean age ± SD: 43.33 (SD not reported) experimental; 45.4 (SD not reported) control	- Experimental: CMF or CAF plus ondansetron + MAK - Control: CMF or CAF plus ondansetron	1 tablespoon (10gm) MAK 4 paste twice daily with milk and 1 tablet MAK 5 twice daily with water during the entire period of chemo	- Toxicity of anticancer chemotherapy as measured by side effects: general well-being, anorexia, performance status as measured with the KPS, leucopoenia, stomatitis, vomiting, diarrhea, alopecia, fever, allergy, pulmonary and neurotoxicity, cardiotoxicity, cutaneous manifestation, pain, weight - Tumor response - Outcomes assessed at baseline and 6 cycles of chemotherapy	- KPS after fourth cycle in favor of MAK - Anorexia after third cycle in favor of MAK - Vomiting after third and fourth cycle in favor of MAK - Stomatitis after fourth cycle in favor of MAK - Weight in favor of MAK	n.a.
Saxena et al. (2008)	Journal article	- RCT - Origin: India - Funding: Maharshi Ayurveda Products	- Female breast cancer patients receiving chemotherapy - Randomized: $N = 214$ - Analyzed: $n = 181$ ($n = 102$ experimental, $n = 112$ control) - Gender: 100% female. - Mean age ± SD: 44 ± 10 experimental; 44.9 ± 8.9 control	- Experimental: CMF or CAF plus ondansetron and dexamethasone + MAK - Control: CMF or CAF plus ondansetron and dexamethasone	2 tablespoons MAK 4 paste twice daily with a glass of milk and 2 tablets MAK 5 twice daily with lukewarm water half an hour after MAK 4, for approximately 18 weeks	- Toxicity of anticancer chemotherapy as measured by side effects: anorexia, vomiting, stomatitis, diarrhea, alopecia, performance status as measured with the KPS, weight, and leucopoenia - Tumor response - Outcomes assessed at baseline and 6 cycles of chemotherapy	- Anorexia in all cycles, however differences were only clearly reported in the fourth cycle in favor of MAK - Vomiting in third and fourth cycle in favor of MAK - KPS in fifth cycle in favor of MAK - Weight in favor of MAK	n.a.

RCT, randomized controlled trial; n.a., not available; SD, standard deviation; MAK, Maharishi Amrit Kalash; CMF, Cyclophosphamide, methotrexate and 5-flourouracil; CAF, cyclophosphamide, adriamycin, and 5-flourouracil; KPS, Karnofsky performance scale.

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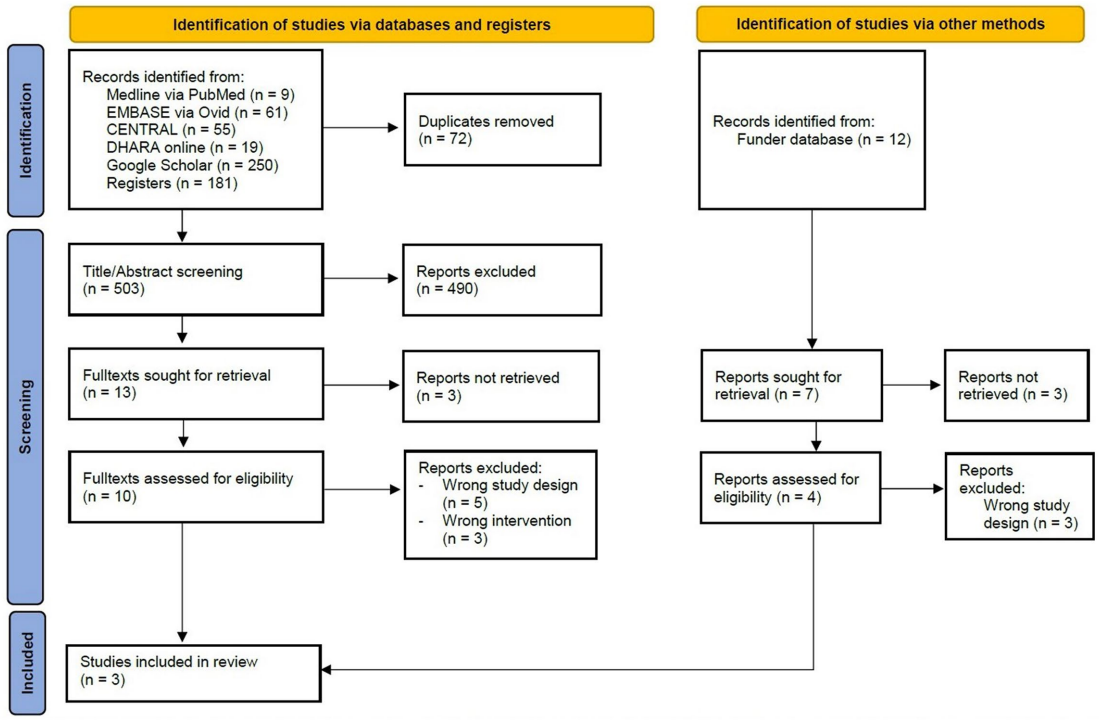

FIGURE 2
Risk of bias as assessed by the Cochrane Risk of Bias tool version 1.

Orme-Johnson, Robinson, Wallace, and Glaser (40). In Saxena et al. (42) and Samaiya et al. (41), a high bias was observed with regard to the blindings of participants and personnel, while for Gelderloos et al. (40) blinding was rated as adequate. Detection bias was rated low for Gelderloos et al. (40) and unclear for Saxena et al. (42) and Samaiya et al. (41). Attrition bias was rated unclear for all studies. The risk of bias with regard to reporting bias in Saxena et al. (42) and Samaiya et al. (41) was rated as high, while for Gelderloos et al. (40) it was rated as unclear. Other bias were considered low in Gelderloss et al. (40) and Samaiya et al. (41) and high in Saxena et al. (42).

4 Discussion

4.1 Summary of evidence

This systematic review provides new evidence as it is the first systematic review on MAK. It is based on three RCTs that included 418 participants in total (40–42). The results suggest that MAK may alleviate the side effects of chemotherapy in breast cancer patients and may positively influence attentional capacity or alertness in healthy adults. The results from these few RCTs complement the findings from other clinical trials suggesting beneficial effects of MAK. A recent scoping review concluded that preclinical studies show promising results for the use of MAK as an anticancer and chemoprotective agent (25). Furthermore, the results of Zanella et al. (19), who placed healthy individuals on a diet with or without MAK, showed that a MAK-enriched diet decreased oxidative stress parameters and increased antioxidant defenses in both short- and long-term treatments (12). Research into the phytochemical aspects of the plants that form the basis for the production of MAK has also shown promising prospects for the treatment of oxidative stress and cancer (44). Experiments in the mouse model also show positive effects of MAK on cancer-associated parameters—although here an effect on tumor incidence but not on body weight was shown (15–17). This is in contrast to the results of the two RCTs (41, 42), which showed positive effects of MAK on body weight but not on tumor response. The effects on cognitive attention parameters found by Gelderloos et al. (40) are complemented by findings from Nidich, Morehead, Nidich, Sands, and Sharma (39). In this study, the non-verbal intelligence of students who received a Maharishi Student Rasayana Food Supplement over a longer period of time within an RCT was compared. The results show an increase in non-verbal intelligence in the MAK group compared to the placebo. However, further research is urgently needed to prove these effects with regard to the effect of MAK on the side effects of chemotherapy and cognitive aging processes. Traditional, complementary and integrative medicine offers a variety of approaches to alleviate symptoms associated with some of today's most pressing medical conditions, such as cancer, pain, and bowel disease, through procedures such as lifestyle changes and manual medicine (45, 46). Together with other procedures from traditional and complementary medicine, MAK might be a promising therapeutic addition.

4.2 Strengths and limitations

To our knowledge, this is the first systematic review of the therapeutic, health-promoting, and preventive effects of MAK without time or language limitations using a broad search strategy. This included searching clinical trial registries as well as gray literature. The results of the review indicate that there is a paucity of high-quality

RCTs on this topic. RCTs on Ayurveda for common medical conditions are mostly scarce (47). Only three RCTs could be included in the present review, which substantially limits the strength of the evidence. The included studies showed a mixed risk of bias. Furthermore, bias due to unpublished data cannot be ruled out. For example, three conference abstracts could not be retrieved as full texts and consequently could not be included in the review (27–29). Furthermore, one potentially eligible study (26), registered on clinicaltrials.gov and categorized as completed with results, could not be retrieved, including results as well. Furthermore, methodological limitations may apply as well. Within the two studies on breast cancer (41, 42), it is not apparent whether the statistical analysis corrected for multiple testing when testing for differences in each chemotherapy cycle. The presentation of the results and the description in the text cast serious doubt on this, which further calls into question the validity of the results. The lack of *a priori* registrations in public study registries, the lack of recording of adverse events, and the lack of mention of defined primary and secondary outcome parameters in all three included studies (40–42) also deserve critical mention. Most of the studies are also relatively old. More recent studies based on current quality guidelines are urgently needed. Finally, it does not become clear from the study on healthy adults which MAK preparation is used (40). It is assumed that it is MAK 5, but this is not explicitly mentioned.

4.3 Clinical implications

Based on the available results, it is too early to make specific clinical implications. As with all dietary supplements, caution is advised when using them in a clinical context due to potential interaction effects with medications. It is also very important in this context that doctors and patients talk openly about the potential use of such supplements.

4.4 Implications for future research

Given that Ayurveda is not only widely practiced in South Asia but has become increasingly popular on a global scale (1, 2), there is a great need for high-quality RCTs to improve the quality of evidence for the effects and safety of MAK. Future RCTs should adhere to the established Ayurveda research quality standards (4) as well as take into account the international quality standards for RCTs, such as the Consolidated Standards of Reporting Trials (48, 49). There is also an urgent need for a structured recording and reporting of adverse events.

4.5 Conclusion

MAK 4 and 5 exhibit potential health benefits *in vivo*, but limited clinical RCTs and a high risk of bias complicate confirming treatment effects. Consultation with the treating physician is necessary, especially when supplementing conventional oncological therapy. High-quality studies are required to confirm MAK's health benefits and to establish optimal dosage and intake duration.

Data availability statement

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

Author contributions

AK: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Visualization, Writing – original draft. MP: Supervision, Writing – review & editing. SG: Supervision, Writing – review & editing. RW: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. MJ: Supervision, Writing – review & editing. CK: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

MP is salaried professor in J. S. Ayurveda College, Nadiad, India. He also treats patients with Ayurveda in the teaching hospital on a regular basis. SG is salaried professor in J. S. Ayurveda College, Nadiad, India. He treats patients with Ayurveda in the teaching hospital on a regular basis. He also receives honoraria for lecturing in courses on Ayurveda at European Academy for Ayurveda, Birstein, Germany. MJ receives consultancy fees from European Academy for Ayurveda, Birstein, Germany and for lecturing in courses on Ayurveda and Yoga at Sonne und Mond, Berlin, Germany. CK receives honoraria for lecturing in courses on Ayurveda and Yoga at European Academy for Ayurveda, Birstein, Germany and at Sonne und Mond, Berlin, Germany and receives consultancy fees from Bruno Zimmer, Oberthal, Germany for scientific advisory. He also treats patients with Ayurveda in a hospital department specialized on Integrative Medicine on a regular basis.

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

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Exploring the gap: attitudes, knowledge, and training needs in complementary and integrative medicine among healthcare professionals at German university hospitals

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Introduction: The use of Complementary and Integrative Medicine (CIM) is very popular among the general population in Germany. However, international studies show that nurses, physicians, and other health care professionals (HCPs) at hospitals often do not feel sufficiently informed about different CIM approaches. Moreover, they do not feel trained enough to counsel their patients appropriately. In the German-speaking context, particularly within university hospitals, research on this subject is scarce. Therefore, the aim of this explorative study was to evaluate attitudes, subjective knowledge, and needs regarding CIM among HCPs with direct patient interaction across all four university hospitals in the federal state of Baden-Württemberg, Germany (Tübingen, Ulm, Freiburg, Heidelberg).

Methods: The multicenter, cross-sectional, anonymous full survey was conducted online using a self-developed, semi-structured, web-based questionnaire. Recruitment took place via all-inclusive e-mail distribution lists of all four university hospitals.

Results: A total of $n = 2{,}026$ participants (response rate varied by location from about 5 to 14%) fully answered the questionnaire. Nurses constituted the largest professional group ($n = 1{,}196$; 59%), followed by physicians ($n = 567$; 28%), physiotherapists ($n = 54$), psychologists ($n = 48$), midwives ($n = 37$), and other professions ($n = 124$). More than two-thirds (71%, $n = 1{,}437$) of the participants were female and 14% ($n = 286$) reported additional training in CIM. The overall attitude toward CIM (10-point Likert scale, 10 = "very favorable") was clearly positive ($M \pm SD$: 7.43 ± 2.33), with notable differences between professional groups: midwives (9.05 ± 1.18), physiotherapists (8.44 ± 1.74), and nurses (8.08 ± 1.95) expressed the highest support, whereas physicians (5.80 ± 2.39) the lowest. 42% of the participants incorporated CIM in patient care (from 33% of physicians to 86% of midwives). Overall, relaxation therapy ($n = 1{,}951$; 96%),

external applications (n = 1,911; 94%), massage (n = 1,836; 91%), and meditation/mindfulness (n = 1,812; 89%) were rated as useful or rather useful for patients. The average self-assessed knowledge level about CIM was moderate (M ± SD: 5.83 ± 2.03). Most of the participants found CIM training at university hospitals important and saw research about CIM as one of the tasks of university hospitals. The participants expressed the highest interest in education for acupuncture/acupressure, relaxation therapies, and manual medicine.

Discussion: This comprehensive survey of health care professionals (HCPs) at university hospitals in Germany reveals a clearly positive disposition toward CIM, aligning with findings from other hospital-based surveys and highlighting differences among professional groups. While most therapies deemed beneficial for patient care are supported by positive evidence, further research is required for others. Given the average self-reported knowledge of CIM, targeted education is essential to meet the needs of both HCPs and patients and to ensure the provision of evidence-based information on the risks and benefits of CIM.

KEYWORDS

complementary medicine, integrative medicine, healthcare professional, attitude, knowledge, needs, university hospital, Germany

1 Introduction

Complementary and integrative medical (CIM) approaches encompass a wide range of methods including nutritional, psychological, and physical approaches (1). While some CIM approaches are recommended in guidelines for health care professionals (HCPs) (2) and show positive results in studies, such as acupuncture (3–5) or relaxation therapy (6) to reduce pain or phytotherapy to prevent urinary infections (7) or cognitive impairment (8) or to reduce chronic constipation (9), others may cause interactions with conventional drugs, such as chemotherapy, and be potentially harmful for patients' health, such as certain vitamins (10) or diets (11). Also, financial risks due to high costs are possible (12).

Although there is an ongoing discussion on the definition of which CIM therapies fall under the umbrella concept, the terms 'complementary', 'alternative', and 'integrative' are constantly evolving, as described by the National Institutes of Health (1). A recent definition was suggested by Brinkhaus and Esch as follows: *"Integrative medicine affirms the importance of the doctor-patient relationship, aims at the whole person, is informed by evidence and uses all appropriate therapeutic, preventive, health-promoting or lifestyle approaches as well as all disciplines of health care to achieve optimal health and healing-emphasizing both the art and science of healing"* (13). In academic and scientific contexts, authors often have used the abbreviation CAM ("complementary and alternative medicine") in the past. In recent years, the term "Integrative Medicine" (IM) or "Complementary and Integrative Health" (CIH) is used to describe an evidence-based approach to implementing these therapies in healthcare (1). For this reason, this study uses the term "complementary and integrative medicine" (CIM), even when referring to studies using CAM or IM as concepts.

There is adequate research available on patients' interest in and demand for CIM. Patients may experience positive effects like resource activation through an improved sense of coherence or patient activation (14) and their efforts toward greater psychological or physical well-being (12, 15). In general, CIM is used for various counseling occasions, for example, by more than one third of patients with cardiovascular diseases (16) and by more than 40% of patients with chronic pain (17). According to international studies, between 32% (18) and 40% (19) of patients in Germany used CIM in the previous 12 months. For cancer patients, a review reported usage by 50% of patients (20) while for some population groups, such as patients with breast cancer, a usage by up to 80% of patients can be assumed (21). Accordingly, recent studies indicate that between 15% (22) and 74% (23) of oncology patients in Germany use CIM during their therapy. Interest in CIM is also high among patients at university hospitals. As we have shown previously, in Baden-Württemberg in Germany patients from different departments of university hospitals had an average usage rate of CIM of 48% for their current disease and 48% asked for counseling on CIM (15). At university hospitals, HCPs such as nurses, physicians, and physiotherapists, are possible points of contact for patients regarding CIM.

According to an international review article, about two-thirds of *nurses* have positive attitudes toward CIM (24). Although more than two-thirds of nurses in Australia discuss this topic with their patients (25) and 50% of nurses report professional use of CIM (26), they also cite a lack of knowledge as a barrier to proper communication about the topic (27). According to quantitative international studies more than two-thirds of nurses report a lack of knowledge about CIM (24). Looking at the attitudes of *physicians*, studies show that they are usually more skeptical about CIM than nurses (28, 29). Like the nurses, only 23% of physicians in a study at a university hospital in Germany considered themselves to be adequately informed (28). Approximately 20% (30) to 60% (31) of general practitioners use CIM in an outpatient setting. Although physicians may be an important source of information on CIM for patients in general (15, 22), there is a lack of evidence toward attitudes and knowledge about CIM procedures for physicians at university hospitals in Germany. As for

other HCPs, midwives are most likely to support complementary therapies (32, 33). Little is known for other HCPs, such as physiotherapists. Looking at all HCPs in hospitals, a study from an academic center in Switzerland showed that 80% of the different professionals do not feel sufficiently informed about CIM (34). Commonly, female hospital staff show a significantly higher level of interest in CIM than male staff (28). However, there is a general lack of research about HCPs and CIM at university hospitals.

Within the framework of evidence-based medicine, which includes patient's views, external evidence and professionals' expertise (35), it is important to know about the attitudes, knowledge and needs of HCPs. As shown, there are several studies concerning several HCP groups in different settings. However, the setting of university hospitals in the German-speaking area has not been thoroughly investigated. Therefore, the aim of this study was to assess the attitudes toward CIM and ratings of specific CIM therapies among different HCP groups at university hospitals in Baden-Württemberg, Germany. In addition, we aimed to investigate HCPs' usage of CIM, their self-assessed level of knowledge about CIM and their interest in training in specific CIM procedures.

2 Materials and methods

2.1 Study design

We conducted an anonymous, multicenter, cross-sectional full survey using a self-administered, semi-structured online questionnaire.

The study was registered in the German Clinical Trials Register (DRKS00015445). According to a statement by the Ethics Committee of the University Hospital and Medical Faculty Tübingen, in accordance with the German Federal Law § 3 Abs. 6 BDSG/LDSG BW, no formal ethics approval is required for the collection of anonymous data.

2.2 Survey instrument

No appropriate validated questionnaire could be found in literature to date. Therefore, we have developed a comprehensive questionnaire based on our research questions and adapted to the context of university hospitals. The questionnaire was pretested profoundly via the concurrent think aloud method (36) and additionally commented by $n = 10$ HCPs (nurses and physicians). After the pretest, the questionnaire was adapted accordingly. The survey was presented via Unipark software (Questback GmbH).

After a detailed introduction, covering the definition of CIM for this survey, the questionnaire contained three sections on content issues ("attitude"; "knowledge and need for information"; and "CIM at university hospitals") and sociodemographic data. It included questions with an endpoint-labeled 10-point Likert scales, such as on attitude (10 = "very favorable") and knowledge about CIM (10 = "very well"), matrix questions with a 4-point Likert scale on different general attitudes toward CIM at university hospitals and on specific therapies (4 = "I agree" or "useful" and response option "cannot judge"), and multiple-choice questions on interest in CIM training and factors influencing attitudes toward CIM. CIM use was asked in a dichotomous way. The therapy list of twenty CIM therapies included therapies from a preliminary study (patient survey (37)) and from various textbooks (38, 39). Examples for each therapy approach were given. Apart from open ended text questions and the category "other," the selection of an answer in the questionnaire was required for proceeding to the next page (so no missing answers were allowed).

2.3 Recruitment of participants

Starting in July 2018, the survey link was separately sent out in sequence via the employee mailing lists of the four university hospitals in the federal state of Baden-Württemberg, Germany (Freiburg, Heidelberg, Ulm and Tübingen). This was followed by two mail reminders per site. The last e-mail was sent in September 2019. Since not every employee had their own personal business e-mail address at all four locations, in three locations internal house mail was additionally used. At one location, nurse department heads were contacted via e-mail and asked to distribute the link using a snowball approach.

2.4 Study population

The study aimed at a full survey of HCPs with direct patient contact at all four university hospitals in Baden-Württemberg with a focus on physicians and nurses.

2.5 Analysis

Only fully completed questionnaires including sociodemographic data (except age, years of work experience and specialty, which were voluntary information) were included in the analysis. In addition, questionnaires were excluded if the occupational group was not involved in patient care (e.g., "administration") or if no occupational group was indicated. HCPs in training were not included. All 10-point Likert scales were scored as quasi-metric ordinal scales. IBM SPSS Statistics 28 was used for descriptive statistical analysis, subgroup analyses and comparisons between HCPs groups.

3 Results

3.1 Response rate

At location 1, about $n = 5{,}500$ professionals were contacted by e-mail. In the mailing list, staff was also included who was not the target group of the questionnaire (not involved in patient care). About $n = 1{,}450$ nurses and other HCPs were contacted via post. The response rate for all was about 5, and 8% for physicians.

At location 2, about $n = 4{,}200$ professionals were contacted by mailing list. The response rate of physicians was about 10%. As nurses and other HCPs did not have comprehensive professional mail accounts, further mail contacts (about $n = 1{,}700$) and the snowball principle were used, and for some departments (e.g., cardiology, psychosomatics) copies with the link were printed due to poor e-mail availability. For that reason, the response rate cannot be exactly determined.

TABLE 1 Sociodemographic data.

Demographic categories	*n*	%
Gender		
Female	1,437	70.9
Male	589	29.1
Profession		
Nurse	1,196	59.0
Physician	567	28.0
Physiotherapist	54	2.7
Psychotherapist/Psychologist	48	2.4
Midwife	37	1.8
Other	124	6.1
Leadership position		
Yes	417	20.6
No	1,609	79.4
Country of training		
Germany	1,960	96.7
Other	66	3.3
Additional training in CIM		
Yes	286	14.1
No	1,740	85.9
University hospital		
Location 1	735	36.3
Location 2	415	20.5
Location 3	550	27.1
Location 4	326	16.1
Total	2,026	100.0

Demographic categories with frequency (*n*) and valid percentage (%).

At location 3, about $n = 3{,}700$ HCPs were contacted via e-mail and $n = 2{,}800$ nurses and other professionals were additionally contacted via house mail, from which max. $n = 2{,}200$ were contacted by both. The overall response rate for physicians was about 10%, for nurses about 14%, based on employee numbers.

At location 4, about $n = 5{,}500$ HCPs were contacted via e-mail and the response rate for all was about 13, 7% for physicians and 19% for nurses, and about 21% for others.

The overall response rate cannot be exactly determined.

3.2 Characteristics of the participants

Table 1 provides an overview of the sociodemographic data. A total of $n = 2{,}026$ HCPs participated, of which more than half were nurses and almost a third physicians, supplemented by other HCPs like physiotherapists, psychologists, midwives, and other professionals. More than two-thirds (70.9%, $n = 1{,}437$) of the participants were female and 14.1% ($n = 286$) reported additional training in CIM. The participants' average age was 43.2 years ($SD = 11.4$), and they had 18.9 years of work experience on average ($SD = 12.1$).

3.3 Attitude toward CIM

3.3.1 General attitude toward CIM

The general attitude toward CIM (Question: "My general attitude toward Complementary and Integrative Medicine (CIM) would best be described as follows:") tended to be clearly favorable ($M \pm SD$: 7.43 ± 2.33; Likert scale: 1 = "very unfavorable," 10 = "very favorable"). Midwives (9.05 ± 1.18), physiotherapists (8.44 ± 1.74), and nurses (8.08 ± 1.95) expressed the highest favorability, physicians (5.80 ± 2.39) the lowest. A Kruskal-Wallis test showed that attitudes toward CIM were influenced by professional group (*chi-square (2)* = 387.725, $p < 0.001$). Subsequent post-hoc tests (Dunn-Bonferroni tests) showed that physicians differed significantly from the other professional groups (except psychologists) ($z = -7.872$ to -18.630, $p < 0.001$).

The attitude toward CIM also differed significantly with gender: Male participants (6.20 ± 2.55) were more skeptical than female (7.93 ± 2.03) (Asymptotic Mann Whitney *U*: $z = -14.334$, $p < 0.001$, $r = -0.318$). Odds ratios in logistic regression have not been calculated due to the high degree of multicollinearity between profession and gender.

Participants who were not in a leadership position (7.57 ± 2.26) had a more favorable attitude than those who were (6.85 ± 2.51) (Asymptotic Mann Whitney *U*: $z = -5{,}349$, $p < 0.001$, $r = -0.119$).

For more details on general attitudes toward CIM, see Table 2.

3.3.2 Attitude toward specific CIM therapies

Table 3 displays the attitudes toward specific CIM therapies in patient care. The therapies that were most frequently rated as useful or rather useful were relaxation therapy (e.g., progressive muscle relaxation, autogenic training) ($n = 1{,}951$; 96.3%), external applications (e.g., embrocations, wraps, pads) ($n = 1{,}911$; 94.3%), and massage (e.g., reflexology) ($n = 1{,}836$; 90.6%).

3.3.3 Attitude toward CIM as task of university hospitals

For attitudes toward CIM at university hospitals see Table 4. Most of the participants agreed or rather agreed that providing CIM to patients ($n = 1{,}408$; 69.5%), as well as research on ($n = 1{,}763$; 87.0%) and counseling ($n = 1{,}601$; 79.0%) about CIM are tasks of university hospitals. Physicians and nurses differed significantly in their attitude toward providing CIM to patients (asymptotic Mann Whitney *U*: $z = -16.049$, $p < 0.001$), counseling about CIM ($z = -10.046$, $p < 0.001$), and research on CIM ($z = -5.304$, $p < 0.001$). Additionally, physicians and nurses showed significant differences regarding interprofessional care for CIM ($z = -12.948$, $p < 0.001$).

3.4 CIM use at university hospitals

41.7% of the participants involved CIM in patient care (Question: "Do you use CIM therapies with patients in your clinical practice?"). The highest use was shown by midwives (86.5%, $n = 32$) and physiotherapists (79.6%, $n = 43$). The lowest use had physicians (33.2%, $n = 188$).

TABLE 2 Healthcare professionals' attitude toward CIM.

Attitude	Answer: "agree" or" rather agree" *n*, %				Answer "cannot judge" *n*, %
	All (*n* = 2,026)	Nurses (*n* = 1,196)	Physicians (*n* = 567)	Other (*n* = 263)	All (*n* = 2,026)
1. A holistic approach to patient care is important to me.	1,938, 95.7%	1,166, 97.5%	516, 90.0%	256, 97.3%	16, 0.8%
2. Patient expectations and values should be taken into consideration in treatment.	1,971, 97.3%	1,165, 97.4%	549, 96.8%	257, 97.7%	13, 0.6%
3. The placebo effect plays an important role in CIM.	1,266, 62.5%	618, 51.7%	501, 88.4%	147, 55.9%	289, 14.3%
4. The placebo effect plays an important role in conventional therapies.	1,017, 50.2%	527, 47.1%	358, 63.1%	132, 50.2%	243, 12.0%
5. The use of CIM has added value to patient care.	1,690, 83.4%	1,078, 90.1%	388, 68.4%	224, 85.2%	111, 5.5%
6. Physicians and nurses should distance themselves from CIM.	268, 13.2%	95, 7.9%	142, 25.0%	31, 11.8%	79, 3.9%
7. CIM contributes to patients' health.	1,694, 83.6%	1,081, 90.4%	385, 67.9%	228, 86.7%	106, 5.2%
8. Patients are harmed in their health by CIM.	159, 7.8%	32, 2.7%	110, 19.4%	17, 6.5%	167, 8.2%
9. Patients are financially harmed by CIM.	537, 26.5%	167, 14.0%	308, 54.3%	62, 23.6%	327, 16.1%

HCPs' rating for attitudes toward CIM (Question: "What is your opinion on the following statements?") on a 4-point Likert scale (1 = "disagree," 4 = "agree") and answer option "cannot judge." *n* = frequency, % = valid percentage. Professionals were divided into three categories.

3.5 Knowledge and communication about CIM

The personal level of knowledge about CIM (Question: "How well do you feel informed about CIM overall?") was assessed as rather average ($M \pm SD$: 5.83 ± 2.03; scale: 1 = "very poorly," 10 = "very well"). Midwives reported the highest level of knowledge (7.24 ± 1.95), physicians the lowest (5.54 ± 2.02).

Less than one third ($n = 578$, 28.5%) of participants agreed or rather agreed that they feel confident in counseling patients about CIM and less than half of the participants ($n = 859$; 42.4%) agreed or rather agreed that they are often asked about CIM by patients. For comparison between professional groups see Table 5.

3.5.1 Education about CIM – past and future training

The vast majority of participants ($n = 1{,}764$, 87.1%) agreed or rather agreed that CIM training at university hospitals is important to them. The importance attributed to CIM in further training (Question: "How important was CIM in your previous training and further training?") was rated as rather low ($M \pm SD$:3.55 ± 2.21; scale: 1 = "not at all important," 10 = "very important"). Midwives saw the highest (7.11 ± 2.41), and physicians the lowest (3.08 ± 1.84) importance.

The most frequently requested topics for training (Question: "For which of the following CIM therapies do you have an interest in further information (e.g., in the form of training courses)?") in a multiple choice question ($n = 2{,}026$) were acupuncture/acupressure ($n = 1{,}025$), relaxation therapy ($n = 984$), manual medicine (e.g., chiropractic, osteopathy, cranio-sacral therapy) ($n = 870$), external applications (e.g., embrocations, wraps, pads) ($n = 829$), and meditation/mindfulness ($n = 806$).

4 Discussion

To the best of our knowledge, this cross-sectional study about attitudes toward, knowledge about and interest in CIM training is the first multicenter full survey at university hospitals in the German-speaking area. The aim of the present study was to investigate the field of CIM at university hospitals within a multicenter study in Germany.

The general attitude toward CIM showed a clear positive trend for all participants ($M \pm SD$: 7.43 ± 2.33), which varied across the professional groups. Our results are consistent with other surveys in the German-speaking area by Trimborn et al. (28) and Aveni et al. (34). The academic centers in Baden-Württemberg revealed that nurses had a more positive attitude compared to physicians. Our results showed that midwifes and physiotherapists are even more favorable toward CIM than nurses. Midwives' support for CIM was already explored in several studies (24, 40). Possible reasons for the discrepancy between physicians and other professionals may be differences in education and practice. While acupuncture, massage, and relaxation techniques are a part of classic midwifery textbooks (41), complementary medicine is often taught separately and during post-graduate education to physicians. Consistent with our results, physiotherapists in Sweden recommended CIM more than physicians and nurses according to Bjerså et al. (42). Our findings again provide support for gender differences in attitudes (28, 43).

Another aim was to examine the attitudes toward specific CIM therapies. Professional respondents in our study found relaxation therapy, external applications, and massage the most useful for patient care. For most of the therapies rated as useful by HCPs, positive effects have been shown in studies, such as reduction of chronic pain (6), or treatment-related symptoms during chemotherapy (44) by *relaxation therapy* or reduction of anxiety and depression (45) by *massage therapy*. For the field of *external applications,* a recent article by Stolz et al. underlined a great potential for independent use by patients (46). Considering the high interest of HCPs in CIM, Mühlenpfordt et al. have underlined a high demand for more future research in this field (47). According to Aveni et al. personal experience is a significant factor for HCPs at a university hospital in Switzerland when forming their opinions on CIM (34). Positive experience with external applications in patient care might be a reason for our results. Given the cost-effectiveness for wraps, etc., this could be another reason for pragmatic approach in patient care.

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TABLE 3 Attitude toward CIM methods in patient care.

CIM method	Answer "useful" or "rather useful" *n*, %				Answer "cannot judge" *n*, %
	All (*n* = 2,026)	Nurses (*n* = 1,196)	Physicians (*n* = 567)	Other (*n* = 263)	All (*n* = 2,026)
Relaxation therapy (e.g., autogenic training, progressive muscle relaxation)	1,951, 96.3%	1,146, 95.8%	549, 96.8%	256, 97.3%	28, 1.4%
External applications (e.g., embrocations, wraps, pads)	1,911, 94.3%	1,172, 98.0%	489, 86.2%	250, 95.1%	25, 1.2%
Massage (e.g., reflexology)	1,836, 90.6%	1,145, 95.7%	441, 77.8%	250, 95.1%	40, 2.0%
Meditation/mindfulness	1,812, 89.4%	1,073, 89.7%	491, 86.6%	248, 94.3%	75, 3.7%
Meditative movement therapy (e.g., yoga, qigong, tai chi)	1,786, 88.2%	1,056, 88.3%	486, 85.7%	244, 92.8%	102, 5.0%
Acupuncture/acupressure	1,780, 87.9%	1,080, 90.3%	458, 80.8%	242, 92.0%	81, 4.0%
Manual medicine (e.g., chiropractic, osteopathy, cranio-sacral therapy)	1,703, 84.1%	1,067, 89.2%	400, 70.5%	236, 89.7%	112, 5.5%
Hydrotherapy/balneotherapy (e.g., Kneipp, alternating showers, steam bath)	1,612, 79.6%	972, 81.3%	422, 74.4%	218, 82.9%	170, 8.4%
Phytotherapy/herbal medicine	1,533, 75.7%	946, 79.1%	380, 67.0%	207, 78.7%	233, 11.5%
Nutritional therapy (e.g., special diets, fasting)	1,531, 75.6%	912, 76.3%	400, 70.5%	219, 83.3%	148, 7.3%
Aromatherapy	1,304, 64.4%	958, 80.1%	185, 32.6%	161, 61.2%	236, 11.6%
Homeopathy	1,191, 58.8%	888, 74.2%	119, 21.0%	184, 70.0%	116, 5.7%
Nutritional supplements (e.g., vitamins, minerals, trace elements)	1,076, 53.1%	688, 57.5%	235, 41.4%	153, 58.2%	227, 11.2%
Microbiotic therapy (e.g., probiotics)	1,009, 49.8%	593, 49.6%	296, 52.2%	120, 46.6%	102, 5.0%
Ayurvedic medicine	965, 47.6%	653, 54.6%	173, 30.5%	139, 52.9%	619, 30.6%
Anthroposophic medicine	905, 44.7%	653, 54.6%	127, 22.4%	125, 47.5%	513, 25.3%
Drainage therapy (e.g., leech therapy, cupping)	813, 40.1%	568, 47.5%	115, 20.3%	130, 49.4%	489, 24.1%
Neural therapy (e.g., wheal therapy)	697, 34.4%	465, 38.9%	132, 23.3%	100, 38.0%	759, 37.5%
Mistletoe therapy	665, 32.8%	463, 38.7%	121, 21.3%	81, 30.8%	762, 37.6%
Other[a]	111, 5.5%	76, 6.4%	14, 2.5%	21, 8.0%	194, 9.6%

HCPs' rating for specific CIM methods (Question: "In general, how useful do you rate the following CIM therapies for patients?") on a 4-point Likert scale (1 = "not useful," 4 = "useful") and answer option "cannot judge." *n* = frequency, % = valid percentage. Sorted by *n* (all) for answer "useful" or "rather useful." HCPs were divided into three categories. [a]*n* = 321 (due to missing data).

In a survey among university hospital patients in Germany by Lederer et al., exercise, herbal medication, and dietary supplements were the three most used CIM methods (15). The effectiveness of some *phytotherapeutic* approaches has been demonstrated in several randomized controlled trials (e.g., turmeric in patients with irritable bowel syndrome (48)) and systematic reviews (e.g., cranberries for prevention of urinary infections (7), St. John's wort for moderate depression (49), and psyllium for chronic constipation (9)). In our study, HCPs did not highlight phytotherapy as useful. A possible reason for this difference in prioritization could be the setting: In the primary care setting, CIM (e.g., over-the-counter-phytotherapy) is often used for self-limiting diseases (50).

For the first time in Germany, the focus on the university hospital setting especially and the attitudes of HCPs working in this setting was explored in our study. Participants showed a distinct positive attitude toward CIM integration at university hospitals. Overall, 80% of all participants and about two-thirds of the physicians agreed or rather agreed that counseling about CIM is a task of university hospitals. According to our study, more than 40% of the participants were already using CIM in patient care. Midwives, physiotherapists, and psychologists showed higher rates of use than nurses in our study. That can possibly be explained by the fact that for physiotherapists, manual therapies are often integrated into their daily work, whereas psychologists are specifically trained in relaxation therapies. In line with other studies, less than half of the participants regularly communicated about CIM with their patients (51). To close this gap, HCPs communicative skills should be trained, especially to address patients' needs. When it comes to CIM in the university hospital setting, the highest acceptance was shown for research: More than 80% of the participants agreed or rather agreed that CIM research is a university hospitals' task. To meet this demand, an expansion of university research centers could be helpful, as in Germany, out of 38 university hospitals, only 13 operate an outpatient clinic for CIM and six have an endowed chair or professorship for CIM research (partly the same) (52). The WHO Global Report on Traditional and Complementary Medicine 2019 highlights the absence of national funding, national expert committees, a national agenda, and a national research institute for CIM in most European countries (Germany included) (53). Given the positive attitude to CIM and the involvement in clinical practice

TABLE 4 CIM as task of university hospitals.

Attitude	Answer "agree" or "rather agree" *n*, %				Answer "cannot judge" *n*, %
	All (*n* = 2,026)	Nurses (*n* = 1,196)	Physicians (*n* = 567)	Other (*n* = 263)	All (*n* = 2,026)
1. Counseling about CIM is one of the tasks of university hospitals.	1,601, 79.0%	1,003, 83.9%	383, 67.5%	215, 81,7%	84, 4,1%
2. Providing CIM to patients is one of the tasks of university hospitals.	1,408, 69.5%	956, 79.9%	262, 46.2%	190, 72.2%	93, 4.6%
3. Research on CIM is one of the tasks of university hospitals.	1,763, 87.0%	1,062, 88.8%	472, 83.2%	229, 87.1%	66, 3.3%
4. An outpatient clinic for CIM at university hospitals. is desirable.	1,442, 71.2%	962, 80.4%	279, 49.2%	201, 76.4%	103, 5,1%
5. A consulting service for CIM at university hospitals is desirable.	1,478, 73.0%	989, 82.7%	294, 51.9%	195, 74.1%	105, 5.2%
6. CIM should be an interprofessional task at university hospitals.	1,588, 78.4%	1,020, 85.3%	356, 62.8%	212, 80.6%	143, 7.1%

HCPs' attitudes toward CIM as task of university hospitals (Question: "What is your opinion on the following statements about CIM at university hospitals?") on a 4-point Likert scale (1 = "disagree," 4 = "agree") and answer "cannot judge." *n* = frequency, % = valid percentage. HCPs are divided in three categories.

TABLE 5 Communication with university hospital patients about CIM.

Attitude	Answer "agree" or" rather agree" *n*, %				Answer "cannot judge" *n*, %
	All (*n* = 2,026)	Nurses (*n* = 1,196)	Physicians (*n* = 567)	Other (*n* = 263)	All (*n* = 2,026)
1. From my point of view, patient interest in CIM has increased in the last few years.	1,553, 76.7%	905, 75.7%	441, 77.8%	207, 78.7%	212, 10.5%
2. Patients often ask me about CIM topics.	859, 42.4%	453, 37.9%	266, 46.9%	140, 53.2%	87, 4.3%
3. I often actively ask my patients about their need for or use of CIM.	542, 26.8%	328, 27.4%	117, 20.6%	97, 36.9%	91, 4.5%
4. I feel confident in counseling patients about CIM.	578, 28.5%	284, 23.7%	187, 33.0%	107, 40.7%	129, 6.4%

HCPs' attitudes toward communication about CIM (Question: "What is your opinion on the following statements about the role of CIM in your interaction with patients?") on a 4-point Likert scale (1 = "disagree," 4 = "agree") and answer "cannot judge." *n* = frequency, % = valid percentage. HCPs are divided in three categories.

at university hospitals according to our study, these may be structural gaps that need to be filled.

Participants in our study supported an interprofessional approach for CIM at university hospitals. More than 70% agreed or rather agreed that CIM at university hospitals should be an interprofessional task, with nurses more likely to agree than physicians. The high demand for interprofessionality was also expressed in a study by Homberg and Stock-Schröer, who used a qualitative approach to investigate the advantages and disadvantages of interprofessional CIM education in Germany and Switzerland (54). They concluded that an interprofessional approach could help to overcome stereotypes. Prill et al. conducted a mixed method study about interprofessional teaching regarding CIM and their participants emphasized the relevance of team meetings as a factor promoting interprofessional collaboration (55). This could also be relevant for university hospitals.

4.1 Knowledge about CIM

Knowledge about CIM was another focus of our study. The self-assessed knowledge (information level) about CIM tended to be average ($M \pm SD$: 5.83 ± 2.03), and only less than one third of participants (28.5%) agreed or rather agreed that they felt competent enough to counsel patients about CIM. Comparison with other studies is rather difficult because the questions were asked differently. In line with several other surveys (24, 27, 34), a lack of knowledge was also mentioned. The discrepancy between positive attitude and a subjective average level of knowledge that was shown in our study, was also found among nurses in the Chang and Chang survey (24). Several other studies cited a lack of knowledge as a main reason for not discussing CIM therapies with patients (27, 51). This may have contributed to the fact that less than 30% of HCPs in our study felt confident in counseling patients about CIM. To address this issue, high-quality evidence-based education on CIM should be provided to professionals, ideally in their training period as participants rated the importance of CIM in their previous education as rather low. For structured training, the definition of competencies to be acquired could also be helpful. For physician training in general practice on CIM, Valentini et al. developed a competency catalog for Germany with a multi-level, peer-based approach (56). This catalog could serve as a basis for other professions.

4.2 Interest in training about CIM

The participants expressed a high interest in training about CIM. More than 80% of the participants agreed or rather agreed that training in CIM at university hospitals is important to them. The top three topics for additional training mentioned in our study were acupuncture/acupressure, relaxation therapy, and manual medicine.

With regard to acupuncture, a high popularity among the patients in Germany (57) is known, and the costs are covered by public health insurance for some indications (58). Furthermore, in Germany, physicians can take structured additional qualifications in acupuncture which are awarded by the medical association (59). Interestingly, acupuncture/acupressure was among the most requested therapies for training at university hospitals, even if it was not among the most useful therapies for patient care. Possible reasons for this high interest on training in acupuncture might be due to the robust body of evidence on acupuncture with, for example, over 2,100 positive recommendations for acupuncture in clinical guidelines for over 200 indications (60).

4.3 Strengths and limitations

To the best of our knowledge, this is the first multicenter study of CIM at university hospitals. We aimed for a full survey study and over $n = 2{,}000$ participants took part in the survey. Therefore, subgroup analyses and comparisons between HCPs groups were possible. Another strength is the comprehensive questionnaire with a detailed list of different CIM methods and examples to ensure a consistent understanding of terms. The web-based and anonymous research design minimized social desirability as a potential source of bias. The tendency toward the middle as a possible bias was avoided using straight scales.

Nevertheless, the results should be interpreted with caution due to some important limitations of our study that need to be considered. First, we did not validate our questionnaire. To the best of our knowledge, no appropriate validated questionnaire has been published. We therefore discussed the questionnaire in an interprofessional team, conducted pretests and tried to explain the terms we used with examples to minimalize comprehension problems. Another limitation of this study is that the process of recruiting participants varied across study sites and therefore the response rate of the study cannot be accurately determined. Furthermore, the response rate across the different locations did not exceed 20 percent at any location or within any profession. Overall, the response rate was lower than in a similar study by Aveni et al., where the response rate was approximately 25% (34). In contrast to our study, e-mail accessibility in university hospitals may be better in Switzerland. It is difficult to draw a balanced picture here and it is to assume that especially HCPs with a very positive attitude regarding CIM have responded to the questionnaire and are overrepresented here. Nonetheless, as the area of CIM is very polarizing in general, it is also to assume that also very skeptical HCPs felt called to take part, especially within the profession of physicians.

Furthermore, it is possible that the link to the survey was distributed beyond the university hospitals since there was no personalized access. To reduce a potential selection bias, the survey invitation mail was formulated as neutrally as possible with evidence-based examples like acupuncture and phytotherapy. Unclear definitions of different therapies included make it difficult in some cases to compare studies. Nevertheless, similar trends can be identified. Also, the transferability of the results to other regions in Germany and internationally should be discussed.

The reasons for participants' attitudes toward CIM were not considered in this study. Supplementary qualitative research may be helpful to address this issue. In addition, barriers to the use of CIM at university hospitals should be addressed in future research.

4.4 Conclusion

The present study emphasizes the pronounced interest of HCPs in CIM within the context of university hospitals in Germany. Despite the interest, the moderate level of CIM knowledge among HCPs coupled with the limited emphasis of CIM within continuing education frameworks, underscores a need for enhanced CIM training. This becomes even more evident for physicians, who were most skeptical and reported the lowest knowledge. Notably, over 40% of the HCPs incorporate CIM into their clinical practice at university hospitals, yet a smaller proportion felt able to discuss CIM competently with patients. Our study elucidates the widespread utilization of CIM by HCPs in a university hospital setting, showing the substantial demand for an evidence-based interprofessional approach to CIM. Finally, our findings indicate a high level of interest among HCPs for comprehensive training in CIM– a component that warrants integration into medical education curricula. To optimize patient care and patient safety, it is essential to identify and integrate CIM modalities with robust scientific evidence, spanning from clinical application to patient communication.

Data availability statement

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

Ethics statement

The requirement of ethical approval was waived by Ethics Committee of the University Hospital and Faculty of Medicine Tübingen. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DH: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Visualization. CK: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Methodology, Project administration, Visualization. RS: Writing – original draft, Writing – review & editing, Conceptualization, Methodology. RH: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision. YS: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision. KH: Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Project administration, Resources, Supervision. ThS: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition,

Investigation, Project administration, Resources, Supervision. TaS: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision. SJ: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision. JV: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization.

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Conflict of interest

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

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Supplementary material

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Development of the Korean Medicine Core Outcome Set for Facial Palsy: herbal medicine treatment of patients with facial palsy in primary clinics

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Introduction: Facial palsy (FP) significantly affects the quality of life of patients and poses a treatment challenge in primary healthcare settings. This study aimed to develop a Korean medicine (KM) core outcome set (COS) for FP, with a focus on evaluating the effectiveness of herbal medicine (HM) treatments in KM primary clinics.

Methods: Outcomes and effect modifiers related to FP treatments were initially identified through related review articles. Subsequently, experts in the field took part in three rounds of modified Delphi consensus exercises to refine and prioritize these outcomes and effect modifiers. Additionally, primary KM clinicians were involved in a Delphi consensus round to assess the suitability and feasibility of the proposed COS in real-world clinical settings.

Results: The initial review of related literature identified 44 relevant studies, resulting in an initial selection of 23 outcomes and 10 effect modifiers. The expert consensus process refined these to 8 key outcomes and 6 effect modifiers, which established the foundation of the COS-FP-KM. Subsequently, primary KM clinicians confirmed the practicality and applicability of the COS, endorsing its suitability for use in KM primary clinics.

Conclusion: The COS-FP-KM establishes a standardized approach for assessing HM treatment effectiveness in FP patients in KM primary clinics. The COS-FP-KM encourages consistent outcome reporting and enhances patient care quality. Future work should aim to integrate broader stakeholder perspectives to refine and validate the COS further.

KEYWORDS

core outcome set, facial palsy, primary care, herbal medicine, Korean medicine

1 Introduction

Facial Palsy (FP) is a medical condition characterized by the sudden onset of unilateral facial muscle weakness or paralysis, often resulting in significant functional and esthetic impairment (1, 2). While there are various causes for FP, including infections, local inflammation, and malignancy, the most common form is idiopathic facial paralysis, known as Bell's palsy (3). This condition, which can occur at any age, significantly impacts the physical appearance, emotional well-being, and overall quality of life of patients (4, 5). It often leads to difficulties in facial expression, eating, speaking, and, in severe cases, specific dysfunctions such as the inability to blink or close the eye, and difficulty puckering the lips or raising the mouth corner, thereby profoundly affecting daily activities and social interactions (3, 6). The prevalence of FP varies globally, but it is considered a relatively common neurological disorder, affecting approximately 10–40 per 100,000 individuals annually (3, 6, 7). In conventional medicine, the primary treatments for FP typically involve the use of medications such as corticosteroids and antiviral agents, often complemented by surgical interventions like facial nerve decompression when necessary (7, 8). However, these treatments often have limited efficacy, particularly in cases of severe palsy or delayed treatment initiation, and are associated with potential side effects (8–11). These limitations highlight the need for more comprehensive treatment strategies in managing FP (7).

In several Asian countries, where herbal medicine (HM) plays an integral role in national healthcare, HM has emerged as a promising alternative treatment for FP, specifically targeting idiopathic peripheral FP, also known as Bell's palsy. Research indicates its efficacy in reducing inflammation, improving symptoms, and providing neuroprotective effects, particularly through the use of compounds like *Radix saposhnikoviae* and *Bombyx batryticatus* (12, 13). Additionally, a study has shown that patients treated with a combination of acupuncture and HM for Bell's palsy experienced not only faster overall recovery but also shorter periods of initial recovery (14). However, the integration of HM into clinical practice faces challenges due to methodological inconsistencies, primarily the lack of standardized outcome measures (15). This lack of standardization in research methodologies and assessment scales leads to fragmented understanding, data inconsistency, and potential reporting bias. Such disparities complicate the decision-making process for healthcare practitioners and create uncertainties for patients considering alternative or complementary treatments (16).

While there is suggestive evidence of the benefits of HM in treating FP, there is an obvious need for clinical trials rigorously evaluating its efficacy. In South Korea, most Korean Medicine (KM) facilities are primary clinics (17), where conducting extensive clinical trials is challenging due to limited personnel and resources. Consequently, reported studies may often not meet the highest research standards or focus on outcomes that might not be the most relevant. The Korean Medicine Clinical Practice Guideline for Facial Palsy recommends combining HM with steroid therapy (18), but evidence for the efficacy and safety of HM is still insufficient (19). To address this, the Korean government initiated a pilot project in 2020 to support HM treatment for idiopathic peripheral FP in primary clinics, with health insurance covering the costs for 10 days of HM treatment that meets specific diagnostic and quality standards (20). However, a critical limitation of this project is the lack of a standardized outcome model to evaluate the impact of HM on Bell's palsy.

A Core Outcome Set (COS) comprises a set of vital outcomes, established through consensus among healthcare professionals and patients, which are essential to be assessed and reported in all clinical trials and practices for a specific medical condition (21). It ensures consistency in data collection and enhances the comparability of research findings across different studies (16). Recognizing the necessity for such standardization in the evaluation of HM treatments for Bell's palsy, this study aims to develop a Core Outcome Set for Facial Palsy in Korean Medicine (COS-FP-KM). The COS-FP-KM will enable the assessment of the effectiveness of HM in treating Bell's palsy in patients visiting KM primary clinics, using consistent and appropriate evaluation variables. This effort is crucial for improving the quality and relevance of research in this field, thereby facilitating more informed decision-making in clinical practice.

2 Methods

In this study, we developed a COS following a structured approach tailored to our specific objectives and scope, as outlined in Table 1. An important aspect of this process was the extraction of effect modifiers, key factors that influence outcomes, to aid clinicians in their history-taking and assessment. Our methodology for developing the COS was aligned with the processes established by the Core Outcome Measures in Effectiveness Trials (COMET) initiative and adhered to standard COS guidelines (22). This development involved three distinct phases, consistent with the methods used in previous studies (23, 24). Initially, we formed a Project Management Group (PMG) responsible for overseeing the development process. This group undertook the task of generating and refining an initial list of outcomes through an extensive literature review. The second phase involved a modified Delphi consensus process conducted by experts in the field. Following this, primary clinicians participated in a similar modified Delphi process during the third phase.

2.1 Phase 1: establishment of project management group and development of an initial list of outcomes and effect modifiers

A PMG was formed for this study, comprising five expert researchers from the Korea Institute of Oriental Medicine. Their responsibilities included an extensive literature review and extracting crucial outcomes and effect modifiers while ensuring the removal of any redundant results. The scope of the COS was determined, followed by a focused review of literature related to FP (Supplementary material 1).

In our analysis, we concentrated on review papers related to HM trials for patients with FP, with a focus on verifying the inclusion criteria and outcomes of the studies incorporated in these reviews. The review papers included a diverse range of studies, including Randomized Controlled Trials (RCTs), observational studies, and case

TABLE 1 Recommendations of the core outcome set standards for development (COS-STAD).

Domains	No.	Methodology	Notes
Scope specification	1	The research or practice setting(s) in which the COS is to be applied.	The COS will be applied in research studies for primary KM clinics.
	2	The health condition(s) covered by the COS.	The disease covered by the COS is facial palsy.
	3	The population(s) covered by the COS.	The target population for the COS consists of patients with facial palsy.
	4	The intervention(s) covered by the COS.	The intervention covered by the COS is HM of KM.
Stakeholders involved	5	Those who will use the COS in research.	KM researchers in primary clinics will use the COS for clinical trials.
	6	Healthcare professionals with experience of patients with the condition.	KM specialists and KM clinicians in primary clinics who participated in COS development.
	7	Patients with the condition or their representatives.	Patients did not participate.
Consensus process	8	The initial list of outcomes considered both healthcare professionals' and patients' views.	The initial list of outcomes included in the COS is identified through a literature review.
	9	A scoring process and consensus definition were described *a priori*.	A Delphi survey and consensus meeting was adopted to select the outcomes.
	10	Criteria for including/excluding/adding outcomes were described *a priori*.	1. Delphi with experts: review of all panels, inclusion criteria was unanimity. 2. Delphi with primary clinicians: 9-point Likert scale and calculation of CVR.
	11	Care was taken to avoid ambiguity of language used in the list of outcomes.	The language and medical terms in our COS ensure uniformity of the outcome terms.

COS, core outcome set; CVR, content validity ratio; HM, herbal medicine; KM, Korean medicine.

reports. For each study, we extracted key information, including study design, target disease, sample size, and various outcomes. Outcomes were categorized into doctor-reported and patient-reported outcomes, and outcomes associated with medical devices. The process involved meticulous examination and verification of each study's design and outcomes. Any discrepancies or disagreements encountered during this analytical stage were resolved through discussion among the research team.

Additionally, we reviewed previously published books and articles pertinent to FP, such as "Korean Medicine Clinical Practice Guideline for Facial Palsy" and other relevant literature on risk factors for FP (18, 25). This review helped us extract recommended outcomes and effect modifiers specific to FP. To streamline our research, duplicate studies and outcomes were removed. The PMG meticulously reviewed and refined the list of outcomes and effect modifiers in alignment with the rationale of this COS, finalizing the list for the next phase of the study.

2.2 Phase 2: expert consensus process through modified Delphi method

In this phase, we collaborated with The Korean Acupuncture & Moxibustion Medicine Society and the Korean Medicine Clinical Practice Guideline for Facial Palsy Development Team for a modified Delphi round. Following a request from the PMG, these organizations recommended a panel of experts, selected for their extensive experience and expertise in the field of facial palsy treatment. Ultimately, five experts agreed to participate after understanding the objectives and scope of the COS.

The modified Delphi round involved distributing materials for review, followed by group feedback sessions and consensus meetings. In the initial round, panel members were presented with the list of outcomes and effect modifiers identified in Phase 1. The process followed a unanimous decision-making approach, where each item was deliberated upon with the option of "consensus in" or "consensus out" to determine its relevance, and conflicts were resolved through discussion, continuing until unanimous agreement was reached. Additionally, panel members had the opportunity to suggest any new outcomes or effect modifiers not previously listed.

In the two following rounds (Rounds 2 and 3), the panel engaged in detailed discussions on all the proposed outcomes and effect modifiers, including those added in the first round. These discussions considered the initial responses from the panel members and were directed toward ensuring alignment with the scope of the COS. The process was iterative, persisting until a collective agreement was achieved on the final compilation of outcomes and effect modifiers to be included in the COS.

2.3 Phase 3: primary clinicians consensus process through modified Delphi method

In this critical phase, primary clinicians, pivotal in the field of FP treatment, were engaged to review the feasibility of previously identified outcomes and effect modifiers. This panel, comprising KM primary clinicians with a minimum of five years of clinical experience, was assembled following recommendations from The Korean Medicine Specialists Association at the request of the PMG. The panel included 11 professionals, with two specializing in facial palsy.

Their task was to assess the practicality of implementing the outcomes and modifiers in KM primary clinic settings. The questionnaire was structured into two sections: the first addressing effect modifiers related to facial palsy, and the second focusing on several distinct outcome measures. These included the House–Brackmann scale, the patient-perceived onset of symptom improvement, the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) & EuroQol Visual Analog Scale (EQ-VAS) assessments for quality of life, and evaluations of patient satisfaction. Each of these outcome measures was rated by the clinicians on a detailed nine-point scale.

Notably, some items such as certain laboratory tests and records of adverse events were not included in this phase. These were deemed essential by the PMG for investigating the safety and effectiveness of herbal medicines in treating facial palsy and were thus considered inherent elements of the COS.

2.4 Data analysis

2.4.1 Expert consensus in phase 2

During the expert-led modified Delphi consensus in Phase 2, we set unanimity as the predefined criterion for achieving consensus on the COS. Decisions were classified as either achieving full consensus "consensus in" or not "consensus out."

2.4.2 Primary clinician consensus in phase 3

In line with our previously published COS studies (23, 24), we employed the Content Validity Ratio (CVR) alongside measures of consensus and convergence to evaluate content validity and the formation of consensus. For the panel of 11 Delphi participants, the critical values for CVR, consensus degree, and convergence were established at $\geq$0.636, $\geq$0.75, and $\leq$0.5, respectively (26, 27).

2.5 Ethics and consent

The study received an exemption from ethical approval by the Institutional Review Board (IRB) of the Korea Institute of Oriental Medicine in Daejeon, Republic of Korea (IRB approval No. I-2203/003-001). Prior to participation, all panel members were required to provide written informed consent, ensuring their voluntary involvement and understanding of the study's objectives and procedures.

3 Results

3.1 Phase 1: development of an initial list of outcomes and effect modifiers

The initial literature search across databases including PubMed, CENTRAL, OASIS, and Science-On yielded a total of 174 studies. Of these, eight were removed due to duplication. Through the screening of titles and abstracts, an additional 163 studies were excluded for not meeting our inclusion criteria. Following a thorough full-text review for eligibility, no additional studies were excluded, resulting in the inclusion of three review studies for detailed analysis (Figure 1). Among these, one review detailed 14 distinct tools for assessing facial palsy, another encompassed two relevant RCTs and four prospective observational studies, and the third review brought in 37 case reports. Consequently, our analysis incorporated a total of 44 studies that were extracted from selected review articles, as enumerated in Supplementary Table S1.

From the three selected review articles, we extracted 44 individual studies, yielding a diverse array of outcomes and effect modifiers relevant to FP. In this step (Step 1), we identified 22 specific outcomes, including several specific scales and assessments for FP, such as the House–Brackmann scale and Yanagihara's unweighted grading system. Subsequently, an in-depth examination of related literature, including the "Korean Medicine Clinical Practice Guideline for Facial Palsy" and other studies addressing FP risk factors (Step 2) (18, 25), contributed an additional nine outcomes and 10 effect modifiers. Following these stages, the PMG engaged in comprehensive discussions to evaluate these items, categorizing them as suitable ("in") or not ("out") for inclusion in the COS for the next phase of the study. After eliminating duplicates from the initial findings, the refined list for the Phase 2 consensus included a total of 23 outcomes and 10 effect modifiers (Table 2).

3.2 Phase 2: expert consensus process through modified Delphi method

In Phase 2, we assembled a panel of five experts, each with a minimum of 10 years of clinical experience in FP and KM, working at facial nerve centers (Supplementary Table S2). These experts actively participated in the initial round of the Delphi process, during which they proposed two new outcomes and six potential effect modifiers. The PMG then evaluated each suggested outcome for potential inclusion in the next round. The questionnaire for the second round included both the newly proposed outcomes and effect modifiers, as well as those carried over from the first round. All participants from Round 1 were invited back. During this round, there was a unanimous agreement to exclude 13 outcomes and nine effect modifiers. Moreover, there was agreement that the items with no consensus would be revisited in Round 3. Accordingly, round 3 questionnaires comprised 12 outcomes and seven effect modifiers without a reached consensus. As in Round 2, all respondents were invited to participate in Round 3. Finally, eight outcomes and six effect modifiers met the consensus inclusion criteria for the COS. Table 3 and Figure 2 present the process involved for each round.

3.3 Phase 3: primary clinicians consensus process through modified Delphi method

In this phase, the panel included 11 clinicians, with two specializing in FP (Supplementary Table S3). Primary clinicians reached a consensus on all proposed items, as evidenced by the CVR surpassing the critical threshold for each question. This consensus affirmed that every item was both pertinent for the COS and practicable for data collection within KM primary clinic settings. The evaluation of effect modifiers and patient satisfaction yielded a high degree of consensus and convergence, reflecting a consistent perspective on the inclusion of these effect modifiers. However, agreement on the practicality of including the EQ-5D-5L

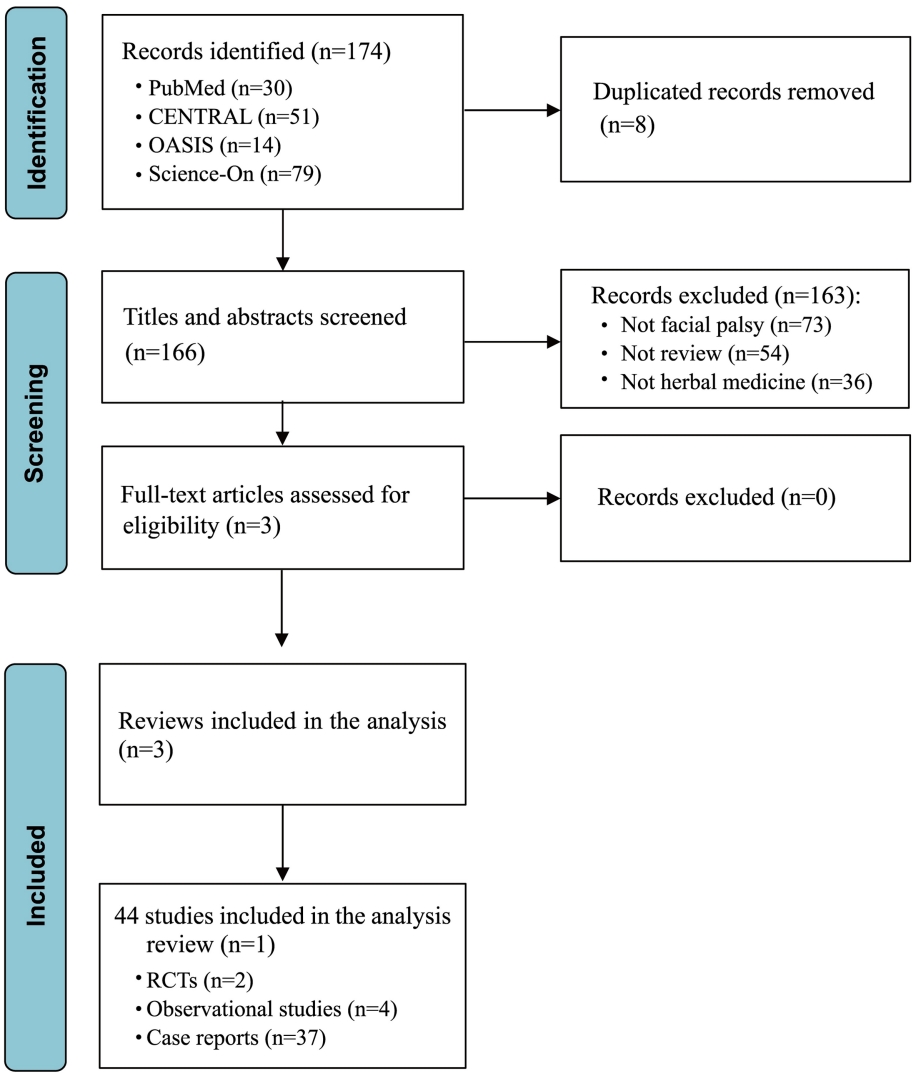

FIGURE 1
Flow chart of selection process. RCT, randomized controlled trial.

and EQ-VAS was less definitive, as indicated by a low level of consensus and convergence, highlighting varying views on their integration (Table 4).

4 Discussion

In the process of creating a COS for HM treatments targeting patients with FP in primary KM clinics, we adhered to the guidelines provided by the COMET initiative (22). This endeavor began with a review of related literature undertaken by the PMG (Phase 1). Subsequent phases involved modified Delphi exercises with experts in FP and KM (Phase 2), and a final phase with clinicians from KM primary clinical settings (Phase 3). These exercises were pivotal in assessing the applicability and feasibility of the COS, culminating in the identification of eight specific outcomes and six effect modifiers for the final COS.

In the development process from Phase 1 to Phase 3, our research was oriented toward understanding the distinct characteristics of FP and its practicality within primary KM clinical settings. FP often manifests suddenly and significantly impacts patient quality of life by affecting facial expressions and functions (1–5). While treatments including corticosteroids, antiviral agents, and HM are typically effective within three weeks to three months (28, 29), around 30% of patients may still suffer from enduring complications such as permanent facial weakness, even after undergoing proper treatment (30). During the consensus process, the PMG and experts agreed on the importance of considering a broad range of physical and psychological factors in the COS for FP. This perspective was crucial, given that FP symptoms can vary widely in severity and impact, and are influenced by an array of external and internal factors.

The applicability of the COS in primary KM clinics was also a key consideration, recognizing that these clinics often have limited

TABLE 2 Summary of outcomes and effect modifiers identified in Phase 1.

	Item	Selected reviews (Step 1)	Related literature (Step 2)	Deliberations by PMG (Outcomes for Phase 2)
Outcomes	House-Brackmann scale	○		In
	Yanagihara's unweighted grading system	○		In
	Sunnybrook scale	○		In
	Facial nerve grading system 2.0	○		In
	Nottingham system	○		In
	Stennert's specific grading system for secondary defect	○		In
	The scale of Peitersen	○		In
	The scale of Murata *et al*	○		In
	Synkinesis assessment questionnaire	○		In
	The scale of Kim for synkinesis	○		In
	Detailed evaluation of facial symmetry	○		Out (Not standardized evaluation)
	Lucille Daniels method	○		Out (Not standardized evaluation)
	Visual analog scale	○		Out (Non-Specific to FP)
	numerical rating scale	○		Out (Non-Specific to FP)
	The evaluation of Na-kamura for synkinesis	○		In
	The evaluation of Haruo Saito for synkinesis	○		In
	The scale of Kim for contracture	○		In
	The scale of Edson Ibrahim Mitrefor facial asymmetry	○		In
	The scale of Scott		○	In
	Proposed comprehensive scale of Bettina Wabbels et al. for the estimation of treatment results of hemifacial spasm		○	In
	Scale for crocodile tear syndrome		○	In
	Scale for quality of life (EQ-5D-5L & EQ-VAS)		○	In
	Satisfaction with treatment		○	In
	Myoneural excitability test	○		Out (Hard to evaluate in KM primary clinics)
	Digital infrared thermography imaging	○		Out (Hard to evaluate in KM primary clinics)
	Electromyography	○		Out (More suitable as effect modifier)
	Electroneurography	○		Out (More suitable as effect modifier)
	Aspartate transaminase		○	In
	Alanine transaminase		○	In
	Blood urea nitrogen		○	In
	Creatinine		○	In
Effect modifiers	Age & Gender		○	In
	Complete paralysis (YES/NO)		○	In
	No recovery within 3 weeks (YES/NO/NA)		○	In
	Postauricular pain (YES/NO)		○	In
	Taste disorder (YES/NO)		○	In
	Ramsay Hunt syndrome (YES/NO)		○	In
	Pregnancy (YES/NO)		○	In
	Diabetes (YES/NO)		○	In
	Severe nerve degeneration on EMG/ENoG (YES/NO/UK)		○	In
	Taking Western medicine for facial palsy (YES/NO)		○	In

FP, facial palsy; KM, Korean medicine; EMG, electromyography; ENoG, electroneurography; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; EQ-VAS, EuroQol visual analog scale.

TABLE 3 Summary of the consensus process during the three Delphi rounds in Phase 2.

Category	Item	Result	Note
Outcomes	House-Brackmann scale	In	
	Yanagihara's unweighted grading system	Out	less aligned with criteria compared to the House-Brackmann scale
	Sunnybrook scale	Out	less aligned with criteria compared to the House-Brackmann scale
	Facial nerve grading system 2.0	Out	less aligned with criteria compared to the House-Brackmann scale
	Facial disability index	Out	Tailored for specific conditions or aspects
	Time to first improvement	In	
	Nottingham system	Out	less aligned with general FP assessment needs
	Stennert's specific grading system for secondary defect	Out	Tailored for specific conditions or aspects
	The scale of Peitersen	Out	less aligned with general FP assessment needs
	The scale of Murata *et al*	Out	less aligned with general FP assessment needs
	Synkinesis assessment questionnaire	Out	Less correlated with evaluation of FP
	The scale of Kim for synkinesis	Out	Less correlated with evaluation of FP
	The evaluation of Na-kamura for synkinesis	Out	Less correlated with evaluation of FP
	The evaluation of Haruo Saito for synkinesis	Out	Less correlated with evaluation of FP
	The scale of Kim for contracture	Out	Tailored for specific conditions or aspects
	The scale of Edson Ibrahim Mitrefor facial asymmetry	Out	Tailored for specific conditions or aspects
	The scale of Scott	Out	less aligned with general FP assessment needs
	Proposed comprehensive scale of Bettina Wabbels et al. for the estimation of treatment results of hemifacial spasm	Out	less aligned with general FP assessment needs
	Scale for crocodile tear syndrome	Out	Tailored for specific conditions or aspects
	Scale for quality of life (EQ-5D-5L & EQ-VAS)	In	
	Satisfaction with treatment	In	
	Aspartate transaminase	In	
	Alanine transaminase	In	
	Blood urea nitrogen	In	
	Creatinine	In	
Effect modifiers	Age & Gender	Out	Less correlated with effect of HM
	Complete paralysis (YES/NO)	Out	Can be substituted with the House-Brackmann scale
	No recovery within 3 weeks (YES/NO/NA)	Out	Can be substituted with the time to first improvement
	Postauricular pain (YES/NO)	In	
	Taste disorder (YES/NO)	In	
	Ramsay Hunt syndrome (YES/NO)	In	
	Pregnancy (YES/NO)	Out	Not directly influence FP outcomes
	Diabetes (YES/NO)	Out	Not directly influence FP outcomes
	Severe nerve degeneration on EMG/ENoG (YES/NO/UK)	Out	Difficult to assess in KM primary clinic
	Taking Western medicine for facial palsy (YES/NO)	In	
	Brain imaging status and results (CT or MRI)	Out	Difficult to assess in KM primary clinic
	Presence of paralysis in upper and lower limbs	Out	Difficult to assess in KM primary clinic
	Symptoms suggesting supranuclear palsy due to organic diseases	Out	Difficult to assess in KM primary clinic
	Hyperacusis (Yes/No)	In	
	Liver disease (Yes/No)	Out	Not directly influence FP outcomes
	Lacrimal secretion disorder (Increase/Decrease/No)	In	

FP, facial palsy; KM, Korean medicine; EMG, electromyography; ENoG, electroneurography; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; EQ-VAS, EuroQol visual analog scale; CT, computed tomography; MRI, magnetic resonance imaging.

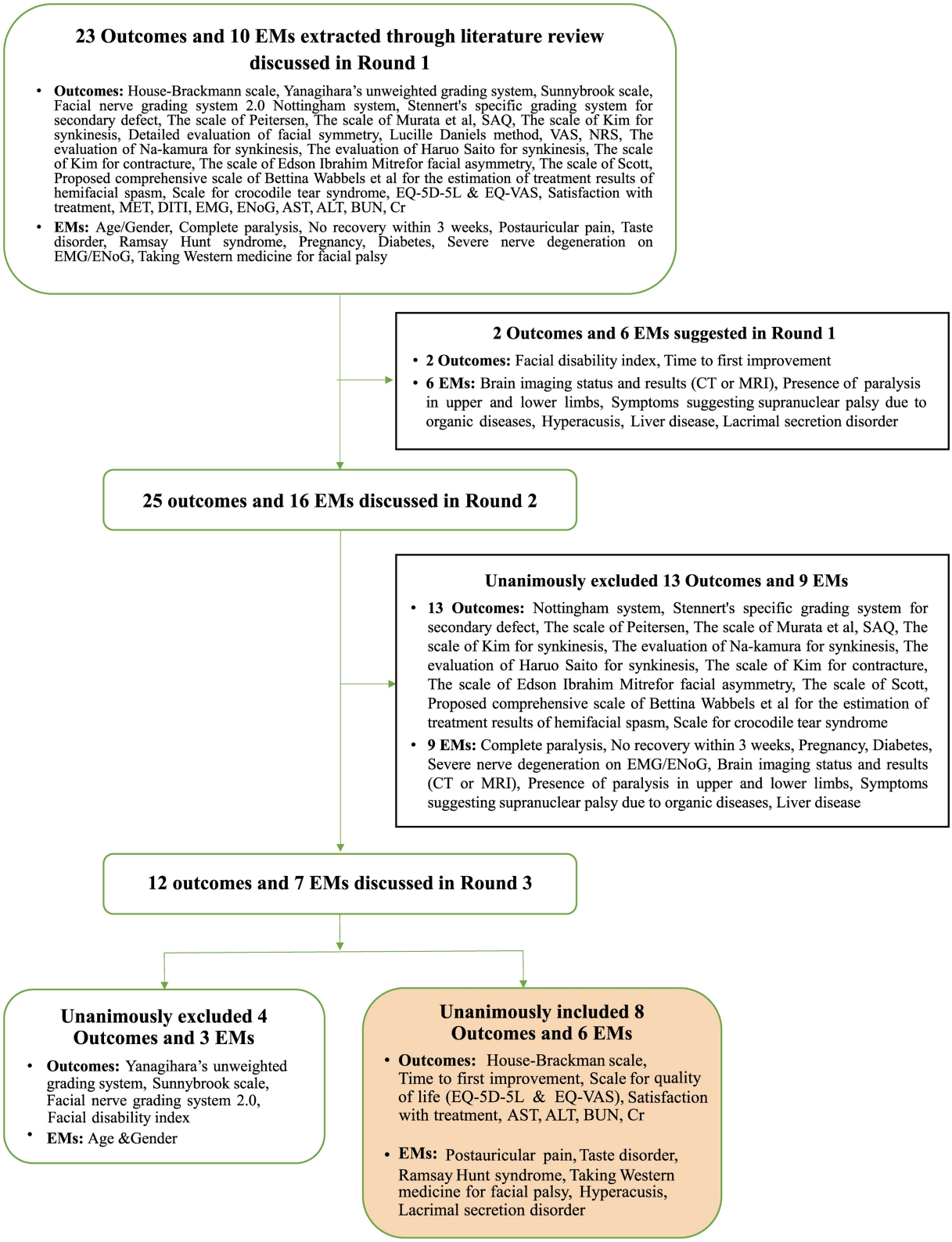

FIGURE 2
Overview of the consensus process during the three Delphi rounds in Phase 2. EMs, effect modifiers; SAQ, synkinesis assessment questionnaire; VAS, visual analog scale; NRS, numerical rating scale; MET, myoneural excitability test; DITI, digital infrared thermographic imaging; EMG, electromyography; ENoG, electroneurography; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; Cr, creatinine.

TABLE 4 Results of the consensus process in primary clinicians.

Category	Question	Mean	Median	CVR	Degree of consensus	Degree of convergence
Outcomes	Time to first improvement	7.91	8.00	1.00	0.75	1.00
	House-Brackmann scale	7.36	8.00	0.82	0.75	1.00
	Quality of life (EQ-5D-5L&EQ-VAS)	5.36	6.00	0.64	0.58	1.25
	Satisfaction of treatment	7.73	8.00	1.00	0.88	0.50
Effect modifiers	Effect modifiers about related HM treatment for FP; 1. Postauricular pain 2. Taste disorder 3. Ramsay Hunt syndrome 4. Taking Western medicine for facial palsy 5. Hyperacusis 6. Lacrimal secretion disorder	7.27	7.00	1.00	0.86	0.50
	Postauricular pain related items 1. Presence of postauricular pain (Yes/No) 2. Duration of postauricular pain (Day) 3. Severity of postauricular pain (VAS)	7.45	8.00	0.82	0.75	1.00

CVR, critical value of ≥ 0.636—suitable for 11 panelists—was judged to suggest consensus among the panelists. A degree of consensus of ≥ 0.75 and a degree of convergence of ≤ 0.5 were judged to indicate that agreement among panel experts was achieved. EQ-5D-5 L, EuroQoL 5-Dimension 5-Level; EQ-VAS, EuroQol visual analog scale; HM, herbal medicine; FP, facial palsy; VAS, visual analog scale.

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resources and personnel for conducting large trials, as previously noted in our studies (23, 24). Therefore, we emphasized the feasibility of implementing the COS in primary KM clinical settings. Drawing from previous studies in KM clinics (7, 29), our goal was to develop a practical and effective COS with simple, accurate outcomes that seamlessly integrate into routine clinical practices without significant disruption. In developing the COS-FP-KM, we paid special attention to selecting outcomes that align with the practical realities of these clinical settings. Considering that a significant portion of KM institutions operates as primary care clinics (17), it was essential to choose outcomes that are feasible to assess within these resource-limited environments.

The COS outcomes for FP, including the House–Brackmann scale, time to first improvement, quality of life scales (EQ-5D-5L and EQ-VAS), and patient satisfaction measures, were selected for their straightforward and efficient applicability. These outcomes were designed to facilitate treatment effectiveness assessments without overburdening clinicians with additional workload or resource demands. Crucially, this approach of reducing clinical workload enhances decision-making quality, as it allows clinicians to concentrate more on essential patient care aspects, thereby streamlining the evaluation process and ultimately leading to better patient outcomes (31, 32). This strategy not only simplifies assessments but also boosts the overall efficacy and efficiency of treatments in KM clinics. Additionally, the inclusion of biochemical parameters such as Aspartate Aminotransferase, Alanine Aminotransferase, Blood Urea Nitrogen, and Creatinine, as well as the monitoring of Western medicine usage, are crucial for evaluating the safety of HM treatments. These outcomes are essential for simultaneously assessing the efficacy and potential side effects of HM, enabling the monitoring of adverse reactions or complications that may arise from HM treatments or their interactions with conventional medications (33, 34). Furthermore, including effect modifiers like postauricular pain, taste disorder, and Ramsay Hunt syndrome in the COS for FP is considered for its potential impact on treatment outcomes and patient prognosis (35). These frequently observed symptoms in FP provide insight into the unique experiences of each patient. This approach leads to the development of tailored and more effective treatment strategies within KM Clinics, acknowledging the diverse manifestations of FP.

While our study is extensive, it faces several limitations impacting the derived outcomes. In the initial literature review (Phase 1), we only included three review papers, potentially overlooking some other relevant trials. This approach might have led to an incomplete coverage of relevant trials, thereby potentially limiting the range of outcomes in our COS for FP. Furthermore, the process of developing the COS encountered a limitation in the panel diversity. Thus, the number of panelists, sourced from a professional society, was relatively smaller than that in comparable studies (36, 37), which could have restricted the variety of insights during the COS development. Additionally, our study primarily involved disease specialists and primary KM clinicians, omitting participation from other vital stakeholders like patients and policy experts. While we attempted to mitigate this shortcoming by having clinicians apply the COS in practical settings and gather patient feedback, a more comprehensive approach involving semi-structured interviews with a broader stakeholder group is recommended for future refinements of the COS.

5 Conclusion

COS-FP-KM is the first COS on FP developed for primary KM care settings. The new tool is expected to standardize outcome selection and reporting, aiding in an efficient evaluation of the therapeutic effects of HM for FP. This COS will be used in the the Korean government HM pilot project, with continuous discussions to enhance the degree of completeness and reliability. Further studies are warranted to involve more relevant stakeholder groups, such as patient representatives and policy experts.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Prior to participation, all panel members were required to provide written informed consent, ensuring their voluntary involvement and understanding of the study's objectives and procedures.

Author contributions

S-DK: Writing – original draft, Writing – review & editing, Formal analysis, Visualization. SK: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation. MJS: Methodology, Resources, Writing – original draft, Writing – review & editing. JC: Methodology, Writing – original draft, Writing – review & editing. P-WK: Methodology, Writing – original draft, Writing – review & editing. MMK: Writing – original draft, Writing – review & editing, Formal analysis. SJ: Writing – original draft, Writing – review & editing, Methodology. CY: Methodology, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration. ML: Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Supervision.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1391544/full#supplementary-material

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Wellness or medicine? Use and perception of Ayurveda in Germany: data from an online-representative cross-sectional study

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Introduction: Ayurveda, South Asia's largest and most relevant system of Traditional Medicine, holds a legal status akin to conventional Western medicine in India and elsewhere. There is an almost complete lack of data on the use of Ayurveda in Germany. The aim of this study was to investigate Ayurveda's utilization patterns, entry points, and factors influencing its use and the perception of Ayurveda among the German population.

Methods: Basis of this manuscript was an online-representative survey which involved 4,065 participants aged 18–75 about the use and acceptance of Traditional, Complementary and Integrative Medicine (TCIM) in Germany. The survey was conducted online using Computer Assisted Web Interview (CAWI) in 2022. The dataset was analyzed descriptively and inferentially.

Results: Altogether 9.3% ($n = 377$) of all survey participants ($n = 4{,}065$) had already used Ayurveda somehow, either more often (1.7%) or at least once in a lifetime (7.6%). Responders associated Ayurveda primarily with Indian Medicine (27.7%) and wellness (18%). Commonly used Ayurvedic services included non-medical treatments at wellness resorts/spas (48.3%), in outpatient practices (27.1%), and hotels (23.6%). 30.2% of the participants believe in Ayurveda's therapeutic potential. 76.7% of Ayurveda users find healthy nutrition important or very important. Nine predictors were found to classify Ayurveda users vs. non-users with spirituality and belief in Ayurveda's therapeutic efficacy as the most relevant ones. Ayurveda seems to be primarily used by well-educated and female individuals, often from higher-income groups and with a rather modern social milieu-orientation.

Conclusion: Study results suggest that about every tenth German citizen has used Ayurveda in the past and about one third believes in its therapeutic potential. Because Ayurvedic therapies are often not evidence-based, there is an urgent need to perform high quality randomized controlled trials to investigate potential effects and safety of Ayurveda and how evidence-based Ayurveda treatments can be integrated into the German healthcare system.

KEYWORDS

Ayurveda, survey, traditional medicine, complementary medicine, integrative medicine, alternative medicine, Germany, cross-sectional study

1 Introduction

Ayurveda is a comprehensive Whole Medical System (1, 2) characterized by a person-centered approach (Patient Centered Medicine, PCM) with system inherent diagnosis and treatment modalities, especially dealing with health promotion, recommendations on nutrition and disease prevention (3, 4). Ayurveda aims to shift focus from a disease-centered model to one centered on the well-being of each individual (5, 6). Regarding their PCM approaches, similarities exist between traditional systems of medicine like Ayurveda and modern approaches of predictive, preventive and personalized medicine. This renders Ayurveda not only "traditional," but also potentially compatible with modern medicine (7–9). "Ayurgenomics" for example, a recently established field of research in South Asia, acts as a bridge between conventional genomics and Ayurveda, facilitating a deeper understanding of individual variations in response to Ayurvedic therapies across various diseases (10). Ayurveda provides comprehensive and cause-oriented traditional approaches for many chronic illnesses such as osteo- and rheumatoid arthritis, neurodegenerative diseases, kidney and liver diseases, irritable bowel syndrome, chronic inflammatory conditions, stress-related disorders, psychosomatic ailments or pain (11). Essentially in the realms of enhancing self-efficacy, salutogenesis, prevention, and healthy aging, Ayurveda offers patients and practitioners potentially valuable health-promoting opportunities (3, 11).

In India and some neighboring South Asian countries, Ayurveda is government-regulated, in India even by an independent ministry (AYUSH) (12), legally at par with conventional Western medicine. As a mainstream medicine it is providing health care opportunities in the most populous country worldwide with currently over 1.4 billion inhabitants. The importance of Ayurveda in Indian healthcare is reflected by the following figures: According to AYUSH, in India alone, more than 750,000 Ayurvedic physicians are officially registered; Ayurvedic medicine is systematically taught, practiced and supported by both AYUSH and union state governments in India in India in numerous universities and colleges universities and colleges (13). Altogether there are 495 Ayurveda colleges in India (13). Among them the university clinic "All India Institute of Ayurveda" (AIIA) (14) stands out as a public beacon-institute for clinical practice and research. Ayurvedic terminology, training and practice were recently standardized in WHO benchmark reports (15–17). In India, Ayurveda is currently (re-)gaining its own prominent place alongside conventional Western medicine, offering patients an integrative and multimodal approach to well-being and patient care (18). As such, in its region of origin, Ayurveda could even be seen (from the emic Indian perspective) as one form of "conventional" medicine in contrast to a predominantly European perception (of Ayurveda) as a foreign traditional medical system implemented either complementary or alternatively to conventional medicine.

The World Health Organization (WHO) describes Traditional Medicine like Ayurveda as *"the total sum of the knowledge, skills and practices indigenous (…) cultures have used (…) to maintain health and prevent, diagnose and treat (…) illness"* (19). WHO's new vision for Traditional Medicine is the evidence-based integration of traditional medicine systems (TMS) into global healthcare. This is one goal of the first Global WHO Center for Traditional Medicine and the WHO Traditional Medicine Global Summit (20). In addition, the WHO highlights the economic dimension as a key argument in favor of TCIM systems like Ayurveda for cost-effective contributions for global health (20, 21). The WHO employs the term Traditional, Complementary, and Integrative Medicine (TCIM), or Traditional, Complementary, and Integrative Healthcare (TCIH) (22). For the sake of inclusivity and clarity, we adopt TCIM as a comprehensive umbrella term in this context. TM serves as a complement, integration, or alternative to conventional medicine (23, 24), represented by phrases such as 'Complementary Medicine', 'Integrative Medicine', and 'Alternative Medicine'. These terms often overlap in content, and their distinctions can be blurred (25). The lack of precision is also evident in the diversity of definitions and differentiations among these methods. Historically, since the 1980s, the term 'Complementary and Alternative Medicine' (CAM), introduced by the National Institutes of Health (NIH), gained traction in the Anglo-American sphere. However, it has been supplanted by the modified term 'Complementary and Integrative Medicine' (CIM), which emphasizes the "integrative" aspect over "alternative," underscoring the incorporation of evidence-based complementary medical practices into conventional treatment modalities (26–28). In Germany, therapeutic TCIM approaches, alongside conventional therapies, enjoy widespread societal acceptance (29, 30). In the past three decades, professional associations and organizations have attempted to bring more standardization and safety to Ayurvedic therapy and education in Germany and Europe. The establishment of the German Medical Doctors Association of Ayurvedic Medicine (Deutsche Ärztegesellschaft für Ayurveda-Medizin, DÄGAM e.V.) (31) in 2011 and the Ayurveda Umbrella Organization Germany (German: Ayurveda Dachverband Deutschland, ADAVED e.V.) (32) are indicative examples of the growing trend of professionalization of Ayurveda in Germany. These organizations, especially DÄGAM and ADAVED (32), are intensively involved in the development of training standards for various medical professions to promote quality assurance and are orientated toward the WHO benchmarks for Ayurveda (15, 16). DÄGAM, e.g., provides a quality certificate for Ayurveda training courses. The Association of European Ayurveda Therapists (Verband Europäischer Ayurveda-Therapeuten e.V., VEAT) (33), the Academic Society of Indian Medicine (Akademische Fachgesellschaft Indische Medizin e.V., AFGIM) (34, 35), the Indian Society for Ayurveda Germany (Indische Fachgesellschaft für Ayurveda Deutschland, IFAD e.V.) and the German Society for Ayurveda (Deutsche Gesellschaft für Ayurveda, DGA e.V.) (36) also promote medical Ayurveda in Europe. However, there is a contrast between these endeavors as well as the therapeutic potential for patients and the fact that there is still *de facto* no reimbursement by statutory health insurances or any kind of official

recognition of Ayurveda in Germany. In principle however, any medical doctor (MD) or alternative practitioner (German: Heilpraktiker) (37) can practice Ayurveda independently within the scope of their professional medical licenses in Germany. In comparison, in Switzerland it is possible to get a federal diploma in Ayurvedic therapy and there are different trainings for physicians or alternative practitioners (38). However, unlike qualification possibilities for the aforementioned, acupuncture or Traditional European Medicine (German: Naturheilkunde/Naturheilverfahren) that exist in Germany, there is no explicit foundation for medical care with Ayurveda methods and billing of Ayurvedic services. In general, the so-called prevention paragraph [§20 Sozialgesetzbuch (SGB) Fifth Book (V)] in Germany supports public health promotion and preventive measures by statutory health insurance funds (39). This opens potential possibilities for Ayurveda to play a role in (reimbursable) public health care, like other already integrated traditional medicine options, such as acupuncture for some indications.

While some previous representative studies in Germany indicated a high usage of TCIM in Germany, there is no such data on Ayurveda. In 2014 a project examined the use of TCIM in Germany, but it is likely that the data has become outdated (40). Despite an anticipated growing interest in Ayurveda as a medical approach, there remains a notable scarcity of robust representative survey data regarding its overall use and user perception of it in Germany (41). This publication aims to provide insights into aspects such as utilization patterns, application contexts, points of entry, and perceptions regarding its efficacy. This work also intends to explore influences of social backgrounds and individual belief systems that might contribute to the use of Ayurveda.

2 Materials and methods

The Charité University Outpatient Clinic for Complementary and Integrative Medicine at Immanuel Hospital Berlin and the Institute of Social Medicine, Epidemiology and Health Economics of Charité—Universitätsmedizin Berlin conducted an online-representative survey about the use and acceptance of Traditional, Complementary and Integrative Medicine (TCIM) from September to October 2022. The study design has been described in detail elsewhere (42). In short, the overall research project encompassed both a representative cross-sectional survey and a qualitative study. This study is based on a cross-sectional online survey using Computer Assisted Web Interview (CAWI) among the German-speaking residential population aged 18–75 years, with a total sample size of 4,065 individuals. The study was approved by the Charité Ethics Committee and registered with ClinicalTrials.gov (NCT05530720). The online panel adheres to the international standard ISO 26362, ensuring that the quality of online sampling is monitored and certified. The procedures for data collection, processing, and storage followed internationally recognized guidelines for clinical studies, including the Declaration of Helsinki and ICH-GCP (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use). In addition, the ethical principles of the accompanying sociological research were followed.

The comprehensive questionnaire used in this study covered a wide range of topics: sociodemographic data, use of TCIM, attitudes toward TCIM, diagnoses for which TCIM was used, importance and familiarity with terms, the role of TCIM in the context of the Covid-19 pandemic, nutrition, Ayurveda, attitude and behavior, Sinus milieu indicator® and the EQ-5D-5L quality of life questionnaire. It contained a module of five items on Ayurveda (Supplementary material 8).

The sample selection was quota-based and structured to ensure representation across different age groups, genders, levels of education, and geographic regions. These quota specifications were established following the methodology standard set by the best4planning (B4P) study, which is known for drawing representative samples (43). The B4P study itself was based on a random selection of over 30,000 individuals. Quota control was employed to address socio-demographic disparities when compared to the general population.

2.1 Statistical analysis

Continuous variables are given as mean ± standard deviation (SD), or median and interquartile range, and categorical variables as frequencies (percentages). Normality of distribution was assessed by the Shapiro–Wilk test. Continuous variables were tested for differences with the Mann–Whitney U test or the Wilcoxon signed-rank test, and categorical variables with the Pearson's χ^2 or the Fisher's exact test. Crosstab analysis revealed patterns, correlations, and trends among categorical (nominal or ordinal) variables. Decision trees (DTs) were used as a non-parametric supervised learning method for classification and regression. The goal is to create a model that predicts the value of a target variable by learning simple decision rules inferred from the data features. We applied Exhausted Chi-squared Automatic Interaction Detection (Exhausted CHAID) and Classification and Regression Trees (CART). Variable importance for predictors in decision trees, such as CHAID and CART, are based on measures of sensitivity. The sensitivity of a variable is a measure of the amount of output variance that is removed when we learn the true value of the predictor. Normalized importance is simply the importance values divided by the largest importance values and expressed as percentages. Variable (normalized) importance as measured by the sensitivity analysis does not predict the order in which predictors appear in the decision tree. In this study, we do not report demographic weighting (age, gender, education, federal state, and city size). The bias would only be minimally reduced, and we found no statistically significant differences between weighted and unweighted results. All statistical analyses were performed using R (R Foundation, version 4.3) and SPSS (IBM® SPSS® Statistics, version 29).

3 Results

The survey took place between September and October 2022, with 41,011 invitations distributed. Of these, 8,821 individuals initiated the survey, yielding a response rate of 21.5%. Based on the exclusion criteria, such as cases where participants had reviewed the study information but did not provide consent or lacked age information, 453 cases were excluded. Furthermore, 2,845 participants were removed as they had already been assigned to filled quotas. Exactly 1,000 individuals discontinued their participation and were consequently excluded from the analysis. Ultimately, 4,505 respondents successfully completed the questionnaire. During the quality assessment process, 18 participants were excluded due to discrepancies identified in the sinus milieu indicator. Subsequently, an

additional 295 participants were excluded for quality-related issues, including anomalous open responses and discrepancies in quality variables. The final data set comprised 4,210 participants. In order not to compromise online representativeness due to the upper age limit of 80 years, this was reduced to 75 years. Thus, the final population-representative data set for the age group 18–75 years comprises a total of 4,065 participants.

Among all participants ($n = 4,065$, aged 18–75) 51.7% were female, 47.9% were male and 0.4% diverse. 42.5% had a higher education (high school diploma, doctorate, university degree) and more than half of the study population had completed primary and secondary school (56.8%). Approximately half of the participants (54.3%) had a net household income between 2,000 and 5,000€, while 7.5% had an income above this amount and 38.2% had an income below this amount. The socio-demographic characteristics can be found in detail in the main publication (42). Among the users of Ayurveda services ($n = 377$) 61% were female, the majority earning between 2000 and 5,000 € per month (60.7%). 53.2% hold a higher school diploma (Table 1). Regarding the sociodemographic characteristics of Ayurveda services use, the parameters age ($p = 0.007$), gender ($p < 0.001$), net monthly household income ($p = 0.005$), education ($p < 0.001$), nutrition ($p < 0.001$), spirituality ($p < 0.001$) and attitude toward TCIM ($p < 0.001$) differed significantly in comparison to non-Ayurveda users (Table 1).

3.1 Use and associations with Ayurveda, entry points and services used

A small percentage (1.6%) of the whole study population reported having used Ayurveda services more than once, while 7.6% had used them at least once. The majority (85.1%) had never utilized Ayurveda services (Figure 1).

Participants' associations with Ayurveda predominantly include Indian Medicine (27.7%) or wellness (18%), a large group (25.4%) had a lack of specific associations. Esoteric concepts, on the other hand, were less frequently linked, with only 7.3% mentioning them.

TABLE 1 Basic characteristics.

		Total	Ayurvedic services used		*p*-value
			Yes	No *or* I do not know	
		4,065	377 (9.3)	3,688 (90.7)	
Age, years		49.3 ± 15.8	47.2 ± 15.8	49.5 ± 15.8	0.007
Gender	male	1,947 (47.9)	146 (38.7)	1,801 (48.8)	< 0.001
	female	2,101 (51.7)	230 (61.0)	1,871 (50.7)	
	diverse	17 (0.4)	1 (0.3)	16 (0.4)	
Net monthly household income	≤ 2000€	1,552 (38.2)	115 (30.5)	1,437 (39.0)	0.005
	2000–5,000€	2,208 (54.3)	229 (60.7)	1,979 (53.7)	
	> 5,000€	305 (7.5)	33 (8.8)	272 (7.4)	
Education	(Yet) no general school-leaving certificate	30 (0.7)	1 (0.3)	29 (0.8)	< 0.001
	Primary / secondary school	2,309 (56.8)	176 (46.7)	2,133 (57.8)	
	A-levels (technical) university entrance qualification without studies, Studies (university, college, university of applied sciences, polytechnic, PhD[2])	1,726 (42.5)	200 (53.1)	1,526 (41.4)	
Nutrition	less important to completely unimportant	1,530 (37.6)	88 (23.3)	1,442 (39.1)	< 0.001
	important / very important	2,535 (62.4)	289 (76.7)	2,246 (60.9)	
Sinus Main Milieus®	Society's Leading Milieus	1,456 (35.8)	149 (39.5)	1,307 (35.4)	0.058
	Modern Mainstream	1,135 (27.9)	95 (25.2)	1,040 (28.2)	
	Milieus of the Future	742 (18.3)	79 (21.0)	663 (18.0)	
	Traditional Mainstream	732 (18.0)	54 (14.3)	678 (18.4)	
Spirituality	yes	896 (22.0)	190 (50.4)	706 (19.1)	< 0.001
	no	3,169 (78.0)	187 (49.6)	2,982 (80.9)	
Attitude towards conventional medicine	mostly positive, very positive	2,565 (63.1)	238 (63.1)	2,327 (63.1)	0.976
	neutral	1,187 (29.2)	109 (28.9)	1,078 (29.2)	
	mostly negative, very negative, do not know	313 (7.7)	30 (8.0)	283 (7.7)	
Attitude towards TCIM[1]	mostly positive, very positive	2,112 (52.0)	277 (73.5)	1,835 (49.8)	< 0.001
	neutral	1,519 (37.4)	87 (23.1)	1,432 (38.8)	
	mostly negative, very negative, do not know	434 (10.7)	13 (3.4)	421 (11.4)	

[1]TCIM: Traditional, Complementary and Integrative Medicine, [2]PhD: Philosophical Doctorate.

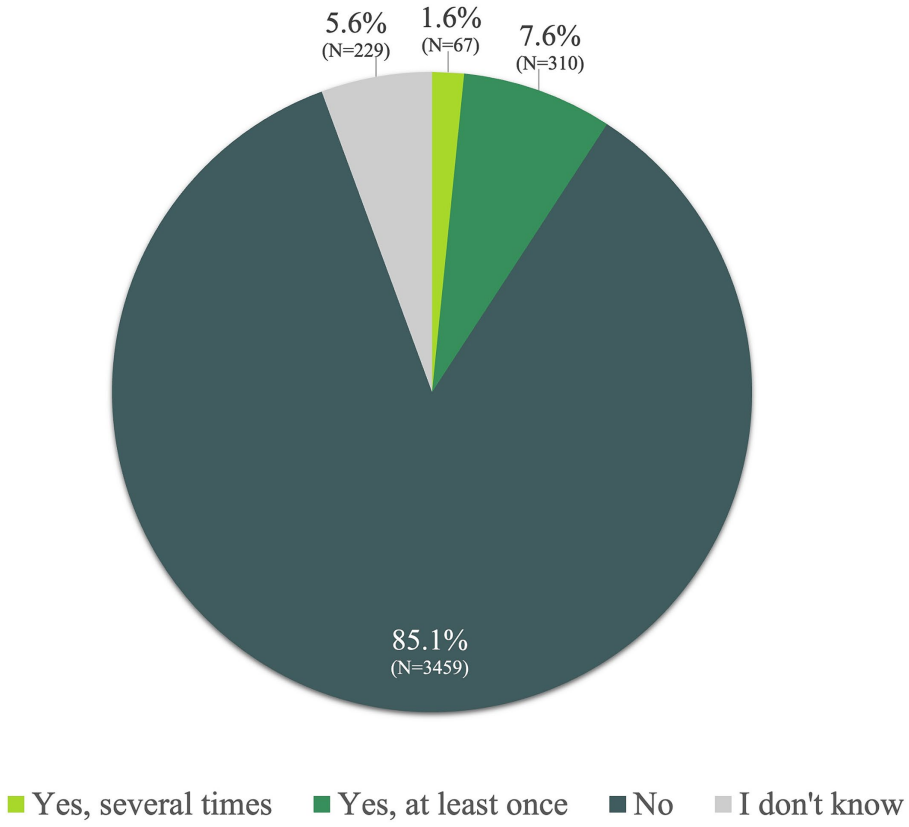

FIGURE 1
Have you ever used Ayurvedic treatments yourself?

Keywords like massage, nutrition, spirituality, or spices were rated lower than 7%. Among Ayurveda users ($n = 377$), the most frequent association was also Indian medicine (36.3%), followed by wellness (20.4%), massage (15.4%) and nutrition (13%). Among non-Ayurveda users the most rated categories were Indian medicine (26.8%), followed by wellness (17.8%), esotericism (7.8%) and massage (5.7%). The association with Ayurveda differs highly significantly between the participants with or without Ayurveda services ($p < 0.001$; Figure 2).

The 377 Ayurveda users stated that they had used a total of 666 Ayurveda services. 42.2% had used Ayurveda products, 39.8% non-medical Ayurveda treatments, 24.9% had had Ayurveda nutritional consultation and 22.3% had experienced medical Ayurvedic treatments, another 22.3% had undergone Ayurveda lifestyle consultation (Table 2).

The Ayurveda users reported accessing Ayurveda services most frequently at wellness resorts (spa; 48.3%), in an outpatient practice (physician or alternative practitioner; 27.1%), and hotels (23.6%). A smaller percentage (9.5% or lower) experienced Ayurveda services online, via educational institutions or other (Figure 3).

3.2 Perception of therapeutic efficacy

6.3% of all participants "definitely" believed in the medical therapeutic benefits of Ayurveda and 23.9% responded "probably." Additionally, 27.8% responded with "neutral" and 26.6% had "no opinion" on it, while 10.8% thought of potential benefits as "not likely" to exist or materialize. Another 4.5% believed that Ayurveda "definitely" had no benefits (Figure 4).

Significantly ($p < 0.001$) more participants who had already used Ayurveda believed in its therapeutic benefits than participants who had no previous experience with Ayurveda. Thus, Ayurveda users answered "definitely" (28.4%) or "probably" (40.1%) in comparison to non-Ayurveda users (4.1% or and 22.3%, respectively; Supplementary Figure 1).

Looking at subgroups who believed that Ayurveda had major therapeutical benefits, 47.4% of the participants who had a "mostly positive" or "very positive" overall attitude toward TCIM also rated the therapeutic benefits of Ayurveda as positive (definitely/probably). If these participants in addition stated that they were spiritual and older than 20 years, then the percentage of these participants who viewed the therapeutic benefits of Ayurveda positively (definitely/probably) increased to 68.1%. Conversely, if the participants' global attitude toward TCIM was negative (mostly or very negative) or if they said they "did not know," then only 7.6% had a positive attitude toward the benefits of Ayurveda. If these participants also stated that they were not spiritual and younger than 40 years, then this percentage was reduced to 5.9%. Further details are provided in Supplementary Figures 2A–C.

3.3 Ayurveda and spirituality

In the total population, 17.9% considered themselves somewhat spiritual and 4.1% as very spiritual, while 38.9% claimed they are not at all spiritual (Supplementary Figure 3). When examining the 9.3% participants who used Ayurveda

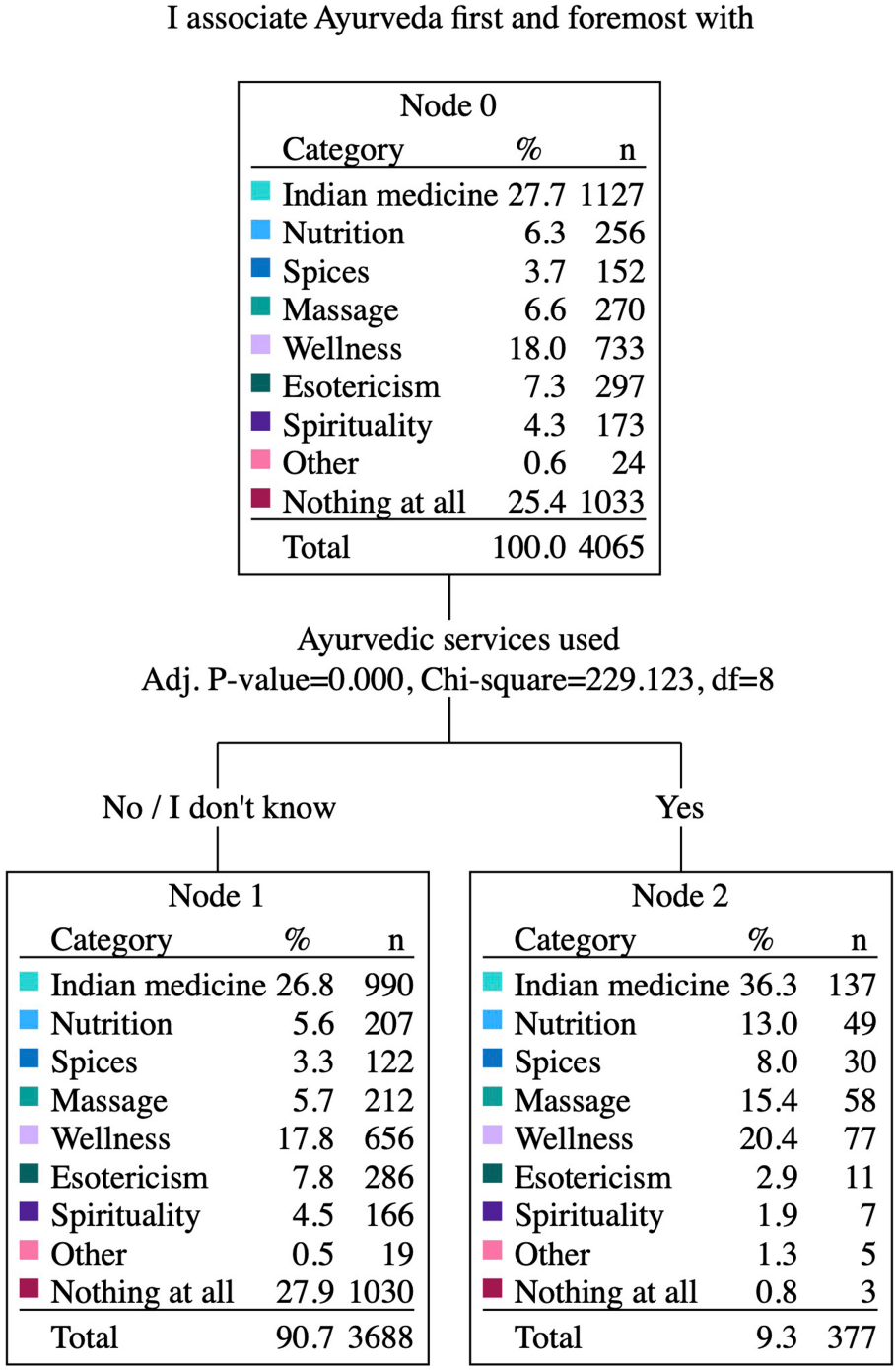

FIGURE 2
I associate Ayurveda first and foremost with...

services, 50.4% were identified as very (13.5%) or somewhat spiritual (36.9%) and 9.8% as not spiritual (Figure 5B). Conversely, among the 90.7% participants who had not previously used Ayurveda services, 19.2% described themselves as very (3.2%) or somewhat (16.0%) spiritual and 41.9% as non-spiritual. Further details in Figures 5A,B.

Moreover, if we compare the religious affiliation, we get a significant difference ($p < 0.001$) between Ayurveda users and Ayurveda non-users (Supplementary Figure 4).

3.4 Classification of Ayurveda users and Ayurveda non-users

Ayurveda users and Ayurveda non-users can be classified using a set of rules or equivalently by decision trees based on nine predictors with an accuracy over 90%. These predictors are in descending order of importance (Figure 6).

Other possible predictors like "gender" (normalized importance 0.5%) or "global attitude to TCIM" (1.7%) are no longer significant in

TABLE 2 Which Ayurveda services did you use? (multiple response).

	Responses		Percent of Ayurveda users
	N	percent	
Ayurveda products (e.g., food, cosmetics, food supplements…)	159	23.9%	42.2%
Non-medical Ayurveda treatments (e.g., by alternative practitioners or physiotherapists)	150	22.5%	39.8%
Ayurveda nutritional consultation	94	14.1%	24.9%
Ayurveda lifestyle consultation	84	12.6%	22.3%
Medical Ayurvedic treatments	84	12.6%	22.3%
Infotainment (TV, movies, internet)	36	5.4%	9.5%
Ayurveda-Training	34	5.1%	9.0%
Other	25	3.8%	6.6%
Total	666	100.0%	176.7%

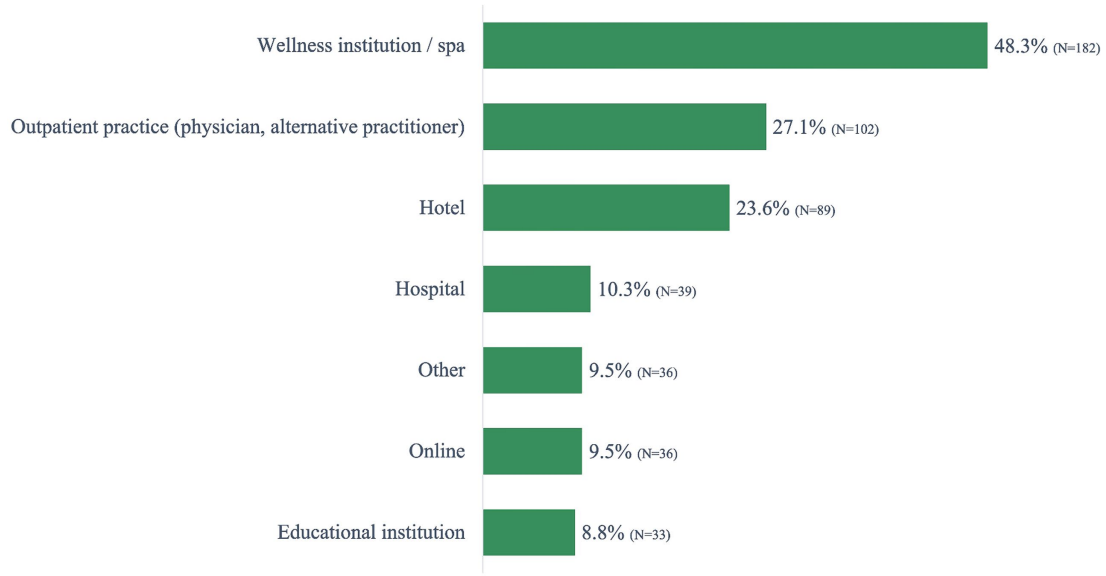

FIGURE 3
Where have you used Ayurveda services? (multiple response).

this multivariate model in contrast to univariate analyses. The following example from this decision tree shows the increasing percentage of Ayurveda users by gradually adding various predictors (Figure 7). Further details of this decision tree are shown in the Supplementary Figure 5.

3.5 Ayurveda users and healthy nutrition

76.7% of Ayurveda users found healthy nutrition important or very important. This proportion is significantly ($p < 0.001$) higher than in comparison to non-Ayurveda users (Supplementary Figure 6). There is also a significant ($p < 0.001$) difference in the choice of diet depending on the use of Ayurvedic services (Supplementary Figure 7). 21.5% of the Ayurveda-users characterized their nutrition as vegetarian, vegan or raw food-vegan/based. 35.3% characterized themselves as flexitarians.

3.6 Distribution of Sinus Milieus® and Sinus Main Milieus® in Ayurveda users

Sinus-Milieus® (available for more than 50 countries) are a social model, which summarizes participants with similar values, a similar lifestyle and a comparable social situation in groups of "like-minded people." The transitions between the milieus are fluid. The Sinus-Milieus® are defined by the social situation (ranging from low to high) and the value orientation (ranging from traditional to postmodern) (44). 39.5% of the Ayurveda users belonged to the Society's Leading Milieus which consist mostly of following three milieus: Post-Materialist (13.5%), Conservative-Upscale (13.3%) and Performer (12.7%). 25.2% belonged to the Modern Mainstream [Adaptive-Pragmatic Middle Class (11.1%), Consumer-Hedonistic (9.5) and Precarious (4.5%)]. Only 3.7% of Ayurveda users came from a traditional milieu (Figures 8A,B).

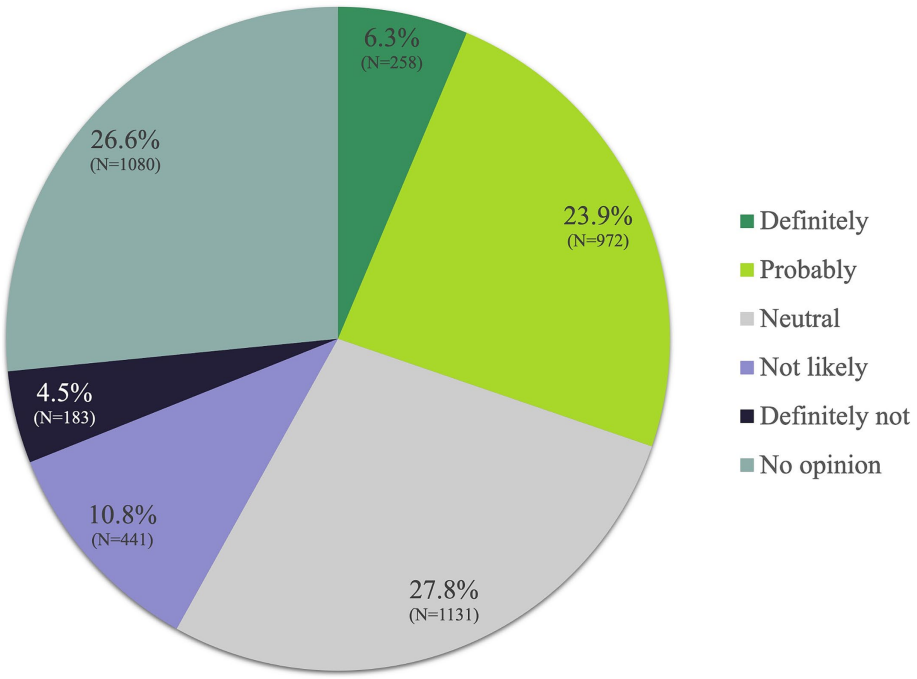

FIGURE 4
Do you think that Ayurveda has any medical therapeutic benefits?

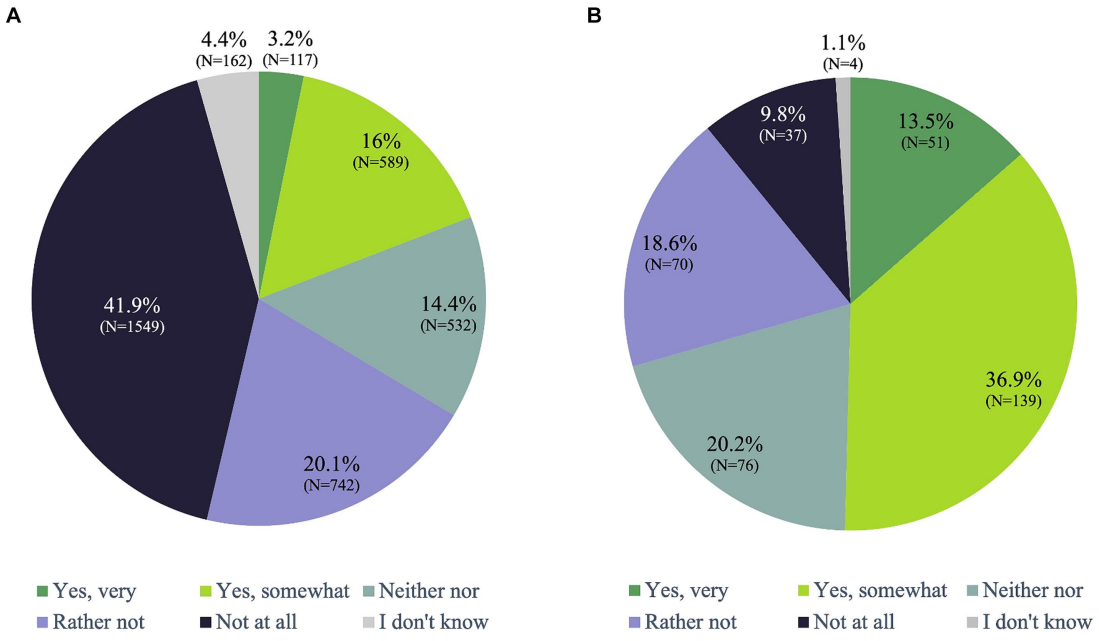

FIGURE 5
Would you describe yourself as spiritual? **(A)** Non-Ayurveda-Users (N=3688, 90.7%), **(B)** Ayurveda-Users (N=377, 9.3%).

The distribution of the Sinus Milieus® differed significantly ($p = 0.001$) between Ayurveda users and Ayurveda non-users. The distribution of Sinus Main Milieus®, on the other hand, is borderline between both groups ($p = 0.058$).

4 Discussion

In this online-representative cross-sectional study involving 4.065 residents in Germany, almost about one in 10 Germans had already

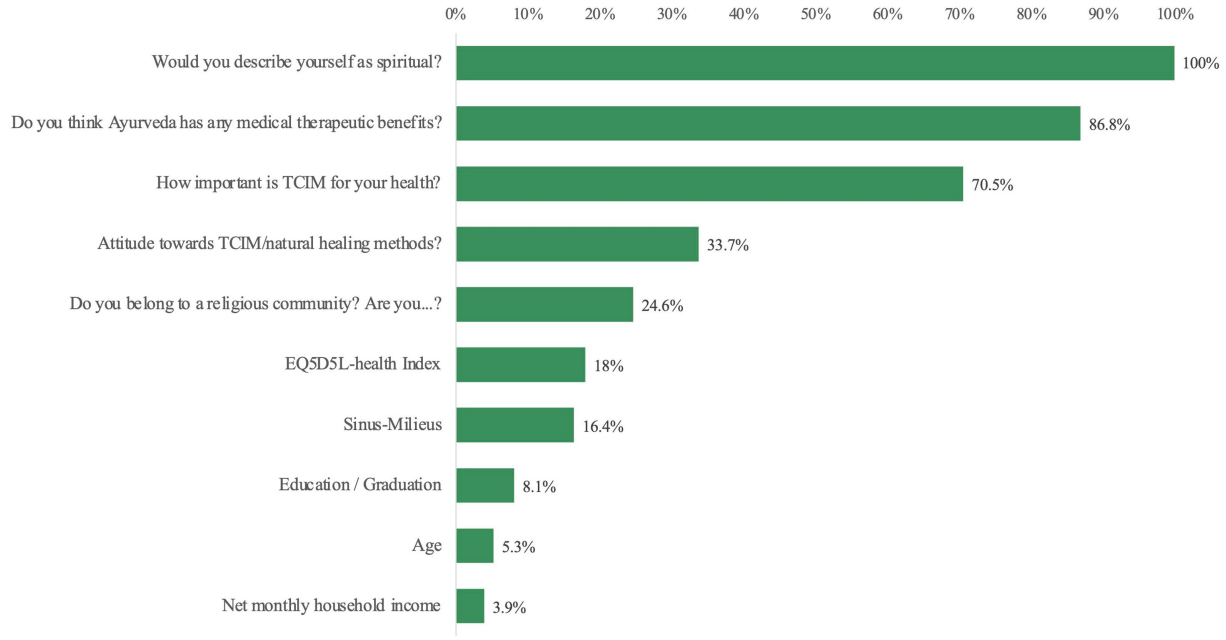

FIGURE 6
Order of normalized importance expressed as percentages to classify Ayurveda users and Ayurveda non-users.

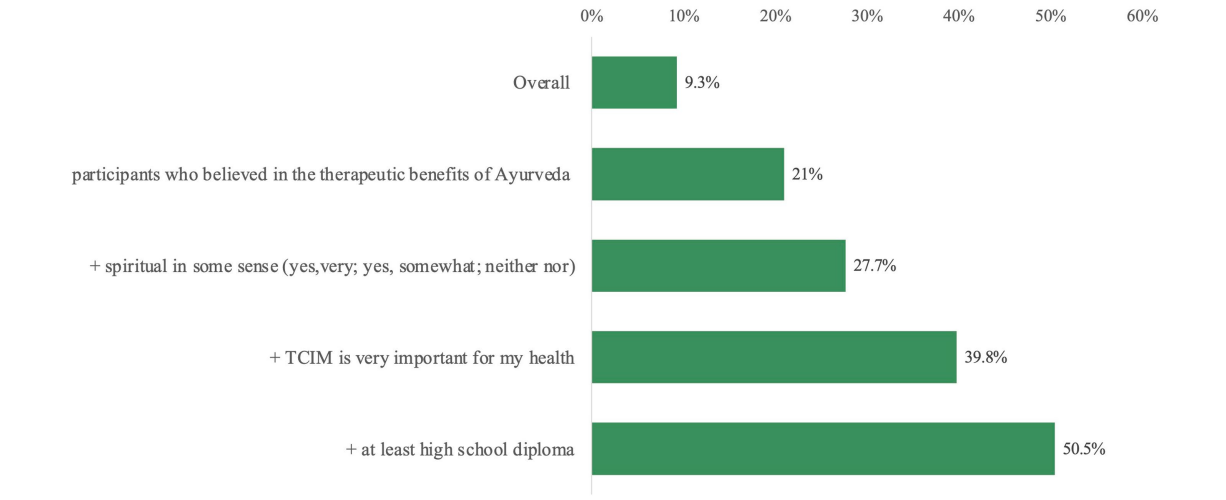

FIGURE 7
Increasing percentage of Ayurveda users within the total population.

used some as Ayurveda identified services. The majority associated Ayurveda with Indian medicine, while almost the same number of participants had no specific associations. Popular Ayurveda services included treatments from alternative practitioners, Ayurvedic products, nutritional or lifestyle counseling and medical treatments, with spa or wellness services providing entry points. Nearly one third of the participants believed in Ayurveda's therapeutic potential. The belief in therapeutic benefits of Ayurveda were fostered by parameters such as a positive attitude toward TCIM and spirituality. Ayurveda was primarily used by well-educated, female individuals, aged between 20 and 40 years, with interest in (vegetarian/vegan) nutrition, often from higher-income groups and with Modern Mainstream or Society's Leading Milieu association. This could correspond to the profile of a "typical" TCIM user in the Western world (45, 46).

4.1 Strengths and limitations

This is the first study on the use and perception of Ayurveda in Germany including a large study population. Limitations of the study include a relatively low response rate at 21.5%, raising minor concerns about the applicability of the findings to a broader population. To enhance generalizability, the data utilized for analysis underwent weighting based on factors such as age, gender, education, federal

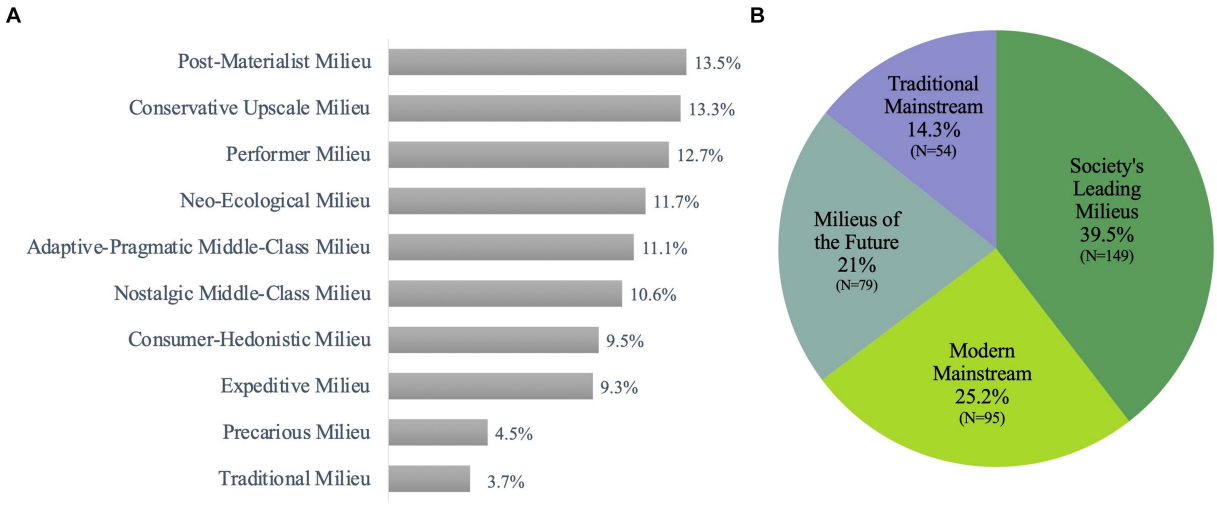

FIGURE 8
Distribuation of **(A)**: Sinus Milieus® and **(B)**: Sinus Main Milieus® in Ayurveda users.

state, and city size (42). However, no statistically significant differences between the weighted and unweighted data could be found, which suggests a sufficient quota system (42).

The phenomenon of low response in surveys is multifaceted and warrants thorough examination. Research has shed light on various factors that contribute to low response rates. For instance, Dillman et al. emphasized the impact of survey design and question quality on participant willingness to engage (47). Additionally, Singer and Kulka highlighted the significance of adequate incentives in boosting response rates (48). Demographic characteristics also play a role with factors such as age, education level, and employment status influencing survey participation (49). These findings underscore the importance of conducting a comprehensive analysis of factors influencing response rates to ensure accurate interpretation of survey results and to inform strategies for improvement. The study utilized an online access panel for surveying, chosen for its high-quality standards in participant selection and maintenance, as well as the implementation of a quota system (50). This approach ensures population-representative insights into the utilization and acceptance of TCIM in the German population. The online approach was selected due to the sensitivity of personal health-related questions. It is important to note that the use of an access panel led to the exclusion of certain populations, like those without online access or with low online affinity. However, this exclusion is not unique to access panels or online surveys in general. The potential under-representation of older people in this study had only a minor impact given the lower likelihood of them having internet access, as this age group was excluded from the analysis sample.

The study provide interesting data on Ayurveda use in Germany, however a limitation was that we did not ask specific details, e.g., regarding the types of Ayurvedic treatments and therapies used by participants. Without this information, it is challenging to determine which Ayurvedic interventions are more or less popular, limiting the insights into the aspects of Ayurveda that are in demand. While the survey mentions common locations for accessing Ayurvedic services, it does not provide a detailed breakdown of the preferences for these locations. Understanding why individuals choose one location over another could provide further context. These and other detailed questions would help us to better understand Ayurveda user demands in Germany. The data did also not contain information about which health conditions or diseases participants sought Ayurvedic treatments for. Understanding the specific health issues for which Ayurveda is being utilized in Germany could offer valuable insights into its effects and potential areas for further research. Moreover, side effects of Ayurveda were not asked. However, these limitations of our study can be addressed in future cross-sectional studies.

Finally, this data-set from a cross-sectional survey does not allow any causal statements. Also, the survey does not offer an in-depth comparison between Ayurveda and other traditional or complementary healthcare options, making it difficult to assess its relative popularity or effects. Those limitations highlight the need for more comprehensive and specific research to fully understand the role and efficacy as well as effectiveness of Ayurveda in the German context.

4.2 Discussion points

Ayurvedic interventions used in wellness resorts/spa facilities could presumably reflect the pattern that health-conscious people without an acute medical need are more likely to use low-threshold entry options and use Ayurveda for health-maintenance, prevention and well-being. While the use of Ayurveda as a wellness service could be a way to reach a wider audience, it could serve the medical visibility and credibility of Ayurveda to differentiate these services from explicit medical and therapeutic Ayurveda-options for specific health needs (51).

Almost one-third of the population (30.2%) believes in Ayurveda's therapeutic potential, while an almost equivalent portion remains neutral or has no opinion on this. Moreover, participants which used Ayurveda in the past rated its potential benefit considerably higher. Scientific evidence in the field of Ayurveda is still at an infant stage in Germany and the European Union; only few methodologically high-quality trials which proof to live up to high (−quality) standards concerning the implemented

methods were published so far (52–55). More methodologically high-quality research, professional communication with the public and public support (e.g., governmental, financial) would be necessary to define potential roles of Ayurveda as a complementary treatment option within the German health care system. Overall, there is a need for more clinical evidence, particularly effectiveness studies, to collect real-world data on Ayurveda interventions outside its countries of origin (56). Although available studies show promising results for Ayurveda in the field of clinical research for some diagnoses, the current state of research is still insufficient, especially against the background of the growing utilization of Ayurvedic services in Germany and the EU. Foremost, more high-quality clinical research is needed at German and European universities to be able to answer questions about the effectiveness of Ayurvedic therapies under local conditions. In this context, AYUSH exchange programs with foreign universities to promote Ayurveda, yoga and other traditional Indian medicine could be a relevant building block for the further development of the academic infrastructure required for this (12).

Spirituality, which appears to be associated with Ayurveda use, indicated by the fact that half of Ayurveda users appears to have a spiritual attitude (57, 58) is notable and requires further attention. Especially as the conception of "spirituality" may vary enormously on a social cultural level between the cultures of origin (India/Germany) and even within the respective milieus. The connection between Ayurveda and spirituality can be traced back to the close historical relationship between Ayurveda and Buddhism, Hinduism and Indian culture in general (59, 60), first described in the Caraka Samhita [see Gupta (61); Caraka Saṃhitā Śārīrasthāna chapters 1 and 5 (62)], which is one of the oldest systematic text collections of on Ayurveda. Previous publications explored the role of religion and spirituality in medical contexts, emphasizing that these elements may influence attitudes and choices regarding the use of Ayurvedic healthcare services. Spirituality plays a crucial role in how Ayurveda is perceived, and in India it coexists with modern medicine (63–66). In a paper of our working group associations were identified between individuals' religious or spiritual affiliations and their choices to either provide or seek access to Ayurveda (67). Importantly, the utilization of Ayurveda did not preclude concurrent use of both modern medicine and TCIM (67). Also, in combination with yoga, Ayurveda has a long tradition in India of mind (−fullness) training, breath work or ethical-philosophical recommendations for everyday life, which also has found a "mainstream-compatible approach" e.g., into fitness- and yoga-studios (11, 68). In a systematic review by Jeserich et al. on the correlation between religion and spirituality (R/S) and the sense of coherence (SOC), a connection was found between R/S and mental health (64). Relevant effect sizes were found in relation to the potential resource of spirituality. These relationships with a sense of coherence, which is an important indicator of the capacity of resilient coping with difficult situations (such as coping with illness), was stronger the more semantically open and non-institutional the spiritual belief system was. The results support the link between R/S and SOC and point to different religious/spiritual pathways to a strong SOC that are influenced by individual and cultural factors (64).

Individuals who utilize Ayurveda services mostly belong to the Society's Leading Milieu (35.5%) with basic values being shaped by either tradition, modernization or re-orientation (69). At the same time, it is noteworthy that Ayurveda utilization can be found across all milieus, with a relatively consistent percentage ranging from 9 to 13.5%. However, the Traditional and Precarious Milieus may be apparent as individuals into whose lives Ayurveda has not yet made significant inroads (44). While milieu-concepts might have been a useful tool for understanding social groups, there could be valid concerns regarding their relevance and potential drawbacks. One of these concerns is the risk of oversimplification and stereotyping, as milieus tend to categorize individuals based on specific characteristics or behaviors (70). India's pluralistic healthcare system does not explicitly promote TCIM, but the various traditional health systems covered by the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, Sowa Rigpa and Homeopathy) (71). Ayurveda is widespread in India as a folk medicine and is practiced alongside Western medicine with diverse Ayurvedic trends and currents (18, 72). Ayurveda also faces "medicalisation," meaning standardization, professionalization and pharmaceuticalization, which may impact the education, knowledge, practice and narrow the holistic view of traditional Ayurveda approaches (73, 74). The Ministry of AYUSH seeks to integrate diverse local health traditions, as well as traditional and complementary medicine into a modern healthcare system (12, 75). The European research network CAMbrella for complementary and alternative medicine (CAM) that operated between 2010 and 2012 and aimed to assess the situation of CAM in Europe, addressed that more research is needed and the integration of evidence-based or -informed CAM treatments into the Western healthcare systems. The findings emphasize the high demand for CAM, its heterogeneity, and the challenges in evaluating its effects due to insufficient integration and lack of validated data. Traditional Indian medicine is only mentioned in passing in one work package to provide a global perspective (76, 77).

The World Health Organization (WHO) is actively promoting the integration of traditional medicine into global health systems, emphasizing evidence-based and scientifically validated methods to guarantee the safety, qualification, and effectiveness of traditional, complementary, and integrative medicine (TCIM) services (20). Key points of the WHO vision include the development of norms and standards, the use of data and analysis to shape policies and regulatory frameworks, the promotion of sustainability and the integration of TCIM. This vision could be an impulse that could trigger corresponding measures at legal and political level for Ayurveda in Germany and Europe (20).

4.3 Further research

More high-quality data are needed to gain a deeper understanding of the use and impact of Ayurveda in Germany, given its growing popularity and potential to complement modern medicine. Furthermore, differentiation between therapy and wellness, and health policy measures are needed to establish scientific credibility, translate Ayurvedic concepts into mainstream western medical thinking and provide access to a wider audience. In addition, potential risks and side effects of Ayurveda should be investigated with adequate methodology. In addition, further methodologically high-quality studies are required to evaluate efficacy and effectiveness of Ayurveda in and outside its countries of origin.

5 Conclusion

Study results show that around one in 10 people in Germany has already used Ayurveda and around a third believes in its therapeutic potential. Ayurveda is mainly used by well-educated, higher-income women, typically between 20 and 40 years of age with interest in (vegetarian/vegan) nutrition and with a rather modern milieu-orientation. The perception of Ayurveda's potential therapeutic benefits is influenced by factors such as a positive attitude toward TCIM and is associated with spirituality. Because Ayurvedic therapies are often not evidence-based, there is an urgent need to perform high quality randomized controlled trials to investigate potential effects and safety of Ayurveda and how evidence-based Ayurveda treatments can be integrated into the German healthcare system.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of Charité – Universitätsmedizin Berlin. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JS: Writing – original draft. MJ: Funding acquisition, Project administration, Visualization, Writing – review & editing. AM: Supervision, Writing – review & editing. ES: Writing – review & editing. MO: Writing – review & editing. MS: Writing – review & editing. BB: Supervision, Writing – review & editing. MW: Data curation, Formal analysis, Software, Writing – review & editing. CK: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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In memoriam

The authors dedicate this article to Boike Rehbein (†11.6.2022). Boike Rehbein was involved in the planning and initiation of the project and sadly passed away during the project.

Conflict of interest

JS works self-employed as a nutritionist and alternative practitioner specializing in Ayurveda. She is also a lecturer at the "Sonne und Mond" Health Center in Berlin, training in Ayurvedic medicine. MJ received grants from the Karl and Veronica Carstens Foundation. CK is a lecturer at the "Sonne und Mond" Health Center, Berlin. He is on the scientific advisory board of the Bruno Zimmer company and a board member of the German Medical Association for Ayurveda (DÄGAM e.V.). BB and his working group were partly funded by the Kneipp-Bund e.V., by the Software AG foundation, by the BKK 24 health insurance company, by the Kneipp town Bad Wörishofen, by the Immanuel Albertinen Diakonie gGmbH and the Karl and Veronica Carstens Foundation. MO is a board member of the Berlin Brandenburg Medical Doctors' Association for Naturheilkunde (Physiotherapy) (ÄN e.V.). ES works as a nutritionist and alternative practitioner specializing in Ayurveda. He is also a lecturer at the "Sonne und Mond" Health Center in Berlin, training in Ayurvedic medicine.

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1408609/full#supplementary-material

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A review of the WHO strategy on traditional, complementary, and integrative medicine from the perspective of academic consortia for integrative medicine and health

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Despite important progress in modern medicine, widely regarded as an indispensable foundation of healthcare in all highly advanced nations and regions, not all patients respond well to available treatments in biomedicine alone. Additionally, there are concerns about side effects of many medications and interventions, the unsustainable cost of healthcare and the low resolution of chronic non-communicable diseases and mental disorders whose incidence has risen in the last decades. Besides, the chronic stress and burnout of many healthcare professionals impairs the therapeutic relationship. These circumstances call for a change in the current paradigm and practices of biomedicine healthcare. Most of the world population (80%) uses some form of traditional, complementary, and integrative medicine (T&CM), usually alongside biomedicine. Patients seem equally satisfied with biomedicine and T&CM, but in the field of T&CM there are also many challenges, such as unsupported claims for safety and/or efficacy, contamination of herbal medicines and problems with regulation and quality standards. As biomedicine and T&CM seem to have different strengths and weaknesses, integration of both approaches may be beneficial. Indeed, WHO has repeatedly called upon member states to work on the integration of T&CM into healthcare systems. Integrative medicine (IM) is an approach that offers a paradigm for doing so. It combines the best of both worlds (biomedicine and T&CM), based on evidence for efficacy and safety, adopting a holistic personalized approach, focused on health. In the last decades academic health centers are increasingly supportive of IM, as evidenced by the foundation of national academic consortia for integrative medicine in Brazil (2017), the Netherlands (2018), and Germany (2024) besides the pioneering American consortium (1998). However, the integration process

is slow and sometimes met with criticism and even hostility. The WHO T&CM strategies (2002–2005 and 2014–2023) have provided incipient guidance on the integration process, but several challenges are yet to be addressed. This policy review proposes several possible solutions, including the establishment of a global matrix of academic consortia for IM, to update and extend the WHO T&CM strategy, that is currently under review.

KEYWORDS

integrative medicine, biomedicine, TCIM, T&CM, World Health Organization, policy, academic consortia for integrative medicine and health

Introduction

Besides biomedicine, several other systems of medicine exist around the globe, some of which already for thousands of years. However, to date, these are largely separated worlds. Several calls from the WHO (1, 2) and World Health Assembly (3, 4)—the supreme decision-making body of the WHO—guide and support the integration of these different healthcare systems. In May 2014, the World Health Assembly adopted the resolution WHA67.18 on Traditional Medicine (TM) (5). Through this resolution, Member States are encouraged to develop and implement policies and actions to strengthen the role of Traditional and Complementary Medicine (T&CM)[1] in national healthcare in line with the objectives of the WHO Traditional Medicine strategy 2014–2023 (1). This strategy has two overall goals to support Member States in: (1) Harnessing the potential contribution of TM to health, wellness, and people-centered health care, and (2) Promoting the safe and effective use of TM by regulating, researching, and integrating TM products, practitioners, and practice into health systems, where appropriate.

Furthermore, the WHO strategy document has three main strategic objectives that lay-out the strategic directions and specific actions for the positioning of T&CM within the countries' health systems (1):

1 To build the knowledge base for active management of T&CM through appropriate national policies.
2 To strengthen quality assurance, safety, proper use, and effectiveness of T&CM by regulating products, practices, and practitioners.
3 To promote universal health coverage by integrating T&CM services into health care service delivery and self-health care.

In the past 10 years, the 2014–2023 WHO strategy has guided the establishment of policy documents, guidelines, technical products, centers, and institutes in support of the regulation, safe use, effectiveness, and integration of T&CM. The 2019 report summarized the achievements of member states in this regard. The authors of this paper acknowledging that considerable progress has been made in many countries in these areas, recognize that a significant number of challenges remain, and new challenges have emerged. The authors represent national consortia of academic medical institutions, from the United States, Brazil, the Netherlands and Germany. Taken together these four consortia represent over 80 academic healthcare centers and over 50 universities.

Aim of this paper

The WHO aims to release a new 10-year T&CM strategy in 2025. The aim of this paper is to (1) describe the status of academic medicine, the integration of T&CM and the role of integrative medicine (IM) in this process, (2) identify remaining challenges related to the objectives of the 2014–2023 WHO strategy document, from the perspective of four academic consortia for integrative medicine, including the establishment of a global matrix of academic consortia for IM and (3) contribute to the future WHO strategy (2025).

Definitions and characteristics

As the field of non-conventional medicines is highly variable and because of a lack of consensus on definitions we begin this paper with definitions and characteristics.

Definitions of (non-)conventional medicine

Many terms and definitions have been used to describe or define non-conventional forms/systems/methods of medicine/healthcare (6), which can lead to confusion. In this paper we use the terminology and definitions as depicted in Table 1.

Characteristics of (non-)conventional medicine

To clarify the differences between biomedicine, lifestyle, traditional, complementary, and IM, it is important to place these within the contextual framework of health care interventions as shown in Table 2: mechanism (is the proposed working mechanism of the treatment plausible from modern scientific perspective?), effectiveness (how much evidence is there for its effectiveness?) and acceptance (to what degree are these treatments accepted and implemented in health care?) (11). Acceptability to patients varies depending on the

1 T&CM is now also sometimes referred to as TCIM.

TABLE 1 Terminology and definitions of (non-)conventional medicine.

Terminology	Definition	Examples
Bio-medicine	Biomedicine, also called modern, allopathic or conventional medicine, is defined as clinical medicine based on the principles of physiology and biochemistry (7). It is the dominant health-care service delivery system from the 19th century onward, taught in university and practiced in hospitals/health systems in most (Western) countries.	Medication, radiation, surgery, high tech interventions, divided into medical specialties
Lifestyle medicine	Lifestyle medicine is a branch of medicine which has as goal to maintain optimal health and to prevent, treat and reverse chronic illness across all life stages. The health interventions used in lifestyle medicine include evidence based behavioral strategies, while considering equity and sustainability, to enhance self-management skills for optimizing nutrition, sleep hygiene, stress management, social connection, sexual health and fertility, physical activity and minimizing substance use and environmental exposures (8) (https://www.eulm.org/what-is-lifestyle-medicine).	Exercise, diet, relaxation, yoga, breathing, sleep mindfulness
Traditional medicine	Traditional medicine has a long history. It is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness (1).	Traditional Chinese Medicine Unani Ayurveda
Complementary and alternative medicine	Complementary and alternative medicine (CAM) refers to a broad set of health care practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant health-care system. It is used interchangeably with traditional medicine in some countries (1). While alternative medicine is used instead of biomedicine, complementary medicine is used in addition to it. It should be noted that the same services and practices may be considered "Traditional Medicine" when practiced in the country of origin and "CM" when used outside the country of origin.	Herbal Medicine Acupuncture Mind–body Medicine Anthroposophic medicine Homeopathy Ayurveda outside India, Chinese Medicine outside China
Integrative medicine	Integrative medicine reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing (9) (https://imconsortium.org/about/introduction/).	All treatment modalities which are safe and effective
Integrative health or Traditional, Complementary and integrative health (TCIH)	Integrative health is a state of well-being in body, mind and spirit that reflects aspects of the individual, community, and population. It is affected by: (1) individual biological factors and behaviors, social values, and public policy, (2) the physical, social, and economic environments, and (3) an integrative healthcare system that involves the active participation of the individual and the healthcare tam in applying a broad spectrum of preventive and therapeutic approaches. Integrative health encourages individuals, social groups, and communities to develop ways of living that promote meaning, resilience and wellbeing across the life course (10).	

population but is important to ascertain. Patient centered care with shared decision making is critical to an effective intervention.

Biomedicine's efficacy and mechanisms are obviously most researched and accepted. Hypotheses on mechanisms follow generally accepted modern concepts of science and medicine. Most clinicians agree that treatments should be evidence-based (e.g., established efficacy in at least two high quality randomized clinical trials; RCTs), and many of the biomedicine treatments are, although certainly not all of them (12–14).

Research shows that lifestyle medicine is insufficiently appreciated, taught, and utilized in health care, even though there is growing evidence for its efficacy (15–17).[2] A lifestyle program consisting of diet / nutrition, movement and relaxation has been proven effective for reversal of coronary heart disease and early-stage prostate cancer (18, 19). Lifestyle interventions have shown to be a safe and cost-effective measure to reduce the risk of progression to type 2 diabetes (20), and to effectively lowering blood pressure in patients with hypertension (21). Promoting lifestyle changes is also an effective intervention for mental health (22). Several studies have shown improvements in overall (mental) health and reduced relapse risk upon lifestyle interventions (22–24). Furthermore, a systematic review on lifestyle interventions adapted to persons with serious mental illness has reported on promising reductions in weight loss and reduction of some risk factors for metabolic syndrome (25). Lifestyle medicine is still underutilized in conventional health care settings, although acceptance is growing (26).

It is argued that T&CM often presents weak or conflicting evidence of effectiveness (27). Possibly not all available evidence is well known. In 2019, at the initiative of the Latin American and Caribbean Center for Health Sciences Information of PAHO/WHO (BIREME/PAHO/WHO), an official Virtual Health Library (VHL) specialized in MTCI was created to gather and systematize evidence in the area (28).[3] There are currently more than 1.5 million bibliographic references on this platform and more than 2,000 systematic reviews grouped into 28 evidence maps that assess the quality of studies and the effect of more than 300 specific interventions

2 www.lifestylemedicine.org/resources/Documents/LifestyleMedicine-LiteratureReview.pdf

3 https://boletin.bireme.org/en/2017/11/29/cooperation-to-strengthen-traditional-medicine-and-complementary-therapies/

on clinical outcomes, e.g., depression, anxiety, quality of life, stress, quality of sleep, pain relief, hypertension, diabetes, and cancer. The T&CM evidence maps prepared in collaboration with the Brazilian Academic Consortium for Integrative Health are all available in open access (29).

Besides concerns about its effectiveness, the proposed mechanisms of action of some of these modalities (for example homeopathy or Reiki) are often based on theories that are not part of modern concepts in science and biomedicine (30, 31). These medicines are therefore generally not accepted and not applied in biomedical healthcare. However, some T&CMs (32, 33) are brought closer to acceptance by contemporary science through rigorous research on effectiveness and underlying mechanisms involved. For example, acupuncture appears to be effective in the treatment of non-specific low back pain (34) and the underlying analgesic mechanism of how acupuncture can modulate the nervous system and pain pathways to alleviate pain have been demonstrated (32, 33, 35–37). Likewise, yoga seems to be effective, e.g., for back pain (38) or cancer-related symptoms (39), and plausible biological mechanisms for these effects have been proposed (40). There is some evidence for dietary supplements such as omega-3 fatty acids (41) and folate (42) for mental disorders. The efficacy of herbs such as St. John's wort (*Hypericum perforatum*) for depression (43) and Ginkgo (*Ginkgo biloba*) for mild cognitive impairment and dementia (44) have been demonstrated. The supplement melatonin has proven efficacy for sleep disorders (45), and probiotics have been shown to have a beneficial and effective role in the prevention and treatment of several diseases including diarrhea (46) and irritable bowel syndrome (47). There also appears to be some evidence for multimodal naturopathic medicine as a complex intervention for cardiovascular disease, musculoskeletal pain, type 2 diabetes, polycystic ovary syndrome, depression, anxiety, and other chronic conditions (27, 41).

Specific modalities do not necessarily stay in one of the categories as depicted in Table 2. They can move from traditional to complementary and even to biomedicine when evidence on their effectiveness and mode of action emerges. In the case of mindfulness-based interventions, several high-quality studies have shown that programs such as Mindfulness-Based Stress Reduction led to clinically relevant improvements in outcomes in several conditions and disorders and are being accepted and implemented to a greater extent within the health care system (48). Specific modalities can also move into the other direction when evidence emerges that they do not work. For example, research does not support the often-heard claim that high-dose oral vitamin C supplements boosts the immunity and decreases the risk of respiratory infections in the general population (49).

Status of academic medicine

Medicine as it is taught in universities and most practiced in academic hospitals, often referred to as biomedicine, is the dominant healthcare system in the (Western) world. This position is not only explained by scientific advancement. It is underscored by social, cultural, economic and political conditions of biomedical knowledge construction (50). Biomedicine has made incredible progress in the molecular and genetic understanding of disease, in high-tech innovations and in available treatments. A lot of suffering has been prevented and many diseases cured (51, 52).

However, not all patients respond well to available treatments. Interventions tend to be fragmented, focused narrowly on single organ systems. Beyond health screenings and vaccination, most care occurs after a patient has become ill. Episodic care can be transactional, poorly coordinated and conducted over many brief visits. It may therefore frequently incumbent upon the patient to coordinate and initiate care. Biomedical health care also often lacks strong tie to public health and community approaches. Another challenge is that non-communicable (lifestyle related) chronic diseases have become endemic. Additionally, there are side effect and safety concerns of many medications and interventions, and the cost of healthcare continues to unsustainably soar. Many healthcare professionals suffer from chronic stress and burn-out in a strictly regulated bureaucratic system of protocols and managed care, which impairs the therapeutic relationship (53). Finally, humanity faces huge healthcare challenges, such as pandemics, shortage of skilled personnel, increase of mental disorders, climate change and war. Biomedicine alone cannot solve all these (54).

Side effects

The incidence of adverse side effects of drugs and interventions have made iatrogenesis one of the major public health problems in developed societies, whose causes, in addition to errors and negligence, are of a systematic nature (55). Patient safety has become a major concern in health care worldwide. Of patients admitted to hospitals, 3.7 to 17.7% are inadvertently harmed by the way their health care is delivered. Avoidable adverse events lead to a greater annual loss of life than traffic accidents, AIDS, or breast cancer (56–58).

Costs

Healthcare costs continue to escalate, taking 17 percent of gross domestic product (GDP) in the United States, 9.5 percent in Brazil, and 10 in the Netherlands (59).[4] The increase of costs seems largely related to chronic disease and lifestyle behavior such as diet, exercise and smoking (60). Indeed, the contribution of lifestyle to modern chronic disease has been estimated at 80% (61, 62) and even 95% (63). One possible strategy to reducing costs is inviting patients to take a more active role in their recovery, for instance by applying therapeutic lifestyle changes like exercise, diet and relaxation (15, 22). There is growing evidence for the effectiveness of lifestyle changes for improving health (20, 21, 25). There is also evidence for the cost effectiveness of lifestyle changes, which can run up to 2,360 dollars per person per year (64). For every $1 invested in the truth anti-smoking campaign, the United States saved more than $6.80. This campaign decreased youth smoking by 22% from 1999 to 2002 and averted $1.9 billion in future health care costs. Every $1 spent on evidence-based

4 https://www.oecd.org/health/health-expenditure.htm#:~:text=There%20was%20a%20rebound%20in,funding%20to%20tackle%20the%20pandemic

TABLE 2 Characteristics of (non-)conventional medicine.

	Conventional medicine	Non-conventional medicines		
	Biomedicine	Lifestyle medicine	Complementary medicine	Traditional medicine
Working mechanism	In accordance to modern science	In accordance to modern science	Not (always) in accordance to modern science	Not (always) in accordance to modern science
Evidence for effectiveness	Generally well documented	Moderate and increasing	Varying levels, but generally low or not yet tested	Varying levels, but generally low or not yet tested
Acceptance by conventional healthcare providers	High	Partial and increasing	Mostly low	Low

programs that increase physical activity, improve nutrition, and prevent tobacco use saves $5.60 in health spending within 5 years and up to $6.20 within 10 years (65).

Therapeutic relationship

Another concern in medicine is the quality of the therapeutic relationship, which seems threatened by managed care, focus on protocols and evidence-based medicine at the expense of patient centered approaches, and a tendency to reductionism, narrowing the view to diseases or symptoms and losing sight of the whole person in their context. The original definition of evidence-based medicine is '(1) the conscientious use of current best evidence in (2) making decisions about the care of individual patients or the delivery of health services, (3) taking preferences and needs of patients into account' (66, 67). However, the last part of this definition is often neglected. This, together with a tendency toward uniformity and efficiency (in the form of guidelines, treatment protocols and clinical pathways) can lead to a 'one size fits all approach', which can impair the therapeutic relationship and is in clear contrast to the original idea of evidence-based medicine (66). The reduction of length of visits to the bare minimum limits the capacity to engage patients in sustainable behavior change, further driving a medication and procedural predominant practice style.

A new paradigm

These concerns and challenges in academic medicine call for a change in the current paradigm and practices, including patient care, scientific research, education, clinician training, and policy (68, 69). Indeed, in biomedicine there is a growing awareness of the need for a multi-dimensional perspective beyond the current paradigm that is primarily focused on medication and technology (70, 71) taking the whole person into account (72). This can be observed in concepts like 'personalized medicine' (73–75), 'shared decision making' (76), 'patient-centered care' (77) and positive health (78).

One such new paradigm is 'integrative medicine', which was introduced by a consortium of Academic Health Centers in the United States in the late 1990's in response to the before mentioned challenges in biomedicine. Currently, this IM consortium has more than 75 active academic health centers as its members (including Duke, Harvard, Stanford, Yale) (16, 79).[5] The Consortium defines IM as: 'the practice of medicine that (1) reaffirms the importance of the relationship between practitioner and patient, (2) focuses on the whole person, (3) is Informed by evidence making use of all appropriate therapeutic approaches, healthcare professionals and disciplines (including T&CM) to (4) achieve optimal health and healing (80)."[6] Other national consortia for IM were founded in Brazil (2017) (81) the Netherlands (2018) (82),[7] and Germany (2024). This third principle includes the integration of T&CM and biomedicine and may help to overcome (some of) the before mentioned challenges to biomedicine by combining their strengths and balancing their weaknesses.

Improving the therapeutic relationship

The focus on an optimal relationship and the holistic approach of IM may increase disclosure and communication, adherence to the treatment plan, improve the therapeutic relationship (83) and enhance treatment outcome (84–86). Treatment outcome has been shown to be highly dependent on the quality of the therapeutic alliance (87–90), while a personalized approach may also improve outcome (74). IM represents a higher-order system of systems of care that emphasizes wellness and healing of the entire person (bio-psycho-socio-spiritual dimensions) as primary goals, drawing on both conventional and T&CM approaches in the context of a supportive and effective physician-patient relationship (71). This approach encourages consideration of how symptoms fit together with a particular focus on how physical and psychological health interplay.

Reducing healthcare costs

Findings from economic modeling research suggest that combining T&CM and biomedicine may improve cost-effective long-term outcomes (91–95), although cost-effectiveness for the majority of T&CM still needs to be evaluated. Examples of interventions that were found to be cost effective compared to usual care are: acupuncture for migraine, manual therapy for neck pain, spa therapy for Parkinson's, self-administered stress management for cancer patients undergoing chemotherapy, pre- and post-operative oral nutritional

5 https://imconsortium.org/member-listing/

6 http://www.imconsortium.org/about/home.html

7 https://www.cizg.nl/home/

supplementation for lower gastrointestinal tract surgery, biofeedback for patients with "functional" disorders (e.g., irritable bowel syndrome), and guided imagery, relaxation therapy, and potassium-rich diet for cardiac patients (91).

Reliable information

IM stimulates scientific research on the safety and effectiveness of T&CM which could prevent false claims and increase safety by providing reliable information to the public. Currently, a collaborative project is ongoing between the Brazilian academic consortium on IM in partnership with the Latin American and Caribbean Center on Health Sciences Information of the Pan American Health Organization (PAHO) to develop evidence maps of clinical effectiveness in T&CM based on systematic reviews of clinical studies (29). Accordingly, it can be expected that the increasing academization and organization of T&CM in the sense of IM will lead to a general promotion and systemization of research activities in this field.

Regulation

Taking T&CM use more seriously, increasing public attention and stimulating research and policy making will also improve regulation of products and therapists. This is reflected in the increasing number of WHO member states who have regulations on herbal medicine in all six regions of the world. Again, the academization of IM will lead to an increased public awareness on the importance of regulation of this field.

Improved treatment outcomes

This could be achieved by developing novel therapies. For instance, Dr. Youyou Tu was awarded the Nobel Prize in 2015 for the discovery of antimalarial properties of artemisinin, a herb that is part of Ayurveda and T&CM (96). Improved outcomes may be achieved by not only looking at symptoms and problems and trying to eradicate them (pathogenesis), but also at the strengths and qualities of patients and finding ways to increase them (health promotion or salutogenesis) (97). For example, it has been shown that integrative oncology, i.e., the combination of biomedical cancer therapies with T&CM, can lead to higher health-related quality of life in cancer patients than biomedicine alone (98).

Inducing a healthy lifestyle

IM has always stressed the importance of a healthy lifestyle. Motivating and teaching patients to improve lifestyle comes with less costs and can increase self-esteem, responsibility for one's own health and more independence from therapists (15, 22–24). It may not only reduce pathology, but it may also enhance health and wellbeing by fostering positive emotions like calmness, empathy and self-actualization (99, 100). Lifestyle medicine, as previously described, is increasingly adopted by biomedicine (101) and may as such may guide the integration process of T&CM into conventional healthcare.

Three examples of specialties in which integrative medicine has been applied successfully are:

> "Integrative psychiatry (1) emphasizes the importance of the therapeutic relationship between clinician and patient using shared decision making and a personalized approach. It (2) focuses on treating the 'whole person' from a holistic perspective, considering mind–body and its systems as interrelated, with biological, mental, emotional, cultural, ecological and spiritual / religious aspects. It (3) seeks to provide the 'best of both worlds' combining biomedicine with T&CM based on evidence for their safety and efficacy. Its focus (4) is on increasing qualities and strengths (salutogenesis) as well as decreasing symptoms (pathogenesis) and it aims for increasing general wellbeing and mental health" (11).

> "Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. It aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment (102, 103)."

> "Pediatric integrative medicine represents an evolution in pediatric care, a paradigm that embodies a philosophy consistent with long-standing holistic principles of quality medical care. It is defined by several core guiding principles: (1) Preventive: True primary care pediatrics is proactive rather than reactive. Prescribing lifestyle solutions to prevent disease is generally preferable to costly and potentially risky treatments. Lifestyle prescriptions may include food, activity, nature, creativity, rest, mindfulness, and connection with others. (2) Context-centered: Children must be nurtured within the context of healthy families, social context, and schools. Health in mind, body, and spirit depends on how suitable the environment is for the child. (3) Relationship-based: Only through open communication and building trust are we best able to work together to ensure each child's optimal health. The connection between health professionals and families has its own healing potential. (4) Personalized: Health is not a one-size-fits-all proposition. Each child carries a unique potential based on a complex interplay of genetic and environmental factors. There is no medical treatment that can be guaranteed as safe for 100% of any population. Each family has the inherent right to make healthcare decisions for their children, keeping in mind the best interests of the child as well as legitimate public health concerns that ethically inform these decisions. (5) Participatory: Creating health should be a collaborative process, actively encouraging participation and putting children and families back in control of their own health. Patient-centered care creates hope and empowers families to make sustainable changes, inspiring children to create the future they deserve. (6) Ecologically sustainable: how we practice

> healthcare affects the environment, which has a measurable and cyclical impact on our health. The health and well-being of all the Earth's inhabitants are intimately tied to the health of our planet. (7) Evidence-informed: Therapies that are evidence-informed while using the safety-effectiveness rubric are considered as part of the treatment plan (52, 104)."

Despite these successful initiatives, academic medicine frequently regards T&CM with criticism, dismay, and distrust. In many countries biomedicine and T&CM are still largely separate worlds, sometimes with hostile attitudes toward another. However, in the last decades this seems to change. The foundation of four academic consortia for integrative medicine is an indication for this. This apparent change in openness to T&CM may be because integration is not only a current tendency in medicine, but also a trend fitting the contemporary spirit of the age in which integration seems to be the most common focus. It can be observed in religion, philosophy, spirituality and psychotherapy as well (105). It is also reflected in the WHO Traditional Medicine strategy 2014–2023.

Assessment of the WHO traditional medicine strategy 2014–2023

The WHO Traditional Medicine strategy 2014–2023 set out ambitious goals for its member states regarding research; regulation of T&CM practices, T&CM practitioners and T&CM products; and integration of these into health systems. It also included self-care and prevention. It proposed three main strategic goals which are reviewed in the next paragraphs. Also recommendations are formulated to inform the upcoming WHO T&CM strategy.

Strategic goal 1: current practice related to active management of T&CM through national policies

T&CM contribute to the Sustainable Development Goal (SDG-3; 'ensure healthy lives and promote well-being for all at all ages') of achieving Universal health Coverage (UHC) and ensuring that all people have access to care (United Nations 2019). Several World Assembly (WHA) resolutions requested the WHO to provide technical support and guidance to member states, for the integration of healthcare services (106). In European countries, T&CM are mostly used complementary to the conventional system (107). The top three reasons for T&CM use are: (1) having an expectation of benefits of T&CM, (2) dissatisfaction with conventional medicine and (3) the perceived safety of T&CM (37%) (108). Another reason reported is that T&CM resonates with one's values or perspectives on health (108, 109). Tangkiatkumjai et al. (108) found that internal health locus of control as an influencing factor for T&CM use is more likely to be reported in Western populations, whereas the social networks is a common factor among Asian populations. Affordability, easy access to T&CM were significant factors among African populations. These factors, along with the greater availability of health information on the internet, and similar degree of satisfaction between T&CM and biomedicine, seem to be driving forces behind the growth in the use of T&CM in Western and Eastern countries in recent decades (110).

T&CM is present in almost every country in the world and the demand for its services is increasing (1). Up to 76% of the world population uses some form of T&CM each year (111). In many countries, they are the main healthcare services to the population since ancestral times (2). T&CM are an important and often underestimated health resource with many applications, especially in the prevention and management of lifestyle-related chronic diseases, and in addressing the health needs of aging populations. In an ideal world, traditional medicine would be an option provided by a well-functioning, people-centered, evidence-informed health care system that balances curative services with preventive care (2).

In the WHO's 2019 Global Report on Traditional and Complementary Medicines (2) it is described that T&CM is an important and often underestimated health resource, specifically in the prevention and management of lifestyle-related chronic diseases, by stimulating a healthy lifestyle and in addressing the health needs of aging populations. In the light of the recent surge of healthy lifestyle interventions in biomedicine and a call for more prevention, in policy making, countries could benefit from the experience and knowledge of T&CM in these field.

Recently, the WHO has introduced the term TCIM (Traditional Complementary and Integrative Medicine) to emphasize the world-wide need to take different kinds of medicine into account. TCIM includes traditional medical systems such as Ayurveda and Traditional Chinese medicine, non-traditional and complementary ones such as Naturopathy, lifestyle medicine (nutrition, exercise, sleep), Homeopathy and Anthroposophic Medicine, and use of natural medicines such as herbs, and mind–body interventions (mindfulness, yoga), besides biomedicine (2).

Whether T&CM is fully integrated, partly integrated or not integrated in the country's dominant health system depends on factors such as national regulations, appropriate education, funding, information, availability of services and multidisciplinary collaboration (2). Different models have been developed and described on how T&CM can be integrated into the conventional health system. They can be classified into five models ranging from coexistence, cooptative, cooperative, collaborative, to patient-centered care (112). The more coexistence and cooptative models for T&CM integration have distinct roles for different health care professionals, whereas the cooperative and collaborative models are team-based, with formalized interaction between the conventional health care professionals and T&CM practitioners (112).

At present, the practice of T&CM highly varies per country and is idiosyncratic. Such practice depends on the personal philosophies, values and clinical perspectives of its practitioners, and the goals of diverse training programs, clinics or hospitals where integrative treatment approaches are employed (113). Asian countries such as China, Japan, and the Republic of Korea have well-established systems of T&CM integration, including supportive legislation, well implemented regulatory systems for herbal medicines, T&CM practices and practitioners, as well as T&CM education systems (114). In African countries, traditional healers and natural medicines are widely used by its population, but hardly integrated into the mainstream health systems (115, 116). An illustrative example of the integration process of T&CM in a European

conventional health system is that of integrative oncology in the German speaking countries. An active group of clinicians, researchers and practitioners have systematically developed a step-by-step basis for integrative oncology care in Germany and Switzerland. They have defined education competencies for oncology physicians regarding T&CM (117). As a next step, they have developed and tested a consultation framework for the training of oncology physicians to advise their patients about the effectiveness and safety of T&CM (118). Furthermore, they also have developed criteria for guiding cancer patients to find a reputable T&CM practitioner (119). Within this collaborative, they also work in parallel to further identify the needs, provide reliable information, foster communication, and support decision-making about T&CM for patients with cancer (120). In sharp contrast to the German speaking countries, in Finland there seems to be no integration of T&CM into the conventional health system. Finland lacks any regulation or guidelines on T&CM, and there is very little academic research on the subject (121). Such world-wide variety in the integration of T&CM seems undesirable, specifically from the needs and perspectives of patients.

In the past decades, the number of countries that have implemented some form of regulation on T&CM has grown. In 1999, only 25 WHO member states had a national regulatory policy on the subject, 45 had national legislation, and 65 countries had specific regulations on herbal medicine. In 2018, a total of 98 of the 194 WHO member states had a national policy, 109 had legislation, and 124 countries had regulations on herbal medicine in all six regions of the world (2). Despite this apparent increase, T&CM is still not regulated appropriately in almost half (49.5%) of the countries world-wide. Take the example of the European Union, where most T&CM modalities are practiced in a very similar way. There are European countries where T&CM or some of its modalities are regulated either as conventional medicine (e.g., chiropractic in the United Kingdom), complementary medicine (e.g., Switzerland), alternative medicine (e.g., Norway), or not regulated at all (e.g., Finland) (122). From the perspectives of its users and open border policies, it becomes apparent that this confusing and disharmonized regulation on T&CM should be addressed more prominently. An often-heard argument against T&CM regulation is that regulation may grant these non-conventional types of medicine and T&CM practitioners undue legitimacy or recognition (123). However, a recent systematic review on the subject concluded that there appears to be broad support for the regulation of T&CM, but that there is wide variation in opinions among the different stakeholders as to how this should be applied (123).

Recommendations regarding goal 1:

- The confusing and disharmonized regulation of T&CM between countries should be addressed more prominently and ultimately be harmonized.
- Strategies of how to stimulate, persuade and guide countries that still lack any kind of regulation should be developed.
- Strategies should be developed on how to make sure countries make more use of the experience and knowledge of T&CM regarding policy making in the fields of prevention, lifestyle and health promotion.

Strategic goal 2: current practice related to the quality assurance, safety, proper use, and effectiveness of T&CM

Despite its increasing popularity, the field of T&CM is faced with many challenges, such as problems with quality standards, unsupported claims for safety and or effectiveness, challenges with sufficient research funding and appropriate research methodologies, lack of familiarity by conventional healthcare providers about evidence-based T&CM, absence of reimbursement mechanisms for T&CM, non-disclosure of T&CM use by patients, and unreliable sources of information. These challenges that T&CM is facing are described in more detail below.

Safety concerns

Users often associate T&CM with nature, and that all that comes from a natural source is good and safe (124). A recent study reported that as much as 90% of users regard T&CM as safe and are not aware that these natural medicines may cause unwanted side effects (108). However, the use of, for example, herbal preparations may involve some risk, potentially translating into adverse effects, interaction with other drugs, and contamination (125). For example, hepatotoxicity, allergic reactions, or gastrointestinal problems have been reported to occur after intake of herbal medicine (126, 127). Furthermore, one of the most prominent risks associated with the combined use of herbal preparations and chemotherapeutic agents in cancer treatment is that of herb-drug interactions. A systematic review revealed that six herbal preparations have potential clinically significant interactions with chemotherapeutic agents in humans (128). Contamination of herbal preparations with heavy metals may pose another serious potential risk to the health of its users. A recent study in which 1,773 samples of herbs around the world were investigated for contamination with heavy metals, almost one-third (31%) had at least one metal that was over the allowed limit according to the Pharmacopeia standards (129). The reporting of adverse effects for other T&CM modalities seems to be of lower frequency and severity as compared to herbal preparations. Nevertheless, for example minor and serious adverse effects such as organ or tissue injuries may occur upon acupuncture treatment (130). Furthermore, the prevalence of adverse effects in meditation-based therapies was found to be 8.3%, like that reported for psychotherapy practice in general (131). Most frequently reported adverse effects related to meditation practices were anxiety and depression (131). Likewise, injury risk of yoga seems to be comparable to that of other physical activity (132). A possible indirect risk with relevance for general safety is that T&CM use may cause a delay in appropriate diagnoses of patients and/or a delay in receiving effective conventional treatment (133). However, epidemiological data do not suggest that T&CM users systematically make less use of conventional medicine than non-users (134), so this supposed risk is probably limited to individual cases.

Lack of standardization

For most T&CM modalities, there is a large heterogeneity in how it is applied in daily practice. For example, T&CM modalities such as acupuncture (135) or yoga (136) encompass a variety of techniques and styles, and the choice for a specific technique if often based on the cultural setting in which it is practiced or practitioners' personal

experiences. The lack of standardization of T&CM practices poses a challenge for integrating the modality within the institutionalized framework of conventional healthcare. Moreover, the lack of standardized T&CM treatment protocols hampers scientific evaluation of its effectiveness and reproducibility of its results. However, standardization of T&CM seems to collide with the intrinsic principles on which it was developed: such as individualized treatment and a holistic (multidimensional) perspective on healing.

Claims of effectiveness

The number of scientific publications on T&CM has doubled in the last decade (137). Although the evidence for T&CM is growing, and some modalities such as mindfulness and acupuncture have found their way in clinical guidelines and recommendations (138, 139), the majority of the broad range of T&CM modalities lacks sufficient evidence to claim effectiveness (140). Therefore, misinformation about the effectiveness of certain T&CM modalities continues to spread and may create false hope among patients about the possible effects of these interventions (141). Specifically in cancer, it is known that patients are eager to try any T&CM treatment as to keep their hope for survival alive (142). Patients need to be protected from false hope, but also from false hopelessness. Therefore, it is of great importance to continue to search for and test promising T&CM modalities.

Research (methodology)

One of the research challenges with T&CM is lack of sufficient funding and finance. In contrast to the large pharmaceutical industry-sponsored research, there is very little industry-based research for T&CM (143, 144). This is mainly because T&CM modalities and natural products cannot be patented, and hence commercial parties that research them cannot guarantee that they will have return on investment of the research. Another challenge and highly debated area is to apply appropriate methodologies to investigate such complex and multidimensional interventions as T&CM (145, 146). Since these procedures are usually already widely used in health care without adequate clinical testing, their scientific testing often follows different guidelines than those of biomedical preparations with their clear sequence from phase I to phase IV studies (147). Additionally, the methodology, especially in the case of non-pharmacological approaches, often has to be adapted, since the usual principles like double blinding or placebo control are difficult or even impossible to realize. Other challenges to the conduct and application of T&CM research may be lack of institutional support, research training and collaboration, and diverse views of evidence (148).

Non-disclosure

Another challenge is that most patients (66%) do not inform their physician about their use of T&CM (109). Reasons for non-disclosure of T&CM use is lack of inquiry from the physician, fear of disapproval from their physician, perception of disclosure as unimportant, belief that the physician lacks knowledge and time on T&CM, and the belief that these modalities are safe (149). Non-disclosure of T&CM use to their treating physician is an undesirable situation since it may lead to potential health risks such as the drug-herb interactions as described above.

Trustworthy information

It seems urgent to facilitate the spread of reliable information on T&CM, as most users get information on these treatments through family and friends, social networks and media, and the internet (142). The quality of this information varies greatly (145, 150), and often contains non-proven claims about T&CM or promotes controversial alternative treatments. It has been reported that users wish to receive unbiased information and advice about T&CM use in open communication with their physician or other health care provider (142, 151).

Lack of knowledge by healthcare providers

Health care providers such as physicians and nurses seem to lack adequate training and knowledge to inform their patients about T&CM use (152–156). It is however important to note that their level of knowledge on T&CM is mostly surveyed through self-assessment. Development of instruments that directly measure their T&CM knowledge are needed (153). Regardless of how their knowledge is assessed, it has been reported that healthcare providers see a need to have better knowledge on the topic to be able to address questions that patients may have (157, 158). Introducing basic knowledge on the safety and efficacy of T&CM into the medical training of healthcare professionals seems to be an important strategy forward to increase their knowledge. Other strategies by which to increase the knowledge among conventional healthcare providers are to enhance interprofessional collaboration with T&CM providers and to facilitate their access to reliable and unbiased information on T&CM (157, 159).

Recommendations regarding goal 2:

- Map the existing evidence base and quality of that evidence for some T&CM (e.g., acupuncture, botanicals, mind body medicine), and make it accessible free of charge through thrust worthy authorities or organizations, such as WHO.
- Stimulate high quality scientific research on T&CM, specially those in high usage by the public.
- Ensure sufficient funding for research on T&CM.
- Systematically address adverse events in clinical trials as well as in clinical care.
- Develop guidelines on how to address safety specifically for T&CM.
- Invest in standardization and treatment protocols, while respecting the personalized nature of T&CM.
- Systematic control of T&CM products on possible components of endangered species (plants and animals).
- Practitioners of biomedicine and of T&CM should provide trustworthy information to the public; balancing between false hope and false hopelessness.
- Train biomedical healthcare professionals in accurate information about T&CM and in the non-judgmental addressing of T&CM during consultation.
- Develop and implement a monitoring system for the safety of T&CM practices and products similar to existing monitoring systems for medicinal products.
- Facilitate the development of guidelines and communication tools for the disclosure of (concomitant) T&CM use with recommendation by the WHO.

- Stimulate educational guidelines/curriculum for basic and general knowledge of T&CM addressed at conventional healthcare professionals.

Strategic objective 3: promote universal health coverage by integrating T&CM services into health care service delivery and self-healthcare

Reimbursement of T&CM services

In many countries, T&CM are the main healthcare services to the population since ancestral times (2). Although up to 70% of the world population depends on T&CM as the first line of treatment, in many countries T&CM is still mainly offered outside the dominant healthcare system. Therefore, costs associated with T&CM use are often not covered by reimbursement systems from government funding or health insurance companies. Most patients thus must pay for T&CM out of their own pocket (91, 160, 161). For the United States it was estimated that in 2007, about 14.9 billion dollar was spend out-of-pocket by US adults for visits to T&CM providers and on purchases of dietary supplements related to pain management (162). It has been demonstrated that out of pocket expenditure on T&CM for supportive care in cancer was significantly associated with increased risk of financial catastrophe and medical impoverishment among upper-middle income countries in South-East Asia (163). Another study demonstrated that job insecurity was associated with less visits to T&CM practitioners (164). Furthermore, it is known that T&CM use is most often attributable to socioeconomic status (SES), i.e., those with a higher SES are more likely to use T&CM than those with a lower SES (165). These findings point to a socioeconomic inequality in possible effective health service use (166).

This lack of reimbursement is undesirable not only from a moral and pragmatic but also from an economic perspective. As was argued earlier in this paper, findings from economic modeling research suggest that combining T&CM and biomedicine may improve cost-effective long-term outcomes (91–95). Therefore, reimbursement of effective T&CM may be better when looking at the whole picture.

Recommendation regarding goal 3:

- Ensure access to T&CM and biomedicine interventions worldwide
- Reimbursement of all healthcare interventions that are safe and effective
- Cost effectiveness research on including T&CM in reimbursement policies, and on the effects of prevention, healthy lifestyle and self-care on healthcare costs.
- Provide information and ensure easy accessible training in effective affordable self-help strategies

Other recommendations

We have argued that the concept and principles of IM provide concrete healthcare actions and measures that are worth to further implement and investigate in the light of the increasing global health threats such as chronic diseases, pandemics, and ever-increasing healthcare cost. We made suggestions concerning the three main strategies in the 2014–2023 WHO Traditional Medicine strategy. We propose three additional suggestions:

1 Fostering international cooperation between Academic Consortia for Integrative Medicine and Health

There is currently no global platform or organization that represents clinical practice, education, and research on T&CM from the perspective of Western academic medicine.

To facilitate the global integration of T&CM, we therefore propose to establish a Global Matrix of Academic Consortia for Integrative Medicine and Health and the WHO, its global and national collaborative centers, T&CM providers, International society for T&CM research (ISCMR), other stakeholders and patient organizations.

The establishment of a Global Matrix of Academic Consortia was originally proposed by the former head of the WHO's T&CM Unit (Dr Zhang Qi) a few years ago. Subsequently, the three national academic IM consortia United States, Brazil and the Netherlands elaborated further on the idea and drafted a first outline. This outline was presented to many stakeholders in May of 2022 during the International Congress on Integrative Medicine & Health in Arizona, USA and during the International Congress on Integrative Medicine in Rome in September 2023. Based on their feedback and suggestions the present paper was drafted and finalized. The next step is to establish a Global Matrix (GM) and to formulate its vision, mission, goals, and objectives. Besides, models for collaboration will be developed centered around the GM's goals and objectives.

The overall goal of our proposed GM is to support the world-wide integration of T&CM by advancing research, academic education, clinical guidelines, policy, and communication on IM, from the perspective of academic medicine. To reach this goal, we foresee the following objectives in the next 5 years:

- To connect academic consortia on T&CM and all other stakeholders and organizations in all six WHO regions: the African Region (AFRO), the Eastern Mediterranean Region (EMRO), the South-East Asia Region (SEARO), the Region of the Americas (AMRO), the Western Pacific Region (WPRO), and the European Region (EURO)
- To support the establishment of academic consortia in the six WHO regions
- To develop and advance a global agenda that sets priorities for research, education, clinical guidelines, policy, funding and communication
- To exchange academic knowledge, implementation experiences and evaluation tools with stakeholder in the field of T&CM
- To provide insight into the evidence status of T&CM, by means of evidence maps of clinical effectiveness in T&CM.

To provide support and collaborate with the WHO, the development of the WHO Traditional Medicine strategy, its 26 WHO collaborating centers on T&CM, the WHO Global TM Center, the regional offices and other stakeholders such as but not limited to ISCMR and PAHO.

2 An international research agenda

An important step forward to address the challenges regarding the lack of (good quality) evidence for (cost)effectiveness, safety and the conduct and application of T&CM research is to develop an international research agenda based on 'gaps' and then address research

priorities. This should also include cost-effectiveness studies, as controlling costs is a major challenge in healthcare. Ongoing mapping studies on the clinical effectiveness of T&CM of the BIREME/PAHO, Brazilian Academic Consortium for Integrative Health and the WHO can assist in this research prioritization by identifying the evidence gaps and weaknesses in methodological designs.

The use of AI in generating evidence could be considered, as there are many research questions and a shortage of people and funds.

Besides (cost) effectiveness of T&CM, there is also a need to focus on implementation science, as there seems to be a gap between the existing evidence and current practices, especially in academic health centers.

3 International policy and guidelines

The status of integration of T&CM varies considerable between member states and depends mainly on personal philosophies, values and perspectives of regulators, clinicians, and practitioners in each country. We recommend that the main challenges regarding quality assurance, safety, proper use, effectiveness, and integration of T&CM as identified in this paper, are addressed in an updated or new WHO Traditional Medicine strategy. However, to tackle these challenges and further the field, we propose that a new policy (strategy) of the WHO is closely linked to the clinical, academic and research practice of T&CM. We are of the opinion that a direct and dynamic interaction between policy, research and practice will support, facilitate, and accelerate the integration of biomedicine and T&CM. To do so a worldwide network of cooperating (consortia of) academic healthcare centers and researchers is needed. A Global Matrix may be the best way to facilitates this, as it connects all involved in T&CM while at the same time ensuring everyone's autonomy.

Conclusion

This paper offers an overview of integrative medicine approaches and offers recommendations for the upcoming update of the present WHO strategy on T&CM from the perspective of academic medicine. With this we hope to contribute to an integrated, compassionate, person-centered global healthcare in which anyone, regardless of their illness, sociodemographic or cultural background, worldview or treatment preference can receive the care he or she needs and is most in line with their values.

Our proposal of the establishment of a Global Matrix should not be seen as an endpoint, but rather as a start. We are aware of many organizations and societies with similar goals; however, our proposal is based on the perspective of academic medicine, which is lacking. We invite global dialog with stakeholders on this proposal and critical issues being put forward.

Author contributions

RH: Conceptualization, Writing – original draft, Writing – review & editing. RG: Writing – review & editing. CP: Writing – review & editing. SS: Writing – review & editing. AL: Writing – review & editing. HC: Writing – review & editing. DG-P: Writing – review & editing. MJ: Supervision, Writing – review & 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.

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Protocol for a scoping review of traditional medicine research methods, methodologies, frameworks and strategies

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Background: The World Health Organization (WHO) has called for the evidence-informed integration of traditional medicine (TM) into health systems. Research rigor requires a good "fit" between research designs and what is being studied. The expectation that TM research fully adheres to biomedical evidentiary norms potentially creates tensions, as TM paradigms have their own distinct features. A scoping review will be conducted to describe and characterize the research approaches used in TM and their paradigmatic alignment with the TM being studied.

Methods: This scoping review protocol was informed by Joanna Briggs Institute (JBI) methods. This protocol outlines an *a priori* conceptual framework, provisionally termed "paradigmatic alignment." The review will include all populations, TM types, research approaches (i.e., methods, methodologies, frameworks, strategies), cultural contexts, and health care settings. Up to 38 English and non-English language databases will be searched sequentially for both published and gray literature until reaching data saturation across relevant concepts and contexts. Analysis will begin deductively, using a pre-piloted data extraction template to describe the TM research approaches. A basic qualitative content analysis of a sample of evidence sources will explore how research approaches are applied or modified to align with the TM therapeutic paradigm, and the manner in which they co-exist, contrast, complement or align with established biomedical research approaches. The findings will be narrated and summarized in charting tables and figures. The review will be reported according to the PRISMA scoping review extension. Consultative engagement with knowledge users across all review stages is planned.

Discussion: Aligned with the principle of Two-Eyed Seeing (*Etuaptmumk*), wherein Indigenous/traditional and biomedical knowledges may equitably co-exist, this review promises to advance scholarly insights of critical value in an increasingly pluralistic, globalized world.

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KEYWORDS

traditional medicine, complementary therapies, research methods, research paradigms, scoping review

1 Introduction

In 2020, the World Health Organization (WHO) announced the establishment of a new global center for traditional medicine (TM) in Jamnagar, India, to further advance the WHO's long-standing call for governments worldwide to appropriately integrate TM into national health systems (1). The *WHO Traditional Medicine Strategy: 2014–2023* emphasizes that TM-related health system advancements "must be supported by evidence," to foster delivery of safe, effective and accessible healthcare (2). However, surveys of WHO Member States consistently identify a "lack of research data" as their primary challenge in this regard (3). To support development of a research agenda for the new global TM center, the WHO has commissioned a series of evidence reviews. The scoping review protocol presented here pertains to one such commissioned study.

In the 2018 *Declaration of Astana,* the WHO explicitly called for the concurrent application of both biomedical and TM knowledges, and their associated practices, in advancing universal access to primary health care worldwide (4). There is strong academic and political pressure for TM to align with the biomedical evidence-based approaches that are widely applied in other areas of health and medicine. However, research methods must also be appropriate to what is being studied. TM takes many forms and is often underpinned by paradigms that differ in keyways from biomedicine (5). Tensions may thus arise in this context, as dominant biomedical research paradigms are not always optimally suited to studying TM approaches.

There remains an active global debate as to what types of research approaches may be most appropriate for the study of TM systems and their affiliated practices. This debate, in part, reflects the paradigmatic differences between TM and biomedicine (and its widely accepted research approaches). Since all research approaches—including standard biomedical methodologies and methods—are underpinned by their own paradigmatic features (6, 7), the question arises as to what types of rigorous research approaches may be aligned with TM paradigms. Indeed, the paradigmatic tenets of TM systems differ considerably from those underpinning dominant biomedical paradigms. Biomedicine is a therapeutic system historically structured around a worldview of "scientific materialism" that mechanistically reduces living systems to their constituent physical parts (8). Over the last 70 years, the biomedical paradigm has faced transformations from within, including the rise of a "biopsychosocial paradigm" (9), that includes social and psychological factors alongside biological considerations (10). In contrast, TM systems, while diverse, tend to be paradigmatically based in worldviews of "holism" (i.e., the whole is greater than the sum of its parts) (11), "vitalism" (i.e., there is a "vital" operating principle that distinguishes living organisms from other parts of the material world) (8), and/or "eco-centrism" (i.e., which situates the planet/nature rather than humans as the central conceptual element, drawing links between them) (11, 12).

TM researchers (13–15), like Indigenous scholars (16, 17), have critiqued the limitations of many mainstream health research norms, reporting methodological challenges with applying many standard biomedical research approaches (13). Some such critiques and challenges are similar to those raised and faced by biomedical researchers (18, 19). For example, in the field of psychotherapy (20), it has proven difficult to establish credible placebo/sham controls for many TM therapies (e.g., acupuncture, energy medicine) (21). Further—like some psychotherapeutic and psychosocial interventions in biomedicine—blinding within TM clinical trials is not possible when conscious awareness and/or learning is a component of the intervention itself (e.g., meditation, yoga, tai chi, expressive therapies). Notably, Cochrane reviewers have judged some psychosocial interventions (e.g., Alcoholics Anonymous, music therapy)—wherein active, participant engagement is (as in many TM therapies) a central therapeutic element—to be at low risk of performance bias, despite lack of blinding of study participants and personnel (22, 23). On the whole, a shift away from reductionist conceptualizations of health and disease has been evident in the biomedical research world in recent years, with a greater emphasis on biopsychosocial models, person-centered care, complexity science, and systems-based thinking (18). Part of this shift has included the development of research and evidence synthesis approaches that more rigorously evaluate health-related interventions—including TM approaches—with a high degree of intervention complexity (24). Further, considerations and strategies raised with respect to the cultural appropriateness of biomedical research approaches in TM contexts [e.g., Indigenous TM (25)] echo those discussed in biomedical contexts (e.g., "cultural psychiatry") (26).

Despite these advances, many TM-specific challenges persist with respect to the alignment of biomedical research approaches with TM paradigms. For instance, the application of randomized controlled trial (RCT) study designs is challenging when evaluating interventions individualized according to TM-specific diagnostic frameworks, which are often strongly distinct from biomedical diagnostic categories; for example, in Chinese medicine, "liver qi stagnation" or "kidney yin deficiency" are common diagnostic categories (13). Related challenges are especially pronounced when a TM intervention is multicomponent (e.g., herbal formulations with multiple ingredients) and/or multimodal (e.g., acupuncture with herbal medicine)—and when treatments for a single patient may be modified over the course of a therapeutic process wherein the bodily conditions are understood to be changing (13). Other challenges arise from the dominant biomedical approach to pharmacological research, as this is based on a biomedical construct of a "single active ingredient." However, the "one-disease one-target one-drug" notion is strongly at odds with many TM conceptual models for herbal medicines, wherein "whole plants" and plant combinations are understood to have various synergistic, additive and antagonistic effects on multiple targets with multiple clinical indications (27). Furthermore, in some TM systems, medicinal plants have spiritual significance and their therapeutic activity is understood in this light (5). Adding to this complexity, "relational" Indigenous knowledges "passed down through oral tradition," as well as "Indigenous sources of knowledge, such as dreams, visions, or spirit" are often poorly considered or devalued within conventional biomedical research (28).

Research about TM—which in many settings carries both clinical and cultural importance—also raises complex sociopolitical and economic questions. For example, the "bioprospecting" approach that underpins much phytopharmacological research may, as the WHO and other United Nations agencies have observed, lead to large profits for pharmaceutical sellers, without concomitant recognition of Indigenous knowledge contributions, or benefit sharing with Indigenous communities (29). Further, it cannot be ignored that TM research—like TM's integration into health systems—occurs within a sociopolitical context of biomedical dominance (5, 30), as well as

inequitable conditions of resource distribution and knowledge production (5).

Over the last 20 years, there has been an exponential growth in TM-related research and evidence synthesis (31–33). Like biomedicine, the field of TM research crosses multiple disciplinary domains, including basic science, pre-clinical, clinical, health services, economic, policy, social science, ethnomedicine and implementation research. The methods and methodologies used range from quantitative to qualitative and mixed methods, Indigenous research designs, and machine learning and omics. Paradigmatic considerations, along with questions of Indigenous cultural and intellectual property, may arise across each of these domains, all of which shape the field's broader, policy relevant evidentiary landscape. To date, however, systematic literature reviews that examine how paradigmatic considerations have been addressed in TM research have been lacking.

Multiple bodies of prior scholarship address the methodological issues to be investigated in this Review. Scholars in the TM field have critiqued the challenges posed by biomedical evidentiary hierarchies, proposing TM-relevant reconceptualizations (14, 15, 34, 35). Similar proposals have been advanced by biomedical researchers concerned with the limitations of dominant research norms (18, 19). Indigenous scholars have advanced a range of paradigmatically-aligned Indigenous research methodologies and methods, including decolonizing approaches, both within and beyond the health research field (16, 17). A previous systematic review by Saini explores areas of methodological "compatibility and convergence" between "[W]estern and [A]boriginal research designs" (36). In addition, TM scholars have developed several guidelines for the conduct and reporting of TM clinical research (37–42). Ijaz et al. scoping review of "whole systems research methods" details multiple adaptations to biomedical clinical research methods used by TM researchers (13). Some TM researchers have applied logic models and program theory to evaluate complex outcomes such as health behavior (43) and global functioning, as well as healthcare services that are integrating TM and biomedicine (44, 45). There are also examples of paradigmatically-aligned clinical practice guidelines for various conditions (46). Scholars seeking research approaches that align with TM therapeutic systems are furthermore adopting research approaches designed to evaluate complex interventions. Examples include, complexity science (47, 48) (which is the interdisciplinarity study of complex adaptive systems (49)) and systems science approaches (50), such as network pharmacology (51, 52) that have "shifted the paradigm from a "one-target, one-drug" mode to a network-target, multiple-component-therapeutics' mode" (52). Likewise, TM-focused social scientists have demonstrated the importance of addressing paradigmatic considerations within TM policy processes (53, 54).

Notwithstanding these examples of TM research, a systematic review of the literature that scopes and summarizes the characteristics of TM research approaches, with reference to questions of paradigmatic alignment, is yet to be conducted.

The scoping review whose protocol is presented in this work therefore aims to: (a) summarize the range of research approaches (i.e., methods, methodologies, frameworks and strategies) currently used (or proposed for use) in the study of TM; and (b) describe the "paradigmatic alignment" of these research approaches with the TM being studied. Scoping reviews are well suited to answering "big picture" exploratory questions such as these, which do not seek to evaluate TM nor exhaustively map all TM research (55–57). As per JBI guidance, an *a priori* conceptual framework, provisionally named "paradigmatic alignment," will steer the review process. The following sections contextualize the review methods by elaborating key definitions and presenting the project's conceptual framework.

2 Methods

An abridged version of this protocol was registered on 17 November 2023 on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY2023110071) (58). The methodology for this scoping review is informed by JBI guidelines (56), and will be reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis Scoping Review extension (PRISMA-ScR) (59). This protocol is reported according to a modified PRISMA-P reporting checklist (Supplementary File S1) (60).

2.1 Research question

The primary, two-part question driving this scoping review is:

a) What are the types and characteristics of the research approaches (i.e., methods, methodologies, frameworks and strategies) applied in, or recommended for application in, TM research; and
b) How do these TM research approaches and their affiliated research paradigms align with the therapeutic paradigm(s) of the TM being studied (i.e., paradigmatic alignment) (Table 1)?

Three related sub-questions are:

1. Where (e.g., regions, countries), by whom (e.g., cultural groups, communities/patients, practitioners, professions, governments, academic institutions) and why (e.g., rationale, purpose) are these TM research approaches being applied or recommended?
2. How have TM research approaches been applied (and/or modified) to suit different TM types, knowledges and practices, and regional, disciplinary or cultural conditions?
3. How do paradigmatically-aligned TM research approaches co-exist, contrast, complement or align with established biomedical research approaches?

TABLE 1 Paradigms and worldviews.

Research paradigm	Therapeutic paradigm	Indigenous worldview
Ontology	Ontology	Ways of being
Epistemology	Epistemology	Ways of knowing
Methodology	Clinical practice	Ways of doing

2.2 Definitions and concepts

2.2.1 Traditional medicine

The WHO defines traditional medicine (TM) as

> *the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences [I]ndigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness* (2).

Further, as WHO observes, some TM approaches may be used outside of their geographies and cultures of origin and are sometimes categorized as "complementary medicine" in such contexts.

While the WHO's definition of TM will provide a basis for the review, that definition is primarily theoretical (i.e., broadly characterizing the TM construct) rather than operational (i.e., specifying what is included within the construct). Ijaz has elsewhere advanced an operational typology theoretically based on the WHO's definition (61). Two key features of the typology make it a suitable basis to inform the review.

First, it is broadly inclusive of a wide range of Indigenous, ethnomedical and otherwise-unconventional therapeutic approaches that are widely used across the globe. This inclusive approach is consistent with the WHO's own indications that it intends the TM construct, in the context of its new global TM center, to include a wide range of "traditional, complementary, and integrative medicine" approaches (1).

Second, the typology draws close attention to knowledge paradigms as a core differentiating factor between TM approaches, whether codified (e.g., Ayurveda, Chinese medicine, homeopathy) or non-codified (e.g., many local Indigenous healing approaches and remedies in the self-care domain). It also acknowledges the overlap between therapeutic approaches that are rooted in TM paradigms, yet strongly incorporate biomedical paradigmatic perspectives (e.g., anthroposophy, chiropractic, naturopathy, osteopathy), and other complementary therapeutic approaches that have developed alongside biomedicine when practiced within the context of a biomedical paradigm (e.g., dry needling, dietary supplements used in isolation to treat a symptom or disease).

2.2.2 Research approaches and domains

In this review, the term *research approaches* will be used when referring to any aspect of the research process (i.e., methods, methodologies, frameworks, and strategies). Research *methods* refers to the specific techniques for collecting, analyzing and reporting research data. The research *methodologies* are the guiding principles and study design that inform the selection and application of the research methods. The theoretical context, rationale and/or guidelines for conducting research may be outlined in a research *framework*. Research *strategies* are the structured plans for achieving the research goals, whether for a single project or an entire field, and may encompass the overall study design(s), task sequencing, and resource allocation.

WHO Member States consistently signal the need for more TM research data to inform regulatory decisions (3). Along with clinical research evaluating TM effectiveness and safety, other evidence (information) is also required when making clinical decisions, providing public health guidance, regulating therapies and practitioners, and delivering health services. For instance, in addition to evidence about the clinical effectiveness and safety of a TM intervention, evidence about modifying factors (e.g., patient/population use; stakeholders' preferences and values; direct and indirect costs; availability, quality control, and regulatory consideration; and the benefits and risks of alternative option, including doing nothing) may warrant recommending or implementing a TM intervention despite low certainty in the clinical evidence and vice versa (62, 63). Another example is the United States of America Food and Drug Administration endorsed framework for evaluating the safety of dietary supplements considers evidence from historical (traditional) use, *in vitro* and animal studies, clinical trials, epidemiological studies, and post-market surveillance (64).

Therefore, the scoping review will examine the research approaches that are applied across a wide range of disciplinary *research domains* including basic science and preclinical research, clinical research, health services research, health economics, health technology assessments, implementation science, social sciences, ethnomedicine, policy research, and Indigenous methodologies [e.g., storytelling, yarning, talking circles, and other culture-specific methods (65)].

2.2.3 Conceptual framework: paradigmatic alignment

Conceptual frameworks can be a "critical element in effectively focusing [a] review and designing the methods to respond to the knowledge question" (66). In line with JBI guidance, an *a priori* conceptual framework will inform all stages of the scoping review's conduct, from sub-question development to search strategy and data analysis (56). This conceptual framework, provisionally termed "paradigmatic alignment," refers to the ways in which a research approach (and its paradigmatic underpinnings) align with the paradigmatic features of the TM therapeutic approach being studied. The principles of Two-Eyed Seeing (*Etuaptmumk*) (67) and a TM-specific concept of "model validity" (13) were used to inform the theoretical underpinnings of this framework and it operationalization.

2.2.3.1 Research and therapeutic paradigms

The term *paradigm* is typically used when referring to "the entire constellation of beliefs, values, techniques, and so on shared by the members of a given community" (68). Based on the work of research methodologists, who have extensively elaborated on the concept of a "research paradigm," for the purpose of this scoping review, paradigms will be understood to include three central elements: *ontology* (understandings about the nature of reality); *epistemology* (how knowledge is acquired, constructed and justified); and *practice* (e.g., methods, methodologies and techniques) (6, 7). Another reason for using this three-part construct is its alignment with the work of Indigenous scholars, who often refer to "*ways of being, knowing and doing*" when describing Indigenous "worldviews" (Table 1) (69, 70).

2.2.3.1.1 Research paradigms

Research methodologists have expounded upon "research paradigms" (such as positivism, post-positivism, realism, constructivism, interpretivism, Indigenous research paradigms) and their application according to the research purpose and context (6, 7).

The research paradigm directs the choice of the study design, data collection, analysis, and interpretation. While a specific research method or methodology may not exclusively belong to a single research paradigm, they will often align with certain research paradigms. For example, quantitative methods typically align with the positivist paradigm, while qualitative methods lend themselves to research that draws on constructivism or interpretivism (7). Notably, it is widely acknowledged that positivist and post-positivist research paradigms (along with associated quantitative methodologies like RCTs) hold sociopolitical privilege over other research paradigms and approaches (6, 7, 18). Further, it will be taken as axiomatic that every research approach has its own ontological and epistemic basis regardless of whether this is explicitly recognized by academic scholars.

2.2.3.1.2 Therapeutic paradigms

Although the term "therapeutic paradigm" is commonly used, it has not been extensively theorized. Notwithstanding, educationalists from various healthcare disciplines have discussed how therapeutic and disciplinary paradigms, along with their related clinical practices, are influenced by the ontologies and epistemologies of both the individual practitioner and their professional bodies (71, 72).

In a comparative analysis of four complex medical systems—contemporary biomedicine, homeopathy, traditional Chinese medicine, and Ayurveda—Brazilian scholar Madel Luz proposed the "medical rationalities" framework (73). Luz observed that all four systems exhibited the characteristics of a complex medical system, as they each have their own distinct cosmology (a construct similar to ontology), elements in which that cosmology is expressed as knowledge, or epistemology—including medical doctrine (that defines and guides foundational concepts for health, disease, etiology, and clinical practice), morphology (that describes that body's micro and macro structures and anatomy), and physiology (that explains the body's functional and regulatory systems) –and, areas in which epistemology and practice intersect—that is, diagnostic and therapeutic systems. In this sense, Luz's model of a "complex medical system" may be provisionally understood as similar to the concept of a "therapeutic paradigm."

Like biomedical paradigms, TM paradigms are not static and continue to evolve and shift (74, 75). In contrast however, biomedical therapeutic paradigms typically wield more political influence globally than contemporary TM therapeutic paradigms (5).

2.2.3.2 Two-eyed seeing (*Etuaptmumk*)

Two-Eyed Seeing, or *Etuaptmumk* (pronounced: eh-doo-ahp-duh-mumk), is a principle advanced by Mi'kmaq Indigenous scholars Marshall and Marshall wherein Indigenous/traditional knowledges and biomedical knowledges may equitably co-exist (67).

As the authors explain, Two-Eyed Seeing (*Etuaptmumk*):

> *refers to learning to see from one eye with the strengths of (or best in) Indigenous knowledges and ways of knowing, and learning to see from the other eye with the strengths of (or best in) Western knowledges and ways of knowing… [and] using both of these eyes together for the benefit of all. We need to utilize Two-Eyed Seeing to determine the benefits both in the modern medical science knowledges and in our Indigenous knowledges … Two-Eyed Seeing encourages that we draw upon both new technologies and traditional practices to lead to better health outcomes for everyone* (67).

This principle has been widely engaged in health research addressing traditional/Indigenous knowledges and ways of knowing, and adopted by government agencies (such as the Canadian Institutes of Health Research) (76). Constituting "Indigenous and Western *knowledge systems* as whole and, distinct in and of themselves, Two-Eyed Seeing holds that each knowledge system can only offer a partial understanding of the world … [and recognises that] no single worldview offers everything" (76). In the context of this scoping review, the central importance of Two-Eyed seeing as a guiding principle is that it explicitly recognizes—within a context of biomedical dominance—the concurrent and fundamentally equal value of distinct forms of knowledge, even though each will necessarily contribute to the domains of research, policy and clinical practice in its own way. In this sense, the principle of Two-Eyed Seeing (*Etuaptmumk*) is closely aligned with the principles of epistemic pluralism and epistemic equity, as explained below.

2.2.3.2.1 Epistemic pluralism and epistemic equity

Epistemic pluralism recognizes that multiple epistemologies (be they various biomedical or TM knowledges) may co-exist despite unequal sociopolitical power dynamics (77). It recognizes that the dominant epistemologies may become so deeply embedded within sociopolitical structures and mass culture that their underlying assumptions appear "neutral" or "universal" despite being culturally and historically situated (78). In this context, the concept of "epistemic equity" or "epistemic justice" holds that diverse epistemologies should be appropriately and fairly valued according to their unique contributions (77). Such an equitable co-existence of diverse epistemologies has also been termed "an ecology of knowledges" by decolonial scholars (79). These principles are closely aligned with the WHO's call for the appropriate integration of TM within biomedically dominant national health systems worldwide (2, 4).

2.2.3.3 Model validity

Model validity is a term that holds multiple meanings across different research communities. However, for the purpose of this review, the TM-specific use of the term will be engaged. Originally referred to as "model fit validity" by Cassidy (80), TM clinical researchers have distinctly used the term "model validity" to denote a principle that emphasizes the importance of aligning clinical research paradigms with the TM being studied (13, 81–84). With reference to biomedical contexts, where there exist commonly held paradigmatic assumptions about etiology, diagnosis, pathophysiology, and outcomes, Jonas and colleagues explain that there is often no "need to evaluate whether research methods have violated these basic assumptions" (81). However, in TM research, whose paradigmatic assumptions diverge from those biomedical, the concept of model validity gains in importance.

Much TM scholastic work has involved the development and application of specific criteria for critically appraising the model validity of TM clinical research (81–84). However, leading on from this, in a scoping review of TM whole systems research, Ijaz and colleagues used the TM-specific construct of "model validity" in their conceptual framework that "represents a commitment to actively preserving these [TM] paradigms and practices in their own right" (13). That conceptual framework aligns closely with the WHO's commitment to "protect[ing] traditional knowledge," articulated in the TM Strategy 2014–2023 (2).

Ijaz and colleagues proposed three inter-related subcategories of the model validity construct—paradigm compatibility, paradigm consistency, and paradigm specificity—with reference to TM clinical research (13). In this scoping review, the model validity construct and its three subcategories will be analytically applied to a wide range of research approaches and domains (including, but not limited to, clinical research) and, thus, require further theoretical elaboration and development. As explained below, this includes a minor adjustment to Ijaz et al. concept of "paradigm consistency," renaming it to "paradigm adapted," with the addition of a fourth subcategory of "paradigm pluralistic."

Paradigm specific research will refer to research approaches originating in a specific (therapeutic or research) paradigm that are best suited for the conduct of studies within that same paradigm. For example, placebo controlled, RCTs were developed by biomedical researchers to evaluate the efficacy of single drugs when used for a single diagnosis and quantifiably-measured outcomes. Similarly, there are traditional and Indigenous research approaches that were designed to study their own practices. For instance, there are numerous examples of culturally specific Indigenous research methods, such as talking circles, storytelling and "yarning" (65). Notably, culturally specific methods that originated in one Indigenous group may be paradigm specific and, therefore, not translatable to other Indigenous groups due to differences in their cultural practices, paradigms, and worldviews (65).

Paradigm compatible research, by contrast, is a research approach that originates in one paradigm yet may also be suitable for studying a different therapeutic paradigm. For instance, a double-blind, placebo-controlled RCT may be used in a model valid manner to evaluate TM interventions where: (a) an inert placebo can be created; (b) a TM therapeutic approach is traditionally used in isolation to treat a singular "generic" symptom; and/or (c) application of a TM therapeutic approach does not require specialized TM diagnosis or therapeutic individualization (e.g., a standardized herbal formula, supplement, or other TM drug for headache, cough, soft-tissue bruising, menopausal hot flashes, sleep quality etc.).

Pragmatic trial designs that use various randomization and recruitment methods, and often include real-world data to evaluate complex interventions in the setting where they are intended to be delivered, are another example of a research method originating in biomedical science that have been appropriately used to evaluate complex, individualized TM interventions in a model valid way (13). Similarly, researchers seeking to investigate complex TM herbal formulations (and their synergistic effects) use network pharmacology methods, developed in biomedical contexts to investigate synergistic drug combinations (85–87).

Paradigm adapted research approaches are those developed within one knowledge system adapted or modified to better fit another paradigmatic context. Examples include the adaption of a biomedical clinical trial method to include TM diagnoses in the inclusion criteria and/or for individualized treatment protocols (13), or community-based participatory research methods that are modified to incorporate "yarning" or "storytelling" (which are culturally-situated methods based in Indigenous oral traditions) (65). The TM extensions to CONSORT and PRISMA reporting guidelines are another example of such paradigmatic adaptations to established research approaches.

Finally, a fourth subcategory, termed *paradigm pluralistic,* will be provisionally added to better operationalize the model validity construct within this scoping review. Paradigm pluralism represents areas of interweaving between paradigms where two or more research approaches from different paradigms are used side-by-side. Examples include Indigenous-led co-research methods that combine ethnobotanical and preclinical research (88), clinical practice guidelines that report the confidence in the TM knowledge along with the certainty/quality of empirical research (89), and regulatory guidance for industry on how to synthesize both TM knowledge and empirical research when making health claims for regulated TM products (90).

Overall, the principle of Two-Eyed Seeing (*Etuaptmumk*) (67) is expressed across all four model validity subcategories, illustrating different ways in which biomedical and TM knowledges have the potential to fruitfully, dynamically and respectfully co-exist in research-related contexts.

2.3 Eligibility criteria

The inclusion criteria will follow the JBI scoping review framework of concept, context, and types of evidence sources (56).

In summary, the evidence sources to be included in this review will:

1. Describe or summarize the research approaches used to study TM;
2. Propose, recommend, or provide guidance for TM research;
3. Critique or articulate a rationale for developing, implementing, or applying TM research approaches; and/or
4. Provide an example of paradigmatic alignment between a specific research approach and the TM being studied.

2.3.1 Concepts

The concepts of interest that will inform the inclusion and exclusion criteria are: (1) traditional medicine, (2) research approaches, and (3) the review's conceptual framework of paradigmatic alignment that encompasses the concepts of research paradigms, therapeutic paradigms, Two-Eyed Seeing (*Etuaptmumk*) (67) and the TM-specific use of the "model validity" concept (13).

Any form of TM that aligns with the WHO's definition will be included (2, 61). Medicines with natural ingredients or derivatives when used in a biomedical setting (e.g., vitamin K for neonates, digoxin for cardiac conditions, vincristine for cancer treatment) will be excluded (91). As will biomedical healthcare approaches and related disciplines (e.g., psychiatry/psychology, physical/physiotherapy, exercise physiology, rehabilitation, occupational therapy, dietetics, lifestyle medicine, public health interventions etc.). The exception are instances when biomedical approaches are used alongside or integrated with TM (91).

The included evidence sources will describe or summarize TM research methods, methodologies, frameworks or strategies (i.e., research approaches). Sources that only discuss TM therapeutic paradigms (along with their associated knowledges and practices) will be excluded.

Based on the primary review question, technically, all documents reporting TM research could be included. Therefore, for pragmatic

reasons, the following will be excluded and will not be actively searched for:

1. Primary studies of TM, except those where it is not possible to identify a literature review that summarizes the relevant methods or methodologies, or when the primary study is deemed to be an exemplar.
2. Secondary studies, review articles, etc. that do not describe, discuss, or critique a TM research approach.
3. Secondary studies, review articles, etc. that only evaluate or discuss TM efficacy, effectiveness, safety, mechanisms of action, or the risk of bias / quality of primary TM studies. Instead, we will include overviews/umbrella reviews, mapping reviews, scoping reviews etc. that summarize review methods and methodologies. The exception will be when paradigmatically aligned synthesis methods or critical appraisal tools are used, or reviews that report a wide range of study designs.
4. Clinical practice guidelines and related consensus statements / Delphi studies for diagnosis or treatment.
5. TM monographs and related evidence sources.

2.3.2 Context

The contexts that will inform the inclusion and exclusion criteria for the scoping review are as follows.

All research domains (e.g., basic science, preclinical, clinical, health services, economic analyses, health technology assessment, implementation science, social sciences, ethnomedicine, and policy research) will be included. Indigenous methodologies such as storytelling, yarning, talking circles, and other culture-specific methods (65), that involve research "of" Indigenous peoples will only be included if the context is TM, either as a standalone concept or when integrated with biomedicine and/or mainstream health services.

All geographical locations, countries, regions, cultural contexts, and health care settings (e.g., community, self-care, primary care, secondary care, integrative or traditional health care, clinical or non-clinical settings) will be included. However, research or activities that do not directly pertain to human health or health care will be excluded, as will research for other purposes such as veterinary, agriculture, or the environment.

2.3.3 Types of evidence sources

The types of evidence sources to be included are broad, including primary and secondary research articles and other types of articles published in peer reviewed journals (e.g., viewpoint and review articles, guidelines for the conduct or reporting of TM research), gray literature (e.g., research theses, guidelines, white papers, reports, and policy documents), and books and book chapters. Inclusion of gray literature is important in the present context due to known barriers faced by TM stakeholders regarding participation within biomedically-dominant scholarly contexts (34, 92–94). Information published on websites, letters to editors, conference proceedings/abstracts, magazine and news articles, and other evidence sources will be excluded unless this is the only example identified in the search for a particular research approach or a key example of paradigmatic alignment. There are no date nor language restrictions, and all efforts will be made to translate potentially relevant evidence sources.

2.4 Search strategy

Free-text and standardized search terms will reflect general overarching TM terms, Indigenous health care approaches, TM whole systems, overarching terms for botanicals and nutraceuticals, and terms for individual TM modalities and therapies. The selection of terms were informed by search terms identified by Ng et al. operational definition of complementary, alternative and integrative medicine for literature reviews (95). The final selection of terms aimed to optimize a balance between sensitivity and specificity by focusing on the TMs terms that contrast biomedical therapeutic paradigms as outlined in a TM typology proposed by Ijaz (61) and an operational definition of Integrative Medicine for primary care research proposed by Hunter et al. (91). TM terms will be combined with terms for research approaches, methodological approaches for evaluating complex phenomena, and other review concepts (e.g., epistemology, paradigm, model validity, fit-for-purpose). Search term syntax, fields and languages will be tailored according to the database that is searched.

To account for the exploratory nature of the scoping review question and sub-questions, database searching will be staggered and continue concurrently with analysis until data saturation is reached (i.e., no new information is identified through further literature searching). This approach draws on qualitative research methodology where iterative techniques, such as the constant comparative method, are applied when determining data saturation (96). While all TM, research domains and research approaches will be included, it is impractical to search for, and include every published example. Therefore, data saturation will focus on sampling the overarching categories outlined in scoping review matrix (Figure 1). These are: (a) the TM research approaches (methodologies, methods, strategies and frameworks); (b) TM research domains (basic science/preclinical research, clinical/health services, and social science/ethnomedicine); (c) different types of TM systems and practices (non-codified Indigenous, codified whole systems, and other complementary therapeutic approaches including self-care); and (d) the various contexts (location, knowledge users) where these TM research approaches were applied, discussed or recommended. To align with the review's focus on paradigmatic alignment, data saturation will emphasize TM therapeutic paradigms that sharply contrast biomedical paradigms.

The Category I databases listed in Table 1 will first be searched using the free-text and standardized search terms outlined in Supplementary File S2 that were designed for the English language. Notwithstanding this English-language bias, relevant articles/citations published in languages other than English will be included and the index terms will be tailored for the databases searched. When data saturation is not reached, additional focused searches for a key population, concept, and/or context will be conducted, including non-English languages (e.g., Arabic, Chinese, French, Hindi, Japanese, Korean, Spanish, Portuguese, Thai) with corresponding search strategies using one or more of the Category I or II databases (Table 2). Except for some secondary focused databases searches, databases will be searched from inception.

Protocol-driven search strategies, will be used alongside iterative search methods, such as citation tracking (97), pearl growing/ snowballing (97, 98), and CLUSTER searching (99). This strategy is recommended for systematic reviews of complex evidence (97–100). Other tools such as PubMed Miner (101) will be used to refine additional

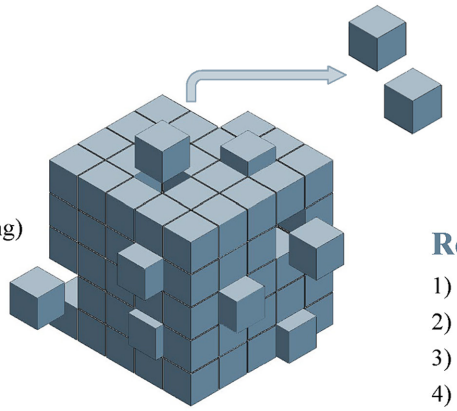

FIGURE 1
Scoping review matrix.

database search strategies. Searches will be supplemented by information and documents known to members of the Review Team, the WHO TM Evidence Task Force, and other knowledge users through the Review Team's regional outreach strategy. Authors will only be contacted about key information that is needed to directly answer the review's questions. All procedures will be documented for transparent reporting.

2.4.1 Screening, selection, and data extraction

All identified citations from database searches that can be exported in RIS format will be collated and uploaded into EndNote 20 software (102) for automatic linking of available full texts and initial screening for duplicates. Covidence systematic review software (103) will then be used for a second screening of duplicates, that will be followed by title/abstract screening, full text screening, and preliminary data extraction of the included articles. For database searches where this strategy is not feasible, we will use alternate comparable methods.

Following calibration exercises, two reviewers will independently conduct title/abstract and full text screening. Inter-rater reliability will be checked and reported using the Covidence functions. Due to the broad nature of the research question, over 10,000 citations may need to be screened. If the inter-rater reliability is high after the first round of screening (e.g., percentage agreement >80%), rapid review methods may be employed for additional rounds wherein, following calibration exercises, single reviewers screen and a second reviewer screens the excluded citations (104). Disagreements between reviewers will be resolved via consensus.

Single reviewers will extract data according to a prespecified, piloted data extraction template in Covidence (Supplementary File S3—draft extraction form); a second reviewer will verify data extraction. The details of any modifications will be reported. Disagreements will be resolved via consensus. Electronic spreadsheets and Taguette software (105) will be used when extracting, sorting and categorizing data for the supplementary qualitative data analyses.

2.5 Quality appraisal

Quality appraisal (e.g., risk of bias) assessments will not be conducted for all included evidence sources. However, if the evidence source was not peer reviewed, then prior to using it to inform the in-depth, qualitative analysis, the JBI Critical Appraisal Tools will be used (106). Notably, the JBI suite includes appraisal tools for different types of textual evidence and all checklists have an overall appraisal recommendation to include, exclude, or seek further information. Single, senior reviewers will conduct the appraisals. The decision to include or exclude an evidence source will be verified by another senior reviewer. Disagreements will be resolved via consensus.

2.6 Analysis and evidence synthesis

The analysis will follow JBI guidance for scoping reviews (56, 107). To account for the substantial heterogeneity and diversity of data that is likely to result from the study's broad, exploratory research questions and the multidimensional sampling frame, subsequent analysis and synthesis of findings, will proceed in stages. This will be informed by the review's conceptual framework of paradigmatic alignment and related concepts previously outlined.

The first stage of the analysis will focus on describing the types and range of research approaches used to study the various forms of TM across diverse contexts. Data extracted in Covidence will be exported into electronic spreadsheets. Analysis will begin by summarizing the characteristics of the evidence sources (e.g., citation details, publication type and year, countries of authors, declarations) and the types of TM, research domains and research approaches that were applied, discussed or recommended. The scoping review matrix in Figure 1. illustrates the overarching categories that will be used for sorting and charting the

TABLE 2 Scoping review and mixed methods systematic review databases to be searched.

Category I	Category II
EBSCOhost • Academic Search Complete • Anthropology Plus • CINAHL Complete • Humanities Source Ultimate • Psychology and Behavioral Sciences Collection • Sociology Source Ultimate **Ovid** • Allied and Complementary Medicine Database (AMED) • EBM Reviews—Cochrane Methodology Register • MEDLINE • APA PsycInfo **Global Index Medicus (WHO databases)** • African Index Medicus (AIM) • Index Medicus for the Eastern Mediterranean Region (IMEMR) • Index Medicus for the South-East Asia Region (IMSEAR) • Latin American and Caribbean Health Sciences Literature (LILACS) • Western Pacific Region Index Medicus (WPRO)	• African Journals Online (AJOL) • Applied Social Sciences Index and Abstracts (ASSIA) • AMEDfind (AMED R&D Project Database) • AYUSH Research portal • China National Knowledge Infrastructure (CNKI) • Chinese Scientific Journals Database (VIP) • Core Outcome Measures in Effectiveness Trials (COMET) Database • Digital Helpline for Ayurveda Research Articles (DHARA) • eMarefa (Digital Arabic Database) • Embase • Enhancing the QUAlity and Transparency Of health Research (EQUATOR) • Ethnic NewsWatch • Google Scholar • Indexing of Indian Medical Journals (INDMED) • Japan Medical Abstracts Society (Ichushi-Web) • Japan Science and Technology Information Aggregator • J-STAGE • Korean studies Information Service System (KISS) • Ministry of health, labor and Welfare (MHLW) Grants system database (Japan) • Scopus • Shodh Ganga • Thai Journals Online (ThaiJO) • ThaiLIS/Thai Digital Collection (TDC) • Wanfang Data • WHO Institutional Repository for Information Sharing (IRIS) • Web of Science (all databases)

data. Additional subcategories may be inductively introduced or developed over the course of the analytic process.

Data extraction in Covidence will include preliminary coding to flag potentially relevant evidence sources (Supplementary File S3—data extraction form) for further in-depth analysis. A basic qualitative content analysis (107) will then be conducted to explore the question of paradigmatic alignment and other related sub-questions. After data immersion, analysis will initially proceed deductively in relation to the review's conceptual framework and the scoping review matrix (Figure 1). Reviewers may also flag emergent topics that were not addressed in the *a priori* sub-questions yet appear relevant to the review. Other qualitative methods, such as "following the thread" (108), the constant comparative method (96), and deductive and inductive thematic methods (109, 110) may, therefore, be indicated as the qualitative content analysis proceeds. After reaching consensus about further topics or sub-questions that warrant further exploration, literature searching and analysis will then continue until saturation is reached. All *post hoc* changes or modification to this protocol will be transparently reported.

Further, in seeking answers to a specific sub-question, or in characterizing a particular topic, reviewers will identify illustrative exemplars. To facilitate knowledge user engagement with review findings, some of these exemplars will be highlighted in the results. When selecting and reporting exemplars, we will aim toward regional and TM disciplinary inclusivity.

A narrative summary of the finding supported by relevant tables and figures will characterize the diverse range of research approaches employed in TM research. Draft charting tables are reported in Supplementary File S4.

2.7 Knowledge user engagement

Involving knowledge users (stakeholders) recognizes their perspectives, expertise, and experiences, ensuring research outcomes are relevant, applicable and useful for end-users. In line with JBI guidance on knowledge user engagement for scoping reviews (111), from the outset, a Review Team was formed, composed of two dozen TM research experts from all global regions (see: Acknowledgements). Review Team members are primarily established scholars in the TM field with training and expertise in a wide range of research methodologies (including biomedical research methods, sociology, implementation science, and Indigenous research methodologies) as well as clinician-scientists with dual biomedical-TM training.

Review team members were also selected with the following principles in mind: regional and contextual representation and representation across diverse research domains and TM types. Following WHO requirements, all Review Team members must formally disclose their varied engagements to manage potential conflicts of interest. The team members provide expert advice on all stages of the review. Membership may be expanded to fill key knowledge gaps. Review Team members will also support regional outreach through their networks. Additional stakeholder consultations that informed the development of this protocol included a roundtable discussion between TM experts appointed by the six WHO regional head offices at the 2023 WHO Traditional Medicine Global Summit, India (August 2023), and feedback from the TM Evidence Task Force of global experts appointed by the WHO to advise on the conduct of commissioned reviews.

3 Discussion

This protocol outlines plans for a scoping review that will describe the range of research approaches used to study various forms of TM and characterize these approaches with reference to the concept of "paradigmatic alignment." Commissioned by the WHO, the review aims to support development of a policy-relevant global TM research agenda. At once, the review's design seeks to advance the WHO's articulated goal of TM's evidence-informed integration within health systems globally, while explicitly recognizing the value of traditional and Indigenous therapeutic knowledges within a biomedically-dominant therapeutic landscape. The review findings will seek to highlight methodological trends and innovations in paradigmatically aligned TM research. As such, the work will reflect demands for healthcare to be informed by the best available evidence.

The conceptual framework proposed for this review aligns well with broader trends in the biomedical context of evidence-based medicine (EBM). "A New Framework for Causal Inference in the Health and Social Sciences" (112), often referred to as EBM+ (18, 113), calls for what is increasingly termed *evidential pluralism*. Proponents of this framework are challenging the dominant evidentiary hierarchy, "which favor[s] probabilistic evidence from clinical trials" (18). The importance of integrating other sources of evidence, such as mechanistic studies and a broader range of quantitative and qualitative evidence, is emphasized (18, 113, 114). Although non-biomedical therapeutic paradigms are not explicitly addressed, the underlying tenets of evidential pluralism echo the perspectives of TM scholars who have similarly critiqued the limitations of biomedicine's evidentiary hierarchy (13–15, 35). Evidential pluralism also parallels the WHO's recognition of both "scientific" (formal) and "tacit" (informal, stakeholder-informed) forms of evidence as contextually relevant to policy making (115). Critically, the planned scoping review extends biomedical critiques of evidentiary norms to recognize the potential contributions of TM therapeutic and research paradigms—that is, their ontologies, epistemologies and practices—to the broader world of health care.

The broad, exploratory nature of the research questions, coupled with the inclusion of a wide range of disciplinary approaches to research, aims to ensure that the breadth of TM research required for clinical decision-making and policy is described. Notwithstanding this strength, the decision will present substantial logistical challenges. There are thousands of potentially eligible evidence sources that are indexed across hundreds of databases in different languages. We considered limiting the search date parameters. However, key documents such as the WHO *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine* (116), published in 2000, would then be excluded. Instead, other compromises are planned. Evidence sources published in languages other than English will not be identified during the first round of database searches, unless they are indexed with the searched controlled vocabulary terms (e.g., MeSH, DeCS), the title or abstract is also indexed with an English-language translation, or they are already known to the review team. Additionally, instead of conducting an exhaustive literature review, we plan to limit our analysis to only describing and characterizing the range of research approaches. Literature searching will stop when data saturation is reached. Thus, the search strategy cannot accurately quantify the frequencies of different research approaches nor to identify gaps in their application according to TM type, health care setting or region.

Operationalizing the conceptual framework is another potential challenge with the execution of this protocol. Although a similar framework was previously used in a scoping review of whole systems clinical research (13) its broader applicability is yet to be ascertained and as such, may require further modifications as the analysis proceeds. As per scoping review guidance that cautions against reviewers synthesizing or critically appraising the findings (107, 117), theoretical, iterative and synthesis methods will not be used. The review will stop short of judging, critiquing or recommending specific research approaches. Notwithstanding, the findings of this review will lay the groundwork for further studies that are designed to explore and interrogate the complexities and challenges with conducting, synthesizing and implementing TM research across global contexts.

Engaging with knowledge users throughout all stages of a literature review is another design strength (111). However, due to practical constraints, most of the knowledge users involved in this scoping review are TM researchers, many of whom reflect either the authors' or the WHO's academic networks. Despite efforts to achieve diverse global and disciplinary representation, there are inevitable gaps. Some of our knowledge users have dual roles as healthcare practitioners or possess broader non-TM research, health service or policy experience. However, there will only be limited, informal engagement with other key stakeholders, such as patients, communities, and practitioners who are not researchers, health service providers, and policy-makers.

Finally, the limitations of the scoping review methodology must be noted. Like other "big picture" reviews (57), scoping reviews are not designed to answer specific questions, such as which TM research approaches are most suitable or should be recommended. Instead, by describing and cataloging the range of research methods, methodologies, frameworks and strategies that have been applied or recommended the findings will provide contextual information about their potential roles in conducting paradigmatically aligned research.

Even though the planned scoping review is focused on a defined field of interest—TM research—with reference to a conceptual focus of paradigmatic alignment, its design, conceptual underpinnings, and anticipated findings may have broader relevance. As previously noted, scholars, clinicians, and decision makers in other fields face similar challenges due to intervention or system complexity, or misalignment of their therapeutic paradigm with research norms. By recognizing the value of multiple approaches to knowledge and practice, the scoping review seeks to advance scholarly insights of critical value in an increasingly pluralistic and globalized world.

Author contributions

NI: Conceptualization, Funding acquisition, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. JH: Conceptualization, Funding acquisition, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. SG: Validation, Writing – review & editing. KT: Project administration, Validation, Writing – review & editing.

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Conflict of interest

JH has received payments, travel and/or accommodation for providing expert advice about traditional, complementary and integrative medicine to industry, government bodies and non-government organizations. NI, JH, and SG have spoken at conferences or provided consultations for which honoraria, registration, travel and/or accommodation have been paid for by the organizers.

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1409392/full#supplementary-material

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Effect of the health and wellness Kneipp concept on health promotion and reduction of sick days for kindergarten children: a cluster randomized controlled trial protocol

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Background: The holistic health and wellness Kneipp concept, has a long tradition in Europe with demonstrated health benefits. Based on the five elements of the Kneipp concept, kindergartens in and around Germany are used to certify "Kneipp Kindergartens" that practice regular Kneipp applications and activities: cold water applications, exercise, nutrition, herbs and mind-body interventions. Little is known about the potential health benefits for children, however. This study protocol describes our study design and intervention of the Kita Kneipp Study to investigate the effect of the Kneipp concept on kindergarten children aged 2–6 years.

Methods and design: The Kita Kneipp Study, registered with the German Clinical Trial Register (DRKS-ID: DRKS00029275), is a confirmatory, mixed-method, two-armed, waitlist, clinical, cluster randomized controlled trial (RCT). Kindergartens in Berlin, Germany that would like to implement the Kneipp concept into their facility will be recruited and randomized to the intervention or control group. Changes in the number of kindergarten sick days will be the primary outcome measure. Kindergarten attendance and reason for absence including illness will be collected on a weekly basis at two time points for 6 weeks from the parents and kindergarten directors: baseline and 1 year after baseline. Secondary outcomes will measure cold symptoms through the Common Cold Questionnaire (CCQ) and National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Scales describing gastroenterological-based symptoms Kindergarten educator sick days will be aggregately reported for the same time period. Kneipp concept activities will be recorded on a weekly basis over the one-year intervention period. To understand the experience of Kneipp concept implementation and possible changes in the kindergarten, expert interviews

will be conducted with intervention kindergarten educators and focused ethnographies will be planned to observe and analyze the intervention activities.

Discussion: This mixed method study design has potential to help identify if the Kneipp concept can be used for salutogenic purposes among young children and provide insights and experience of the implementation and practicing a holistic health and wellness concept in a kindergarten setting.

KEYWORDS

Kneipp, child health promotion, salutogenesis, kindergarten, hydrotherapy, lifestyle wellness, integrative medicine, common cold questionnaire

1 Introduction

Kneipp therapy is a holistic health, lifestyle and wellness approach that is embedded within German traditional medicine, based on complementary and naturopathy health concepts. The concept is named after the German priest and healer Sebastian Kneipp (1821–1897) who promoted the use of cold-water application from hydrotherapy in combination with a holistic health concept. Five principal elements are used for maintaining and sustaining health: temperature stimuli through cold (and warm) water applications, exercise, wholesome, plant-based, regional and seasonal nutrition, herbs and mind- body approaches (see Figure 1: Five Elements of Kneipp). This system, known as Kneipp therapy, is most well-known in German speaking countries and has one of the largest lay organizations for health and wellness in Germany (1). Kneipp therapy is used by trained and untrained practitioners in health promotion and for the prevention against diseases across a lifespan (2).

Childhood infection, especially in young children, creates a societal burden because a sick child at home requires a caregiver, who often must take a free day off work (3). Children and educators often experience cross-infections in kindergartens, contributing to the total burden of illness (4).

There is extensive research about the positive effects of a healthy diet and exercise on children's overall health (5, 6). However, there is further research needed on Kneipp interventions especially with focus on the (cold) water applications and their effects on children's health.

In a recent systematic review, evidence of the effects of Kneipp therapy across the life cycle were summarized; beneficial effects were noted for a wide range of conditions including varicose veins,

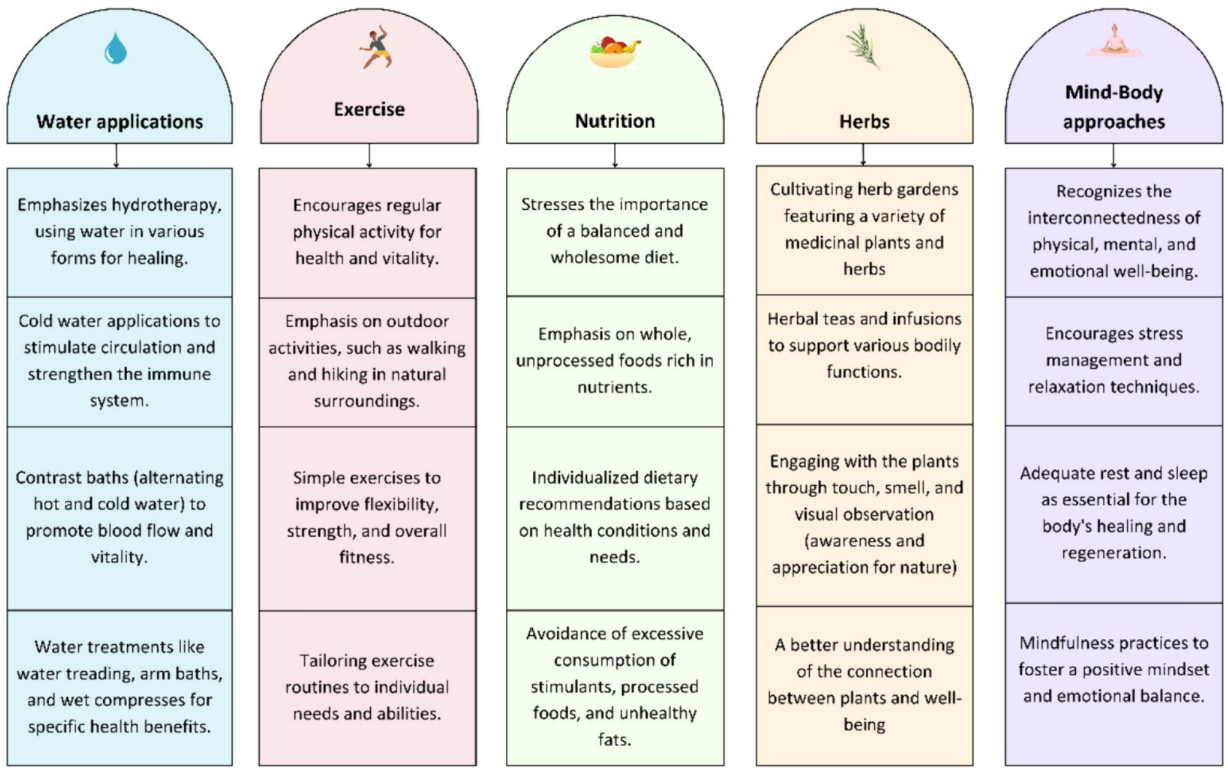

FIGURE 1
Five Elements of Kneipp.

menopausal syndrome, fever in children, absenteeism related to upper respiratory tract infections, hypertension, mild heart failure, sleep disturbances, cognition, and emotional functioning (7). The overall health benefits for children are inconclusive however, and few studies have been conducted with children and Kneipp therapy. Two pilot studies conducted with children aged 3–6 years that provide the foundation for this study found no significant reduction in infections through secretory IgA or fever but did demonstrate a lowered number of sick days for this sample (8, 9).

German kindergarten facilities, daycares through preschool system caring for young children between the ages of one to 6 years old, are currently being certified with a Kneipp concept that implements all five elements in the day care setting (10). Therefore, investigating whether a possible correlation exists between an implemented Kneipp concept and the number of absent sick days of children in such facilities would be of interest. For this purpose, we have planned a study with the aim to evaluate effects by monitoring absent sick days of children in kindergartens intending to implement a Kneipp concept and comparing this to data from kindergartens who are waitlisted to implement the Kneipp concept until after the study data has been collected. In order to evaluate the process of the concept-implementation and experiential dynamics, a qualitative approach will be used.

The following study questions will be examined:

- Quantitative hypothesis: Will the implementation of a child-friendly Kneipp concept in kindergartens improve health of kindergarten children aged 2–6 years, resulting in fewer illness-related absences from the kindergarten?
- Qualitative research question: How does the kindergarten-appropriate implementation of the holistic health and wellness Kneipp concept change the overall quality of work, dynamics, and atmosphere within the kindergarten?

2 Methods

The Kita Kneipp Study is a confirmatory, mixed-method, two-armed, waitlist, clinical, cluster RCT that was registered with the German Clinical Trial Register (DRKS-ID: DRKS00029275) on November 10, 2023, and approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin (Application number: EA2/122/22, approved on Mai 09, 2023). It follows the standards of the Helsinki convention of good clinical practices.

This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Guidelines for reporting study protocols (11).

2.1 Study setting

Prior to study data collection, the study team interviewed already-certified kindergarten directors to find out aspects of the Kneipp concept that worked well in the kindergarten setting or were potentially problematic. This expert input was used to adapt our study design to the recruited facilities.

Kindergartens that had interest in becoming certified as Kneipp kindergartens and whose personnel wanted to take part in an applied Kneipp training for kindergartens were to be recruited to the study through contacts at the Berlin Senate level who have access to a network of Berlin kindergartens. A requirement for participation is the willingness of the facilities to be randomized. Further, inclusion criteria stipulated that the kindergarten facilities be compatible for Kneipp interventions, for example that they had suitable shower facilities, outdoor spaces, and room for indoor exercise (12). Included kindergartens will be recruited in Berlin, Germany. Informational evenings are to be held with kindergarten directors, caregivers and personnel to inform about the project, and to answer questions about the study purposes, design, data protection and inclusion. Written consent for participation in the study is required from all caregivers and educators.

The study will be conducted with two-time measurement periods, each 6 weeks long. Parents will complete an online at the end of each week of the data collection period. At the beginning of each measurement period, parents will be asked to complete an initial onboarding questionnaire containing socioeconomic background information about the family. The first measurement period will be planned in autumn 2022, followed by a second measurement in the autumn of 2023. Kindergarten directors will also be asked to record absences and reasons for absence of the participating children and educators and report them after completion of each 6-week data collection period.

The quantitative data of the study will evaluate the number of sick days and symptoms for children aged 2–6 years in kindergartens that implement kindergarten-appropriate, Kneipp applications, compared to the kindergartens in the waitlist group.

2.2 Eligibility criteria

Eligibility crite shown in Table 1.

2.3 Interventions and blinding

Prior to being randomized into the group, kindergartens will be matched-paired according to socio-demographic information for Berlin neighborhoods and address (13, 14). Then kindergarten pairs will be cluster-randomized via computer randomization program by a team member without prior or background knowledge of kindergartens into the immediate start or waitlist group. Once they are allocated by the randomizing computer program into intervention or waitlist groups, they will be informed which group they are in. If a kindergarten declines to take part in the study based on group allocation, another replacement kindergarten will be selected for the recruitment vacancy.

2.3.1 Intervention group

First, the kindergarten educators of the intervention group will receive a planned 4-day (40 h) training of the Kneipp concept (see Figure 2: Curriculum Overview. Kneipp Educator Training) (10). The training will be focused on integrating the Kneipp concept with young children in the kindergarten setting with the 5 elements. Educators from intervention facilities will be trained together to allow an

TABLE 1 Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Kindergartens	• Berlin kindergartens seeking certification as Kneipp daycare facilities with Kneipp-Bund e.V. • Interested in participating in associated training via Sebastian Kneipp Academy. • Willingness to engage in pair-randomized group assignment. • Must provide pedagogical staff for training as Kneipp educators in autumn 2022 or 2023/24. • Implementation of Kneipp concept immediately after training.	• Kindergartens already implementing holistic health concepts (e.g., Kneipp, anthroposophical). • Staff restricted from participating in training. • Facilities unsuitable for implementing the Kneipp concept. • Daycare center involved in another study preventing participation in this one.
Educators	• Healthy educators, regardless of gender • Working in the participating facilities • 18–65 years of age • Informed consent available	• Serious chronic or acute illnesses inhibiting participation. • Not speaking or understanding German
Caregivers	• Caregivers, regardless of gender • 18 years and older • At least one child in a participating daycare center included in the study. • Informed consent available	• Serious chronic or acute illness preventing participation in the data collection. • Not speaking or understanding German at the appropriate level for reading and completing study information
Children	• Healthy children, regardless of gender • 2–6 years • Care in the participating kindergartens during study period • Consent of the caregivers	• Serious chronic or acute illness • Not speaking or understanding German • Age under 2y/o

exchange among participants, enhance collective learning, share insights, and foster an environment for discussions. The training program will be conducted by two experienced trainers from Kneipp-Bund e.V.: one with expertise in hydrotherapy and mind–body practices, and the other specialized in herbs and nutrition.

The waitlist group will also complete the training after the last data collection period. While there will be project mandate as to which interventions must be conducted, the educators in the intervention group will be encouraged to commence interventions directly after the training, particularly with emphasis and daily practice of cold-water applications. (see Figure 1: Five Elements of Kneipp) Intervention activities will be reported on a weekly basis by the kindergartens and recorded by the team. Furthermore, a qualitative methodology is employed to evaluate whether introducing the Kneipp concept will affect factors such as stress levels, quality of work in the kindergarten environment, interactions among children and educators. This involves conducting focused ethnography (15) on two separate days (one in spring/summer and one in autumn/winter) to obtain a better overview of the applications used in different seasons. Semi-structured interviews will be conducted with educators and kindergarten directors to understand and evaluate the use of the interventions, as well as to detect possible changes among kindergarten group dynamics and kindergarten educators. Maximum variation sampling strategy will be applied to provide rich and diverse perspectives, used for answering the qualitative research question. All kindergarten directors and at least 2 other educators from all the intervention facilities will be interviewed. The interviews will be conducted in the kindergarten facilities by a medical doctorate student (MG) until data saturation is reached. Throughout the process regular meetings with a group of qualitative researchers will be organized, where the means of data collection and analyzing process will be discussed, evaluated and reflected.

Another focus of the qualitative evaluation is to assess the feasibility of conducting larger multi-centric randomized studies in this context and the potential future implementation of hydrotherapy in kindergartens.

2.3.2 Waitlist group

The educators in the waitlist group serving as the control will not begin practicing the Kneipp concept until after the second data collection period, after which they will participate in a training.

2.4 Outcomes

The primary outcome measure is the number of absent days due to illness among 2-6-year-old children in randomized Berlin kindergartens for the Kneipp concept intervention kindergartens compared to the matched waitlist kindergartens over two time points (baseline prior to the intervention and 12 months after baseline).

Additionally, the CCQ (16) and the NCI-CTCAE Scales (17) describing gastroenterological-based symptoms will be used as a secondary outcome measure at each of the two timepoints as well. The study will also gather data on the number of days educators are absent due to sickness. This information will be subjected to statistical analysis as an additional secondary outcome measure, aiming to identify potential correlations between the absence of educators and that of the children.

Summarized findings will identify categories and themes from the qualitative content analysis of observations and interviews highlighting the practice and experiences of implementing Kneipp in the kindergarten and perceived changes.

2.5 Sample size

The sample size selection was formed by a preceding non-randomized controlled study (8) which focused on kindergarten

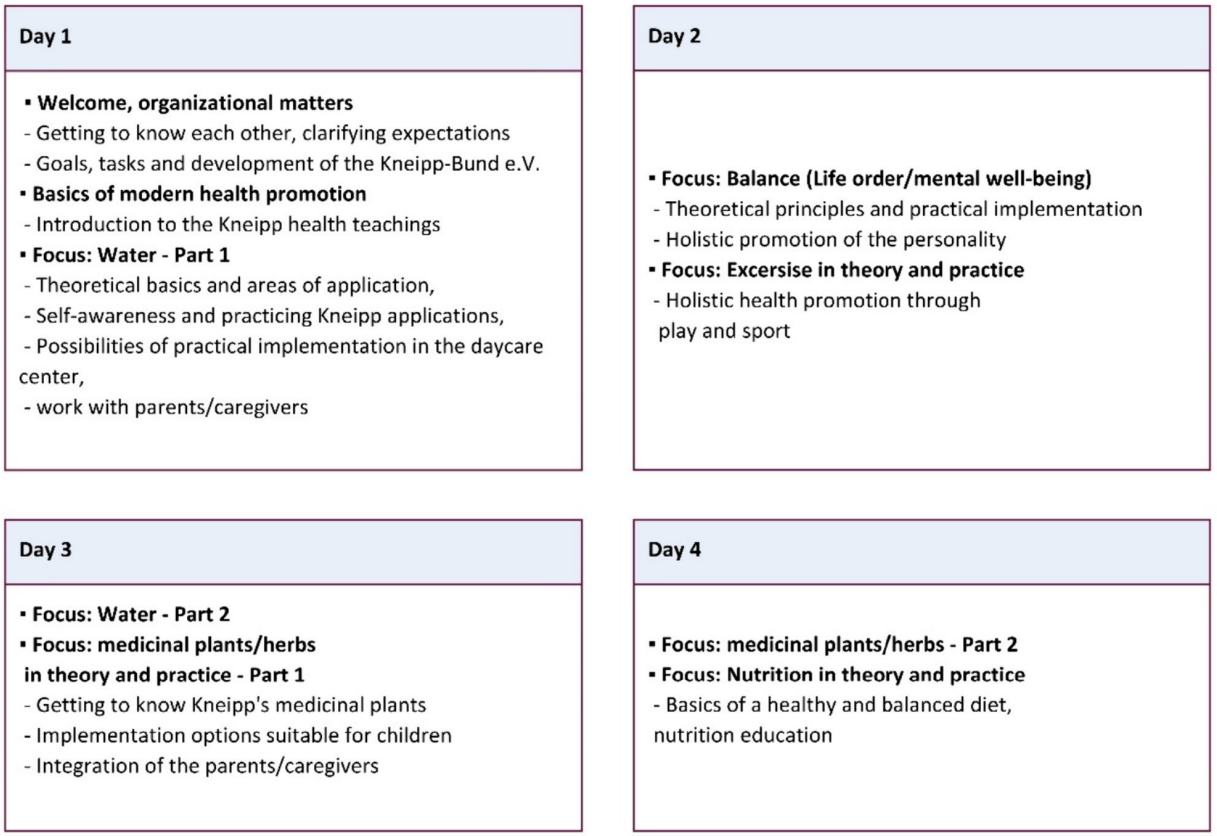

FIGURE 2
Curriculum overview. Kneipp Educator Training.

sick days as a primary outcome. The study employed a Chi2-Test (categorizing kindergarten sick days as yes/no), revealing an effect size of ω (omega) = 0.41, equivalent to a Cohen's d = 0.66 (8). Recognizing the non-randomized nature of the prior trial, the effect size was conservatively adjusted in half to φ (phi) = 0.205. With standard parameters set at α (alpha) = 0.05 (indicating a 5% probability of error in two-sided testing for differences), a power of 80% (β (beta) = 0.20), and accounting for an estimated dropout rate of approximately 20%, the optimal sample size for the current study was determined to be 240 child participants. The number of recruited matched kindergarten pairs will be based on the total calculated sample size.

Using a sampling strategy of maximum variation, semi-structured qualitative expert interviews will be planned with up to 15 kindergarten educators in the intervention facilities, while two focused ethnography observations will be each of the intervention kindergartens.

2.6 Recruitment, randomization, and assignment of intervention

Gate keepers at the Berlin governing structures responsible for kindergartens, contact leads from cooperative partners in Berlin will identify interested kindergartens. Members of the study team (SB – experienced scientific researcher, study coordination, AT – study administration) will contact these via email in which a flyer about the project will be included as additional information. Once interested, kindergartens will be contacted via telephone and site feasibility will be assessed for inclusion.

After being recruited to the study, kindergartens with a similar socio-economic level will be match-paired according to statistical demographic analysis of locations in Berlin (14).

The kindergartens will then be randomized within their matched pair to either the intervention or the waitlist group using the randomizing function of Python 3.10.6, executed by an experienced biostatistician (FK). The allocated study group will not be blinded, as this would not be possible due to the nature of the interventions. Therefore, the kindergartens, caregivers and children will be aware whether they are in the Kneipp or in the waitlist group.

2.7 Data collection and management

The study will be conducted with two-time measurement periods, each 6 weeks long, whereby caregivers will complete an online questionnaire via online survey based on the CCQ and the NCI-CTCAE Scales describing gastroenterological-based symptoms at the end of each week of the data collection period.

At the beginning of each measurement period, caregivers will be asked to complete an initial onboarding questionnaire containing socioeconomic background information about the family. The first measurement period will be planned in autumn 2022, followed by a

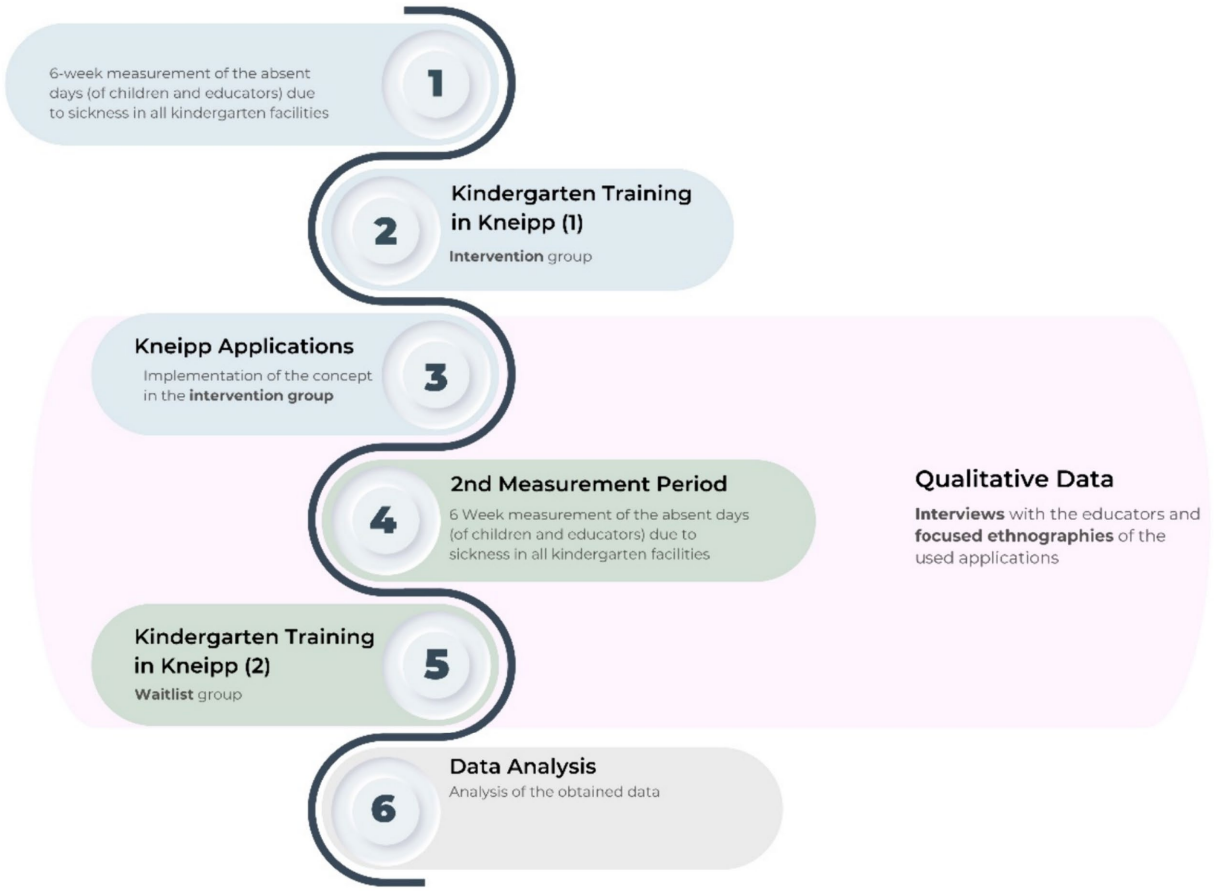

FIGURE 3
Data collection flowchart.

second measurement in the autumn of 2023 (see Figure 3: Data Collection Flowchart).

All teachers and caregivers will be informed about the purpose and implementation of the data collection as part of the evaluation via printed information sheets. The educator's and parent's written consent to participate will be collected (on paper) by the kindergarten directors. The following data will be recorded: Name, gender, date of birth, email, telephone number. Consents will be filed in a project folder and stored in a lockable office belonging to the kindergarten directors. The folders will be periodically checked during site visits by the study team (SB, MG – medical doctoral student, study coordination).

Focused ethnographies will be planned with the kindergarten staff to ensure that visits coincide with planned interventions. Based on these visits, willing staff will be asked to participate in a separately scheduled expert interview. Interviews will be audio-recorded, auto-transcribed via f4x (audiotranskription.de), corrected and pseudonymized. Transcripts and observation protocols will be uploaded and analyzed on a single computer with the qualitative analysis software MAXQDA 24 (Release 24.2.0).

At the beginning of the study, the study coordinator (SB) will create an electronic folder with a pseudonym for each participating kindergarten on a secure server. Documentation files with the following data will be stored in this folder:

- Main target parameters (missed days because of an infection)
- Secondary target parameters (CCQ)
- Interview audio and transcripts
- Interview and observation field notes.

All results will be analyzed through anonymous aggregated data (quantitative part) or with the use of pseudonyms (qualitative part).

All collected study data will be collected and handled conforming to the Berlin Data protection Law (Berliner Datenschutzgesetz – BlnDSG) and in adherence with the Declaration of Helsinki code of ethics. The files will be stored in their anonymized and/or pseudonymized form after completion of the study on a Charité server for 10 years. Within the electronic survey system (SoSci), the participants are encrypted using IDs and are therefore not identifiable. The study coordinator (SB) will store the encryption list and will keep it in a locked cabinet. Access to the collected data will be restricted to members of the study team (SB, AT, MG, MB, GS, SW).

The onboarding and weekly questionnaires will be sent using the collected parent emails using the Charité version of the software SoSci (Program-Version 3.5.00).

After an initial invitation, caregivers who have not completed the survey will be reminded to complete it on a weekly basis over 6 weeks.

Additionally, a study assistant (AT) will contact caregivers of missing entries via telephone. In addition to the online entries, the missed kindergarten days will be documented by the kindergarten facilities and likewise measured at the two time points for 6 weeks at baseline and 12 months after baseline.

The total number of kindergarten educator sick days will also be documented without descriptive personal data and kindergartens will report the used interventions weekly to the study assistant.

2.8 Statistical methods

The study will be published in a peer-reviewed academic journal. Analyses of data will be performed after the collection is finalized according to the following hypotheses:

- Primary Efficacy Hypothesis (Infection days leading to absence):
- Primary Null Hypothesis (H0): Implementation of a child-friendly Kneipp concept in the kindergartens does not lead to a significant reduction in infection-related absenteeism, after 12 months.
- Alternative Hypothesis (H1): Implementation of child-friendly Kneipp concept in the kindergartens results in a significant reduction in infection-related absenteeism, after 12 months.

Participant characteristics, stratified by groups (Kneipp vs. Control) will be presented. For continuous variables, descriptive statistics such as mean, standard deviation, and range will be calculated, while frequencies and percentages will be used for categorical variables.

The primary outcome will be the number of sick days reported to the kindergarten. To account for the expected overdispersion (right-skewed data because of high zero counts) in the count data, we will employ a negative binomial regression model. This model will include the group (Kneipp vs. Control) and the number of sick days at baseline as predictors. We will integrate unique kindergarten identifiers to determine if cluster effects exist.

For secondary outcome analysis, we will conduct an independent t-tests to compare the mean Common Cold Questionnaire (CCQ) scores between the Kneipp and Control groups. To investigate the interaction effects of group and sex, and group and age on CCQ scores, a two-way ANOVA will be performed. This model will include the main effects of group, sex, and age, as well as their interactions. If significant interactions are identified, post-hoc analyses will be conducted. Correlation analysis will involve calculating Spearman's correlation coefficients to assess the relationships between CCQ scores and the number of sick days, and between CCQ scores and age. The correlation (ρ) will be interpreted based on conventional guidelines. To compare the frequencies of health outcomes such as colds, bronchitis, lung inflammation, antibiotic use, and gastrointestinal infections between the Kneipp and Control groups, chi-square tests will be performed. If the assumptions of the chi-square test are violated due to expected frequencies being less than 5, Fisher's exact test will be used instead.

The compliance analysis will be conducted by considering both the Intention-to-Treat (ITT) and Per-Protocol (PP) populations. The ITT population will include all children from whom kindergarten reports are available. The PP population will consist of children who strictly followed the prescribed treatment and for whom complete data is available.

For handling missing data in the ITT approach, multiple imputation will be used. Sensitivity analyses will also be performed to compare the results from the ITT and PP approaches to ensure robustness of the findings.

To ensure the validity of our model assumptions, normality of the data distribution for continuous outcomes will be assessed using the Shapiro–Wilk test. If necessary, data will be transformed using appropriate methods, such as log transformation, to meet the assumptions on the statistical tests. All analysis will be considered significant if $p < 0.05$ and will be conducted using R in its current version.

Qualitative data, focused ethnography observation protocols and interview transcripts, will be analyzed with content analysis with a combined deductive and inductive analysis (18).

2.9 Monitoring

Regular site visits will be done in all kindergarten facilities by the study team (SB, MG, AT) to insure the complete and secure documentation of the study data. These will be kept in a specific folder and stored in a cabinet in a locked office.

2.10 Harms

The safety protocols will be created and then adapted to the kindergarten environment based on potential harms listed in the NCI-CTCAE (17) that could occur within the framework of the interventions. The forms will be discussed with experts (developer of the Kita Kneipp-intervention curriculum and a methodological expert) and linguistically adapted to laypersons' terms.

The risks of this study are low. Nevertheless, there is a possibility the application of the Kneipp concept could place an additional time burden on educators. There is no risk for the children.

A steering committee made up of external experts for Kneipp therapy and prevention research will meet quarterly to discuss problems and monitor safety. Additionally, the quality assurance office of the Charité will be consulted on safety measures. Site visits will be planned during the duration of the study.

Adverse events (AEs) are not to be expected as a result of participation. However, should any occur, the applications can be stopped immediately by the educators. All adverse events and suspected cases will be documented by the educators or the daycare center management and reported to the study management (SB, AT, MG) within 24 h. If there are any directly reported AEs related to Kneipp, the interventions will be immediately stopped and reviewed by the quality assurance team (GS – principal investigator, SB, FK, SS – experienced biostatistician, WS – experienced clinical study coordinator). Symptoms to be recorded are: general, skin, falls, and breathing, and a three-point scale (mild, moderate or severe) will be used (see Supplementary material: Adverse Events Documentation Form).

2.11 Auditing

The interventions observed at two time points not only will provide data for the qualitative part but will enable the study team to observe and supervise the applications.

3 Discussion

To our knowledge, this planned study is the first of its kind to specifically investigate the effects of a Kneipp intervention in kindergarten facilities. As a low-cost measure with some indicated potential to improve the health of children (8, 9), this confirmatory, mixed-method, two-armed, waitlist, clinical, cluster-RCT study shows promise for presenting evidence of a Kneipp intervention within a daycare setting. A prior RCT study about hydrotherapy in children aged 3–7 years old (intervention group – hydrotherapy and saline inhalation, control group - saline inhalation), without the holistic aspect of Kneipp found no significant results regarding incidence of colds and average duration of cold episodes (19). Seeing if a broad health-promoting concept such as Kneipp would be more beneficial is of interest. In addition to the primary and secondary outcomes the qualitative documentation has the potential to not only track the effects but also to describe how the intervention is conducted with the children and perceived by the educators. That would help recognize and evaluate possible challenges and potentials of applying such a holistic approach in childcare facilities.

Several limitations to this confirmatory study design can be considered. The pre-selection based on socio-demographic information and cluster grouping of the kindergartens to be randomized may introduce some allocation bias into the randomization process. Further, the study primary and secondary outcomes rely on self-reported measures of data gathering on the part of parents and kindergarten directors. The open-label study design could influence the subjective experience of the cold and sickness symptoms and how they report or attend kindergarten. Caregivers may show some response bias, as they are informed of the purposes of the Kneipp concept. Nevertheless, the primary measure will be double recorded by caregivers and kindergarten directors to achieve a closer approximation for internal validity. Further, the CCQ relies on the recall of symptoms by caregivers that could be affected over time. For minimizing this limitation, caregivers will be prompted to fill out the form on a weekly basis and a member of the study group (AT) will monitor the responses and, if needed, a reminder e-mail will be sent.

4 Ethics and dissemination

4.1 Protocol amendments

Any changes to the protocol which may have an impact on the study conduct, potential benefit of the study group or may affect its safety, including modifications of the study objectives, design, population, sample sizes, procedures, or significant administrative changes will require a formal amendment to the protocol. Such an amendment will be approved by the Ethics Committee of Charité – Universitätsmedizin Berlin.

4.2 Consent or assent

A researcher from the study team will explain the trial to the directors of the kindergarten facilities. Educators and caregivers/caregivers will receive a document explaining the study purposes and a written consent form which will be collected from the educators and stored in a locked office in a secure folder in the facilities (See Supplementary materials). If there are any questions left, online meetings will be organized, where caregivers and educators will have the opportunity to talk to the project coordinator or principal investigator (SB or GS). Through regular visits in the kindergarten facilities throughout the whole study period, the same form and written consent will be collected from newly hired kindergarten staff, who will also get the chance to talk to a study researcher (SB or MG) and be informed of the study plan and purposes. Furthermore, information brochures about the used Kneipp interventions will be distributed in the kindergartens, providing additional information for the children's caregivers on the used applications. Illustrated cards with the interventions will be used to explain the method in a child friendly way to the study population.

4.3 Confidentiality

Personal information about the children, their caregivers, and the educators will be securely stored in a locked office in the facilities. The interviews done with the educators will be auto transcribed and corrected to pseudonymize any personal information.

4.4 Declaration of interest

The study is being financially supported by a German health insurance company – 'MKK – Meine Krankenkasse'.

4.5 Access to data

Upon completion of the study, all anonymized data, custom written codes, and comprehensive documentation will be deposited in a dedicated online repository. The repository will be public, allowing open access to the dataset.

4.6 Ancillary and post-trial care

No follow-up services are provided to participants after their involvement in the trial has ended.

4.7 Dissemination policy

Two publications with the results (one on the quantitative and one on the qualitative part) is planned to be submitted in a peer-reviewed academic journal and made public to other researchers, participants etc. At the end of the study (November 2024) participants – parents and educators, researchers from the study group, the sponsor and

Kneipp-Bund e.V. members will additionally gather to discuss the results.

Author contributions

MG: Investigation, Visualization, Writing – original draft, Writing – review & editing, Formal analysis, Project administration, Data curation. SS: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. MB: Software, Writing – review & editing, Investigation. FK: Methodology, Formal Analysis, Validation, Data curation, Writing – review & editing. AT: Data curation, Investigation, Project administration, Writing – review & editing. MJ: Conceptualization, Methodology, Writing – review & editing, Funding acquisition. WS: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. SB: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing, Visualization. GS: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1412971/full#supplementary-material

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Effectiveness and safety of acupuncture modalities for overweight and obesity treatment: a systematic review and network meta-analysis of RCTs

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Introduction: The effectiveness and safety of acupuncture in the treatment of obesity have not been assessed. This poses a challenge for clinicians who choose to use acupuncture in the treatment of obesity, as they are unable to prioritize this approach based on outcome variables.

Methods: In May 2024, a literature search of five databases was conducted. Only randomized controlled trials evaluating body weight (BW), body mass index, waist circumference (WC), and adverse events in patients with a body mass index (BMI) of 25 or higher for various acupuncture modalities were included. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials, version 2. Pairwise meta-analysis (PMA) and Bayesian network meta-analysis (NMA) were performed using a random effects model for quantitative synthesis.

Results: Fourteen studies (n = 868) were included. The included studies evaluated the following acupuncture modalities: electroacupuncture (EA) (N = 6), laser acupuncture (LA) (N = 2), auricular acupuncture (AA) (N = 5), and manual acupuncture (MA) (N = 3). The PMA found that adding EA to usual care (UC), compared to UC alone, reduced BW (MD = 2.46, 95% CI = 1.12 to 3.80, I^2 = 58%, REM, N = 3, n = 157). The NMA of BW showed the following effect sizes for UC alone versus each acupuncture modality combined with UC: LA (MD = 2.09, 95% CI = 0.04 to 3.86), EA (MD = 2.04, 95% CI = 0.88 to 3.50), AA (MD = 1.69, 95% CI = −0.11 to 3.58), and MA (MD = 1.02, 95% CI = −0.82 to 2.94). The probability of each modality being the optimal treatment was evaluated using the surface under the cumulative ranking curve. EA was the most efficacious for BW and BMI, while LA was the most efficacious for WC.

Discussion: EA and LA can effectively complement clinical obesity management. The number of included studies was limited, and publication bias may have occurred, necessitating a cautious interpretation of the results. Furthermore,

most studies lasted between six and 12 weeks. Future clinical studies of acupuncture for obesity should include longer follow-up periods.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=387788, identifier CRD42023387788.

KEYWORDS

acupuncture, overweight, obesity, systematic review, network meta-analysis

1 Introduction

Obesity, a major global health problem, is defined as abnormal or excessive fat accumulation (1). The World Health Organization defines overweight as a body mass index (BMI) of 25 or more and obesity as a BMI of 30 or more (2). The global prevalence of obesity has more than doubled since 1980 (3), affecting approximately 30% of the world's population (4). The obesity epidemic continues to escalate (5), and based on current trends, it is predicted that up to 50% of the population will be overweight or obese by 2030 (6). Obesity is not just an energy imbalance caused by fat deposits but is associated with a range of health problems. Excessive adipose tissue increases cardiac activity, leading to anatomical changes that adversely affect pulmonary, endocrine, and immune function (7). Obesity impairs vascular homeostasis and leads to vascular dysfunction (8). Furthermore, metabolic syndrome associated with abdominal obesity is associated with a 2-fold increased risk of coronary heart disease and cerebrovascular disease and a 1.5-fold increase in all-cause mortality (9). Therefore, obesity is a risk factor for cardiovascular disease and diabetes (10), and increases the risk of other conditions, including musculoskeletal disorders and certain types of cancer (11). Moreover, obesity has a significant impact on healthcare costs (12). In 2011, obesity accounted for between 0.7 and 2.8 percent of the total healthcare spending in the United States (13). Individuals with obesity incurred healthcare costs that were approximately twice those of individuals with a normal weight (13). Severe obesity can reduce the quality of life (14), leading to negative physical, social, and psychological effects. Given the multifaceted interactions between obesity and many other conditions, treating obesity is essential for enhancing life expectancy and improving health outcomes.

Current management options for obesity include lifestyle modification, pharmacotherapy, and bariatric surgery. The United States Food and Drug Administration has approved several medications, including orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide, for long-term use in the management of obesity. However, recent studies have reported adverse effects of pharmacotherapy, such as an increased risk of cancer associated with lorcaserin use (15), and acute myocardial infarction in patients with cardiovascular disease treated with naltrexone/bupropion combination therapy (16). Bariatric surgery is generally recommended for patients with severe obesity with a body mass index (BMI) of 40 or more or a BMI of 35 or more and at least one obesity-related complication (17). GLP-1 receptor agonists, the most recent class of anti-obesity medications, have been observed to cause weight regain upon discontinuation (18). Furthermore, they are expensive and unavailable for long-term use (18). Studies have shown that appropriate bariatric surgery is associated with reduced complications and favorable cost-benefit ratios in the long term (19). However, short-term complications, such as infection and embolization (20), and long-term complications, such as metabolic disorders including metabolic acidosis and alkalosis, arrhythmias, and hormonal disruption, have been reported (21). Therefore, currently available treatments for obesity have several clinical limitations, including limited use in patients with underlying medical conditions, potential complications, and long-term safety concerns. A clear need exists to explore other effective treatments that can complement existing management strategies.

East Asian traditional medicine employs a diverse array of approaches to treat obesity, including herbal medicine, acupuncture, qigong, and lifestyle therapy (22, 23). The effectiveness of acupuncture in the treatment of obesity has been previously demonstrated (24). There are various modalities of acupuncture used in the treatment of obesity, including the following: Different modalities of acupuncture include electroacupuncture (EA), which uses electrical currents to enhance stimulation; laser acupuncture (LA), which uses low-level laser beams instead of needles; auricular acupuncture (AA), which targets points on the ear; and manual acupuncture (MA), the traditional form of acupuncture. Gao et al. (25) conducted a meta-analysis of 13 studies and reported that EA significantly improved BMI, waist circumference (WC), and waist-hip ratio compared with body acupuncture, moxibustion, and other treatments. Furthermore, Kim et al. (26) conducted a meta-analysis of 27 studies that demonstrated that body acupuncture and moxibustion significantly improved BMI compared to lifestyle modifications (diet, exercise), no treatment, and placebo acupuncture (PA). However, no comparisons were made between these interventions. In addition, Zhang et al. (27) conducted a network meta-analysis of acupuncture treatments for obesity. However, the study did not compare the effectiveness of various acupuncture treatments with usual care (UC) and presented effect sizes as standardized mean differences, which is not an intuitive approach for clinicians.

As discussed above, no studies have compared the effectiveness and safety of different acupuncture modalities for the treatment of obesity when used in combination with UC. For clinicians who have decided to use acupuncture in the treatment of obesity, the lack of evidence poses challenges in terms of the prioritization of treatment based on a given outcome variable. Network meta-analysis is a relatively new research methodology that extends the concept of meta-analysis and allows the ranking of treatment

effect sizes through direct and indirect comparisons of multiple treatments (28). This study aimed to compare the effectiveness and safety of various acupuncture treatments for obesity in combination with UC. A network meta-analysis was conducted to provide a basis for selecting the most appropriate acupuncture modality for clinical practice.

2 Materials and methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting systematic reviews that incorporated network meta-analyses of healthcare interventions (29). The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023387788).

2.1 Search strategy and information source

The initial search was conducted on 4 August 2022, in five English-language electronic databases: Medline (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica Database (Embase), Allied and Complementary Medicine Database (AMED), and Cumulative Index to Nursing and Allied Health Literature (CINAHL), for articles registered before that date. The second search was performed on 8 May 2024. The search strategy used three categories: "Obesity," "Acupuncture Modality," and "Randomized Controlled Trials." The three categories were combined using the "AND" Boolean operator with keywords specific to each database. The detailed search terms are listed in Supplementary Table 1.

2.2 Inclusion and exclusion criteria

2.2.1 Type of study design

The inclusion criteria were randomized controlled trials (RCTs). Other studies, such as case reports, reviews, and meta-analyses, were excluded.

2.2.2 Type of population

The inclusion criteria were studies involving individuals with a BMI of 25 or higher, including simple and complex obesity, regardless of sex or age (30).

2.2.3 Type of experimental group intervention

The selection criteria were as follows: (1) studies that used any of the following interventions in isolation: MA, EA, scalp acupuncture, AA, pharmacopuncture, fire acupuncture, warm acupuncture, acupotomy, acupoint catgut embedding, and LA.

The exclusion criteria were as follows: (1) studies that used acupuncture without intradermal insertion, such as auricular acupressure, and (2) studies that used acupuncture with needles embedded in the body, except for AA and catgut embedding.

Specific acupuncture modalities were defined as follows: (1) MA was defined as acupuncture that was maintained for < 1 h to distinguish it from buried acupuncture; (2) if EA was used, even partially, regardless of the acupuncture point, it was classified as EA; (3) AA was defined as acupuncture that was maintained for a certain amount of time with the needles remaining in place for a certain amount of time; and (4) acupressure was excluded for AA but was included as acupuncture if the author used the term acupuncture.

2.2.4 Type of control group intervention

The studies employed no treatment, lifestyle interventions, Western medicine, or PA as controls. Given that individuals participating in weight loss studies are typically highly motivated (31), the control group interventions were collectively referred to as "UC," and only PA was categorized separately.

2.2.5 Type of outcome

The primary outcome measure was body weight (BW; unit: kg). The secondary outcome variables were WC (cm) and BMI (kg/m^2) (32). Additionally, we dichotomized the adverse events (AEs) and dropout rates. The dropout rate was calculated as the number of participants who dropped out compared to the number of participants who were randomized. AEs were calculated as the number of participants who experienced AEs compared to the number of participants who were analyzed.

The study's selection criteria were as follows: (1) studies that included at least one of the following outcomes: BMI, BW, WC, and AEs as outcomes; (2) studies that reported change data (mean $\pm$ standard deviation) for the outcomes.

The specific criteria were as follows: (1) for studies comprising two experimental groups of the same kind of intervention with different doses, we selected and used only one data set from the group with the larger intervention dose; (2) for studies measuring the outcome on multiple occasions throughout the procedure, we employed the final outcome measurement; (3) for studies comprising more than one placebo group, we selected and used only one data set with the more pronounced placebo effect to obtain conservative results; and (4) for studies with incomplete outcome measurements, we requested data from the first or corresponding author by email.

2.3 Study selection and data extraction

The titles and abstracts of the retrieved studies were initially reviewed based on the inclusion/exclusion criteria. The full texts of potentially eligible articles were cross-reviewed to make the final selection. The process of selecting and excluding the literature was conducted independently by three researchers (YK, HK, and HJ). In the event of a discrepancy, a consensus was reached through discussions between the researchers. If a consensus could not be reached, another researcher (JL) was consulted for the final selection.

Data extraction was performed independently by two researchers (YK and HK) according to the data template form. The data template comprised the key characteristics of the study (publication year, first author's country, journal name, and study design), subject information (sample size, sex, and age), intervention details (acupuncture points, stimulation, needle type, treatment duration, frequency, and type of

intervention), and outcomes (mean and standard deviation of BW, BMI, WC, and AEs).

2.4 Risk of bias assessment

Two researchers (YK and HK) independently assessed the quality of the included studies according to Cochrane ROB 2.0 (33). The risk of bias was evaluated for each study based on five categories: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of outcomes; and (5) bias in the selection of reported outcomes. Each category was rated as low, with a few concerns, or high, according to the degree of bias. Disagreements between the two researchers were resolved through discussion; in cases of unresolved disagreements, a third researcher (JL) was consulted.

2.5 Quantitative synthesis

2.5.1 Pairwise meta-analysis (PMA)

PMA was performed to directly compare the effect sizes of each intervention and control groups (34). PMA was performed using Review Manager (Version 5.4, Cochrane Collaboration, Oxford, UK). For continuous variables (BW, BMI, and WC), the mean difference (MD) and 95% confidence interval (CI) were used, and a random-effects model was applied to account for the heterogeneity of the various interventions used in the treatment. For binary variables (AEs and dropout rate), the risk ratio (RR) was used, and a random-effects model was applied. The PMA results were visualized using a forest plot. The I-square value was used to evaluate heterogeneity (35).

2.5.2 Network meta-analysis (NMA)

2.5.2.1 Reviewing the assumptions of network meta-analysis

NMA relies on four assumptions: connectivity, homogeneity, transitivity, and consistency of the network (36). These assumptions must be met to ensure the reliability of the results. Network connectivity was assessed visually using a network plot, which allowed for the examination of direct and indirect connections between studies. We confirmed that at least one closed loop was observed and that every study had at least one connection. Homogeneity between studies was assessed using the I-square test. As the intervention details varied across studies, we used a random-effects model to account for both within- and between-study variability in our statistical analysis. Transitivity and consistency examine whether the results of direct and indirect comparisons are consistent. The statistical test of transitivity was a consistency test, and we used the net-split method to test the transitivity and consistency of each intervention comparison.

2.5.2.2 Setting of network meta-analysis

We conducted a Bayesian NMA using the "gemtc" package (Version 1.0-1)[1] in R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) to, directly and indirectly, compare the effects of interventions and controls (37). We used the MD for continuous variables and applied a random-effects model (38). The model employed a Markov chain Monte Carlo (MCMC) simulation, and we ran 200,000 simulations, discarding the initial 5,000 simulations to exclude MCMC bias and taking samples every five simulations. We assessed the model convergence using the Brooks-Gelman-Rubin method and evaluated the model convergence by assessing the degree to which the potential scale reduction factor converged to 1 (39).

Network forest plots were used to visualize the effect sizes of each intervention. Nodes were used to represent various interventions and edges to represent head-to-head comparisons between interventions. Rank plots were used to illustrate the probability of each intervention being ranked according to treatment. The surface under the cumulative ranking curve (SUCRA) (40) was represented based on these plots. A SUCRA value closer to 1 and a higher number indicate that the treatment has a relatively better effect, whereas a value closer to 0 indicates a lower effect of the intervention.

2.6 Publication bias

To assess the possibility of publication bias and minor study effects in the network meta-analysis of the main (BW) and secondary outcomes (BMI and WC), we used funnel plots and Egger's regression tests. A funnel plot was constructed by plotting the effect sizes of the included studies against their standard errors. Asymmetry in the plot suggests the presence of a publication bias or minor study effects (41). Furthermore, to quantitatively assess the asymmetry of the funnel plot, we conducted Egger's regression test (42). A p-value less than 0.10 was considered indicative of significant asymmetry and potential publication bias. Analyses were conducted using the R package "netmeta" (version 2.7-0).[2]

3 Results

3.1 Study description

A total of 4,932 studies were identified from five English-language databases. After the initial screening of titles and abstracts, 212 studies were reviewed in full text, and 14 RCTs (43–56) with 868 participants were included in the final analysis (Figure 1). Details of the 198 excluded studies are shown in Supplementary Table 2. Of the 14 studies, 11 were in English (43–46, 48–51, 54–56), one was in Chinese (47), and two were in Korean (52, 53). The characteristics of the included studies, including the year of publication, country, age, sex, number of participants, type of intervention and control group, type of outcome, and occurrence of AEs, are summarized in Table 1. Four interventions were used in the included studies: (1) MA+UC; (2) AA+UC; (3) EA+UC; and (4) LA+UC. Of the 14 studies, three included the MA+UC intervention (45, 46, 53), five included AA+UC (44, 45, 49, 50, 54) six included EA+UC (43,

1 https://cran.r-project.org/web/packages/gemtc/index.html

2 https://github.com/cran/netmeta.git

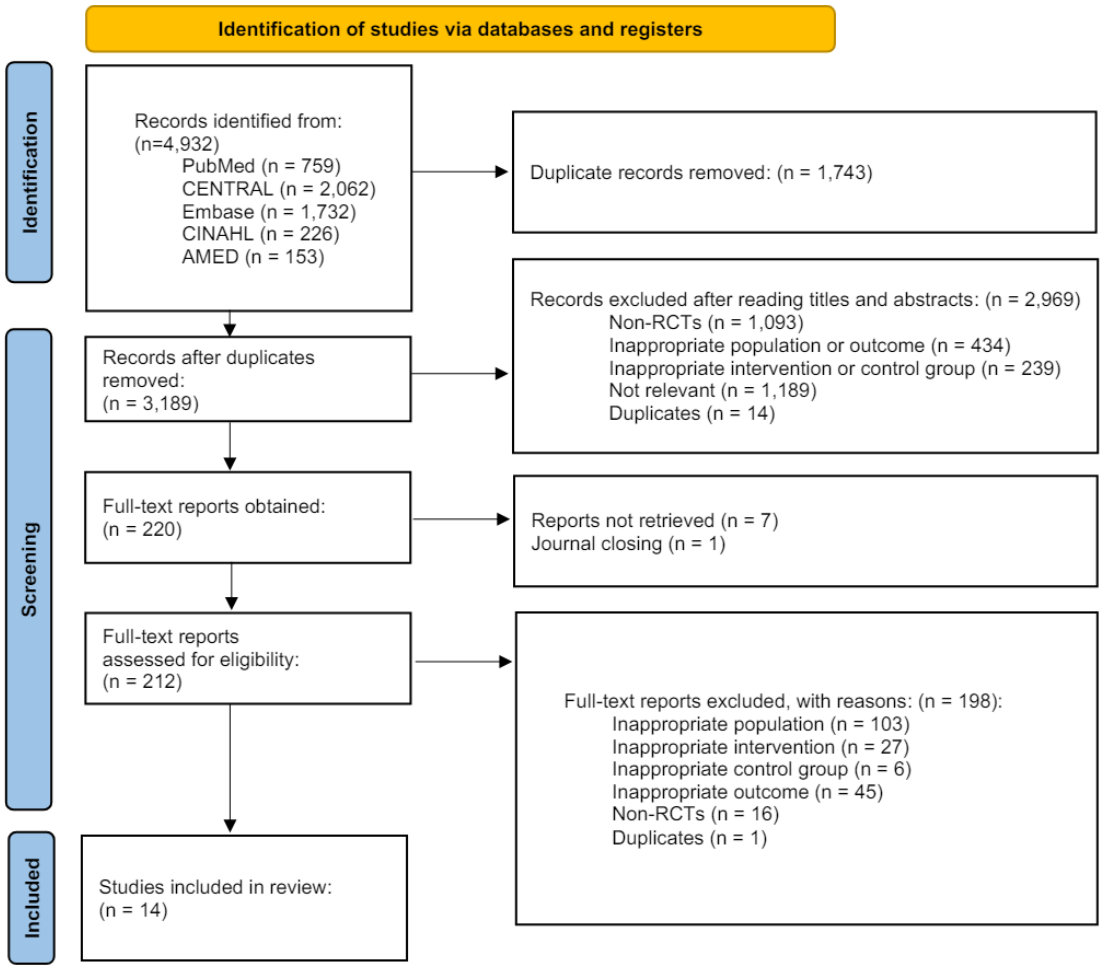

FIGURE 1
Prisma flow chart. AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; RCT, randomized controlled trial.

47, 50–52, 55), and two included LA+UC (48, 56). Two control interventions were used in the studies: (1) PA+UC and (2) UC only. Of the 14 studies, nine included PA+UC (44, 46, 48–50, 52–55), and five included UC only (43, 47, 51, 53, 56). Two of the 14 studies were three-arm studies (50, 53) (MA vs. UC vs. PA and EA vs. AA vs. PA), and the other 12 were two-arm studies. Detailed descriptions of the characteristics of the interventions used in these studies, including the acupuncture points, stimulation, needle retention time, and needle type, are summarized in Table 2.

3.2 Risk of bias assessment

In the deviations from intended interventions category, two studies (51, 54) received a rating of "some concern" and three studies (44, 45, 49) received a rating of "high." The three studies were rated as "high" due to some participants discontinuing the intervention or dropping out because of treatment ineffectiveness without providing a detailed explanation. All studies received a rating of "low" for the measurement of the outcome category. Overall, the risk of bias was assessed and observed to be low in four studies, "some concern" in seven studies, and "high risk" of bias in three studies (Supplementary Figure 1).

3.3 Pairwise meta-analysis

3.3.1 Pairwise meta-analysis on BW

The PMA was performed to assess the effectiveness of various acupuncture treatments in combination with UC versus UC alone on BW. The difference was significant for EA+UC versus UC alone (MD = 2.46, 95% CI = 1.12 to 3.80). For AA, no studies with this design were performed. In addition, various acupuncture treatments in combination with UC versus PA combining with UC for BW showed significance for LA+UC vs. PA+UC (MD = 1.90, 95% CI = 1.25 to 2.55), and one study was included (Supplementary Figures 2a, b).

3.3.2 Pairwise meta-analysis on BMI

A PMA was conducted to assess the effectiveness of various acupuncture treatments in combination with UC versus UC alone on BMI. The difference was significant for EA+UC versus UC alone (MD = 1.50, 95% CI = 0.77 to 2.22). For MA and AA, no studies

TABLE 1 Characteristics of included randomized controlled trials.

Study ID, country	Age (year) Mean (SD)	Initial BMI (*BW) mean (SD)	Sex (M/F or female %)	Number of patients R [T/C (total)] → A [T/C (total)]	Intervention type	Type of control group	Outcome measure	Adverse events (*n*) reported
Hsu et al. (43), Taiwan	Real 40 (11.5) UC 41.3 (9.9)	Real 33.8 (3.4) UC 33.7 (2.9)	100%	24/24 (48) → 22/20 (42)	EA+UC	UC only (exercise)	BW, BMI, WC, HC, WHR, glucose, cholesterol, triglyceride	Real: mild ecchymosis (3), abdominal discomfort (1) UC: none
Kim et al. (53) Korea¶	Real 38.6 (5.7) Sham 37.4 (6.0) UC 39.3 (6.5)	*Real 78.112 (11.503) *Sham 70.246 (7.653) *UC 67.267 (7.917)	100%	UC 18/24 Sham 18 (60) → UC 8/12 Sham 13 (33)	MA+UC (diet)	UC only (diet) PA+UC (diet)	BW, BFP, cholesterol, triglyceride, HDL-C, LDL-C	NR
Hsu et al. (44) Taiwan	Real 40.0 (10.5) Sham 39.4 (13.6)	Real 31.6 (3.9) Sham 31.2 (3.9)	100%	30/30 (60) → 23/22 (45)	AA+UC	PA+UC	BW, BMI, WC, HC, glucose, triglyceride, cholesterol, HDL-C, LDL-C, insulin, leptin, adiponectin, ghrelin, HOMA-IR	Real: minor-inflammation (1), mild tenderness (7) Sham: mild tenderness (2)
Chung et al. (52) Korea	39.6 (11.5)	Real 28.87 (2.15) Sham 28.25 (3.26)	NR	13/13 (26) → 12/11 (23)	EA+UC	PA+UC	BW, BMI, WC, WHR, ASF, BFR, VFA, BULIT-R, KoQoL, BSQ	Real: bluish (6), abdominal discomfort (3) Sham: abdominal discomfort (1), dizziness (1)
Yang et al. (47) China	18–42	*Real 74.58 (7.54) *UC 75.60 (8.31)	7/54	31/30 (61) → 31/30 (61)	EA+UC (diet, exercise)	UC only (diet, exercise)	BW, WHR	NR
Abdi et al. (54) Iran	Real 37.3 (1.0) Sham 38.7 (1.1)	Real 32.15 (0.47) Sham 31.40 (0.41)	NR	102/102 (204) → 86/83 (169)	AA+UC (diet)	PA+UC (diet)	BW, BMI, WC, Body fat, HC, WHR, FBG, TC, triglyceride, HDL-C, LDL-C, anti-HSP27, anti-HSP60, anti-HSP65, anti-HSP70, hs-CRP	None
Abdi et al. (55) Iran	Real 36.9 (8.7) Sham 37.4 (9.1)	Real 32.30 (0.52) Sham 32.74 (0.59)	NR	98/98 (196) → 79/82 (161)	EA+UC (diet)	PA+UC (diet)	BW, BMI, WC, Body fat, HC, WHR, FBG, TC, triglyceride, HDL-C, LDL-C, anti-HSP27, anti-HSP60, anti-HSP65, anti-HSP70, hs-CRP	None
Lien et al. (49) Taiwan	Real 39.2 (11.6) Sham 40.7 (9.7)	Real 29.9 (3.2) Sham 30.6 (4.1)	100%	30/30 (60) → 24/23 (47)	AA+UC (diet)	PA+UC (diet)	BW, BMI, WC, HC, WHR, glucose, triglyceride, cholesterol, HDL-C, LDL-C, adiponectin, insulin, ghrelin, leptin, HOMA-IR, WHO BREF life-quality scores	Real: dizziness (1) Sham: none

(Continued)

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TABLE 1 (Continued)

Study ID, country	Age (year) Mean (SD)	Initial BMI (*BW) mean (SD)	Sex (M/F or female %)	Number of patients R [T/C (total)] → A [T/C (total)]	Intervention type	Type of control group	Outcome measure	Adverse events (*n*) reported
Darbandi et al. (50) Iran¶	(EA) Real 38.0 (0.9) Sham 38.0 (1.3); (AA) Real 39.0 (1.8) Sham 37.9 (1.5)	(EA) Real 33.4 (1.3) Sham 33.0 (1.5); (AA) Real 33.4 (2.6) Sham 32.0 (3.9)	0%	20/20 (40) → 20/20 (40);	(EA) EA+UC (diet); (AA) AA+UC (diet)	(EA) PA+UC (diet); (AA) AA+UC (diet)	BMI, WC, HC, TFM	EA: None; AA: None
El-Mekawy et al. (56) Egypt	Real 54.4 (4.4) Sham 52.8 (4.6)	Real 39.91 (3.43) Sham 42.78 (5.27)	100%	14/14 (28) → 14/14 (28)	LA+UC (diet, exercise)	UC only (diet, exercise)	BW, BMI, WC, HC, WHR, TC, HDL-C, LDL-C, TG, FBG, Serum insulin, HOMA-IR	NR
Fogarty et al. (46) Australia	> 18	NR	NR	24/22 (46) → 19/16 (35)	MA+UC (diet, exercise)	PA+UC (diet)	BW, EDRC scale, SF-36v2 health survey, STAI, BDI-2	NR
Tseng et al. (48) Taiwan	Male 42.6 (15.1) Female 37.8 (10.6)	Real 31.2 (5.3) Sham 30.7 (5.6)	11/41 78.85%	26/26 (52) → 26/26 (52)	LA+UC	PA+UC	BMI, WC, HC, WHR, BFP, Appetite sensations (Fullness, Hunger, Satiety, Desire-to-eat, Overall well-being)	None
Yasemin et al. (45) Turkey	(MA) 32.7 (12.3); (AA) 39.1 (7.9)	(MA) 36.6 (6.7); (AA) 38.6 (4.7)	100%	(MA) 25 → 17; (AA) 25 → 21	MA+UC; AA+UC	None	BW, BMI, WC, HC, BFP	MA: Allergic rash (1); AA: None
Ni et al. (51) China	Real 30.79 (8.8) UC 30.50 (9.53)	Real 30.37 (4.75) UC 31.12 (4.94)	Trial 11/17 Control 11/15	30/30 (60) → 28/26 (54)	EA+UC (diet, exercise)	UC only (diet, exercise)	BW, BMI, WC, WHR, FPG, FIN, ISI, HOMA-IR	NR

¶Study with three arms. A, Analyzed; AA, auricular acupuncture; ASF, thickness of abdominal subcutaneous fat; BDI-2, Becks depression inventory; BFP, body fat percentage; BFR, body fat ratio; BMI, body mass index; BSQ, body shape questionnaire; BULIT-R, Bulimia test revised; BW, body weight; C, control; EA, electroacupuncture; EDRC, eating disorder risk composite; F, female; FBG, fasting blood glucose; FIN, fasting insulin; FPG, fasting plasma insulin; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein; HSP, heat shock protein; ISI, insulin sensitivity index; KoQoL, Korean obesity of QoL; LA, laser acupuncture; LDL-C, low-density lipoprotein cholesterol; M, male; MA, manual acupuncture; NR, not reported; PA, placebo acupuncture; R, randomized; STAI, state-trait anxiety inventory; T, treatment; TC, total cholesterol; TFM, trunk fat mass; UC, usual care; VFA, visceral fat area; WC, waist circumference; WHR, waist/hip ratio. *Body weight.

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TABLE 2 Details of the included acupuncture and related therapies.

Study ID, country	Acupuncture points	Stimulation	Needle retention time	Needle type (width, length)	Treatment sessions	Frequency (period)
Hsu et al. (43) Taiwan	CV6, CV9, ST28, KI14, ST26, ST40, SP6	(Needles in the lower legs) Rotated back and forth until the subjects had the sensation of Deqi; (Needles in the abdomen) Intensity: 500 Ω (12–23 V) Frequency: 42 Hz Dense-disperse wave	40 min	Length 3.8 cm	12	2 per wk (6 wks)
Kim et al. (53) Korea¶	LR1, SP1, LU8, SP5	1 stimulation per treatment; Rotated back and forth until the subjects had the sensation of Deqi; Applied pressure to LU8 1 min when waking up at home, right before a meal, eating a snack, or drinking tea	30 min	0.20 mm × 1.5 mm	12	3 per wk (4 wks)
Hsu et al. (44) Taiwan	Hunger, Shenmen, Stomach, Endocrine	One ear per treatment 6 treatments for the two ears in 12 sessions	3 days	Length 2 mm	12	2 per wk (6 wks)
Chung et al. (52) Korea	CV12, CV6, ST25, SP15, SP14; One side of LI4, LI11, ST36, ST44 (M: left side, F: right side)*	Rotated in LI4, LI11, ST36, ST44*; Intensity: 0.27–1.3 mA Frequency: 24 Hz Continuous wave	30 min	0.4 mm × 75 mm	10	2 per wk (5 wks)
Yang et al. (47) China	CV12, ST25, CV4, ST36, ST40, SP9, SP6, BL20, BL21, Ashixue	G6805-2A electroacupuncture machine A level middle, B level 3/4	30 min	NR	15	1 per day (7 wks) 3 days rest between every session
Abdi et al. (54) Iran	Shen Men, Stomach, Hunger point, Mouth, Center of the ear, Sanjiao	Inserted the ear-pressing plaster with seed into the acupuncture points	3 days	NR	12	2 per wk (6 wks)
Abdi et al. (55) Iran	ST25, GB28, CV12, CV9, CV4, SP6 LI 11, ST40 for the excess syndrome (patients with higher energy)*; CV6, SP9 for deficiency syndrome (patients with lower energy)*	Rotated back and forth until the subjects had the sensation of Deqi; Intensity: 500 Ω (12–23 V) Frequency: 30–40 Hz Dense-disperse wave	20 min	Length 3.8 cm	12	2 per wk (6 wks)
Lien et al. (49) Taiwan	Shenmen, Stomach, Hunger, Endocrine	One ear treatment 6 treatments for the two ears in 12 sessions	Remained until next treatment visit	1 cm × 20 mm	12	3 per wk (4 wks)
Darbandi et al. (50) Iran¶	(EA) ST25, GB28, CV12, CV9, CV4, SP6; LI11, ST40 for excess syndrome (patients with higher energy)*; CV6, SP9 for deficiency syndrome (patients with lower energy);* (AA) Shenmen, Stomach, Hungry point, Mouth, Center of the ear, Sanjiao	(EA) Intensity: 500 Ω (12–23 V) Frequency: 30–40 Hz Dense-disperse wave; (AA) Inserted the ear-pressing plaster with the seed into the acupuncture points	(EA) 20 min'; (AA) 3 days	(EA) Length 3.8 cm; (AA) NR	12	2 per wk (6 wks)

(Continued)

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TABLE 2 (Continued)

Study ID, country	Acupuncture points	Stimulation	Needle retention time	Needle type (width, length)	Treatment sessions	Frequency (period)
El-Mekawy et al. (56) Egypt	CV4, CV9, CV12, ST25, ST36, SP6, ST40	Power output 5 mW Pulse frequency 5,000 Hz Pulse radiation of 200 ns Energy density 2 J/cm^2	2 min	Wavelength 904 nm	36	3 per wk (12 wks)
Fogarty et al. (46) Australia	LI4, LI11, ST36, ST44, LR3, Shenmen, Hungry, Stomach	Gentle lift/thrust and rotation (not in those with eating concerns)	30 min	(MA) 0.20 mm × 40 mm / 0.25 mm × 40 mm (AA) 0.16 mm × 10 mm	12	2 per wk (6 wks)
Tseng et al. (48) Taiwan	ST25, ST36, ST40, ST44, LI4, LI11, SP6, PC6	Maximum power output 150 mW Power density 0.417 W/cm^2 Energy density 4 J/cm^2	10 sec	Wavelength 808 m	24	3 per wk (8 wks)
Yasemin et al. (45) Turkey	(MA) LI4, LI11, ST25, ST36, SP6, SP9, CV12, CV6; (AA) Anti-aggression, Stomach	(MA) 1 stimulation per treatment; (AA) Both sides for auricular acupuncture Stimulated 3 times a day for 30 s	(MA) 30 min; (AA) 15 days (Replaced every 15 days)	(MA) 0.25 mm × 25 mm; (AA) 0.22 mm × 1.3 mm	(MA) 24; (AA) 6	(MA) 2 per wk (12 wks); (AA) 1 per 2 wk (12 wks)
Ni et al. (51) China	BL21, BL20, BL25, BL27, EX-B3, CV12, LR13, ST25, CV4, CV6, ST36, ST40, SP6	Intensity: 1–10 mA Frequency: 2/100 Hz Disperse-dense wave	30 min	Back-shu points: 0.30 mm × 40 mm Front-mu points: 0.30 mm × 40 mm / 0.30 mm × 50 mm	36	3 per wk (12 wks)

*Individualized care according to traditional medicine theory. ¶Study with three arms. AA, auricular acupuncture; EA, electroacupuncture; MA, manual acupuncture; NR, not reported.

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with this design were performed. In addition, various acupuncture treatments in combination with UC versus PA combining with UC for BMI showed significance for EA+UC vs. PA+UC (MD = 0.37, 95% CI = 0.10 to 0.63), AA+UC vs. PA+UC (MD = 0.34, 95% CI = 0.18 to 0.51), and LA+UC vs. PA+UC (MD = 0.77, 95% CI = 0.51 to 1.03). For LA, only one study was included; for MA, no study with this design was conducted (Supplementary Figures 2c, d).

3.3.3 Pairwise meta-analysis on WC

A PMA was performed to assess the effectiveness of various acupuncture treatments in combination with UC versus UC alone for the treatment of WC. The difference was significant for LA+UC vs. UC alone (MD = 5.35, 95% CI = 3.27 to 7.43). One study was included for LA. For MA and AA, no studies with this design were conducted. In addition, various acupuncture treatments combined with UC versus PA combined with UC for WC were significant for EA+UC vs. PA+UC (MD = 3.56, 95% CI = 0.74 to 6.39). For LA, one study was included, and for MA, no study with this design was performed (Supplementary Figures 2e, f).

3.4 Network meta-analysis

3.4.1 Assumption of NMA

In this study, we applied a random-effects model to the analysis under the assumption of homogeneity and verified the connectivity of the network by visualizing it as a network plot (Figure 2). To verify transitivity and consistency, we conducted a net-split test, including direct, indirect, and network estimations, and observed no studies showing heterogeneity. The results of the net-split test are shown in Supplementary Figure 3. Additionally, we used Markov chain MCMC diagnostics to estimate the effects of the Bayesian analyses, which are represented in Supplementary Figure 4. We performed Gelman-Rubin diagnostics, which are represented in Supplementary Figure 5.

3.4.2 Comparative effectiveness of acupuncture modality on BW

An NMA of BW revealed the following effect sizes for UC alone versus each acupuncture modality in combination with UC: LA (MD = 2.09, 95% CI = 0.04 to 3.86), EA (MD = 2.04, 95% CI = 0.88 to 3.50), AA (MD = 1.69, 95% CI = −0.11 to 3.58), and MA (MD = 1.02, 95% CI = −0.82 to 2.94). Combined treatment with LA and EA significantly reduced BW compared with that in UC alone. The other interventions showed a tendency to reduce BW compared with that in UC only, but the difference was not significant (Figure 3A). Based on the SUCRA, the probability of being the best treatment for reducing BW was highest for EA (0.8006), followed by LA (0.7830), AA (0.6737), MA (0.3911), PA (0.2962), and UC alone (0.0553) (Figures 4A, 5A).

3.4.3 Comparative effectiveness of acupuncture modality on BMI

An NMA of BMI revealed the following effect sizes for UC alone versus each acupuncture modality in combination with UC: EA (MD = 0.97, 95% CI = 0.17 to 2.00), LA (MD = 0.91, 95% CI = −0.13 to 1.84), AA (MD = 0.85, 95% CI = −0.19 to 2.03), and MA (MD = 0.15, 95% CI = −1.46 to 1.89). EA combined treatment significantly reduced BMI compared to that in UC alone. The other interventions showed a tendency to reduce BMI compared to that in UC only, although the difference was not significant (Figure 3B). Based on the SUCRA, the probability of being the best treatment for reducing BMI was highest for EA (0.8035), LA (0.7373), AA (0.7176), PA (0.3616), MA (0.2517), and UC alone (0.1284) (Figures 4B, 5B).

3.4.4 Comparative effectiveness of acupuncture modality on WC

An NMA of WC revealed the following effect sizes for UC alone versus each acupuncture modality in combination with UC: LA (MD = 4.67, 95% CI = −0.06 to 9.51), EA (MD = 3.45, 95% CI = −0.27 to 7.42), AA (MD = 1.38, 95% CI = −3.62 to 6.68), and MA (MD = 1.29, 95% CI = −6.61 to 7.47). Combined treatment with LA and EA significantly reduced WC compared to that in treatment with UC alone. The other interventions showed a tendency to reduce WC compared to that in UC only but were not significant, as the 95% CI included zero (Figure 3C). Based on the SUCRA, the probability of being the best treatment for reducing WC was highest for LA (0.8685), followed by EA (0.7577), AA (0.4891), MA (0.4648), PA (0.2501), and UC alone (0.1698) (Figures 4C, 5C).

3.5 Safety

The analysis showed that the main reported adverse events in the experimental group were 9 cases of mild ecchymosis, 7 cases of mild tenderness, and 4 cases of abdominal discomfort. In the control group, the main adverse events were 2 cases of mild tenderness, 1 case of abdominal discomfort, and 1 case of dizziness. The PMA of AEs demonstrated no significant differences between UC alone and each acupuncture modality in combination with UC. However, the incidence of adverse events was observed to be significantly higher in the combination of each acupuncture modality with the UC group than that in the PA+UC group (RR = 4.05, 95% CI = 1.61 to 10.20) (Supplementary Figure 6). The drop-out rate was not significant (Supplementary Figure 7).

3.6 Publication bias

To assess the possibility of bias in the NMA of the main outcome, BW, and the secondary outcomes, BMI and WC, a funnel plot was used for visualization. The Egger test and visual inspection suggested the possibility of publication bias. Therefore, this study should be interpreted with caution because of potential publication bias. A funnel plot is shown in Supplementary Figure 8.

4 Discussion

4.1 Summary of findings

We conducted a systematic review and network meta-analysis to compare various acupuncture modalities for patients with

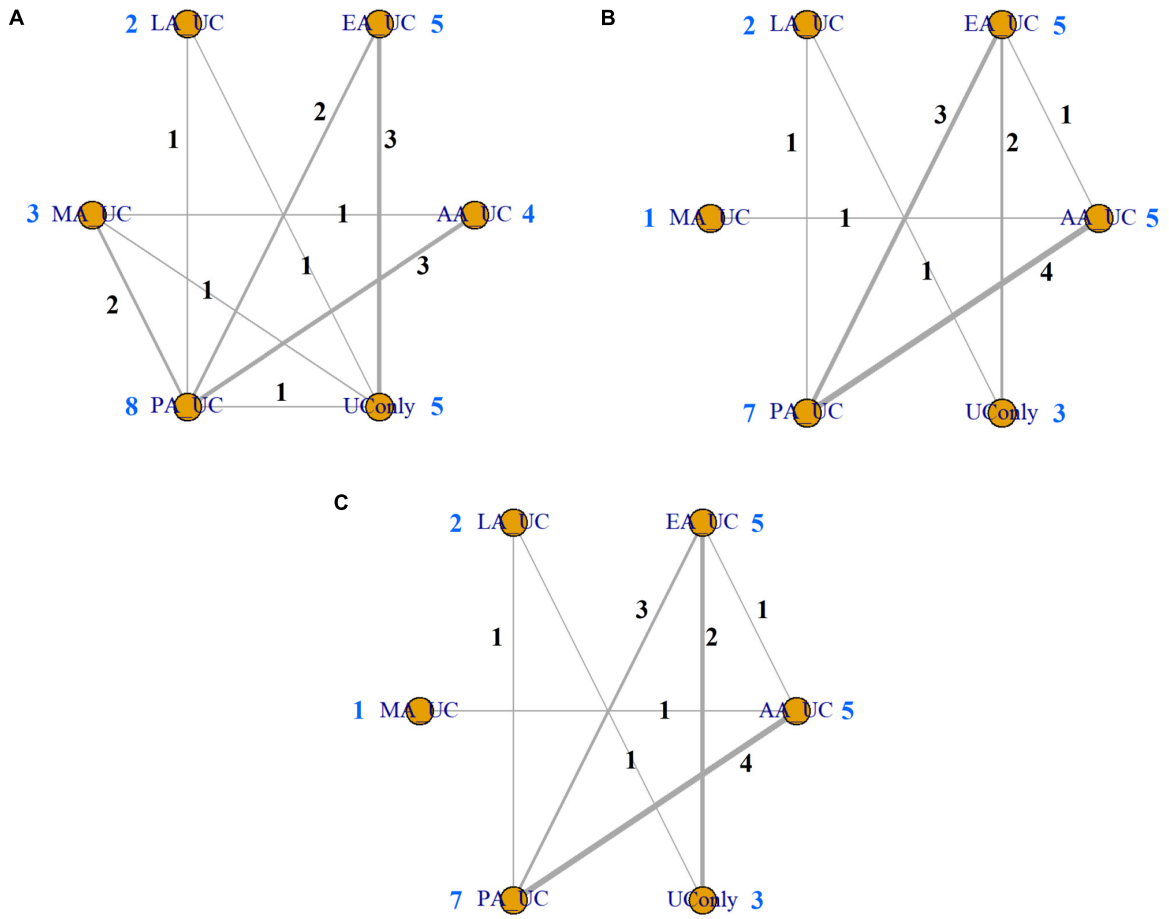

FIGURE 2
Network plot. **(A)** Body weight. **(B)** Body mass index. **(C)** Waist circumference. Network plots showing direct and indirect comparisons among various acupuncture modalities. The node size represents the number of studies included. AA, auricular acupuncture; BW, body weight; BMI, body mass index; EA, electroacupuncture; LA, laser acupuncture; MA, manual acupuncture; PA, placebo acupuncture; UC, usual care; WC, waist circumference.

obesity and overweight. Fourteen RCTs with 868 participants were selected for the analysis. The PMA results demonstrated that the combination of EA and UC significantly reduced both BW and BMI compared to those in UC alone. NMA revealed that the combination of EA and UC significantly reduced BW, BMI, and WC compared to those in UC alone. Additionally, the combination of LA and UC significantly reduced BW and WC. The probability of each modality being the optimal treatment was evaluated using SUCRA; EA was identified as the most efficacious treatment for BW and BMI, whereas LA was the most efficacious treatment for WC. Acupuncture treatment did not increase the incidence of side effects or serious adverse events.

4.2 Debate

4.2.1 Comparison with existing literature

Kim et al. (26) conducted the first systematic review with a separate meta-analysis of the effects of distinct modalities on obesity, comparing the effects of MA, pharmacopuncture, acupoint catgut embedding, LA, AA, and EA with those of PA. To address the issue of a limited sample size, Kim's study described the effect estimates of outcomes with different units as standardized mean differences. In contrast, the current study described the effect estimates of BW, BMI, and WC as mean differences to provide an intuitive reference for clinicians in decision-making. Zhang et al. (27) was an NMA study that compared the effectiveness of different treatments for obesity, including AA, stimulation, acupuncture, pharmacotherapy, and relative therapy. The study was limited to simple obesity, included acupressure as an intervention, and permitted combination therapy between the interventions to establish the treatment groups. By contrast, this study is more representative of the obese population encountered in clinical practice, including patients with a wide range of complications. Furthermore, the study evaluated the efficacy of a single acupuncture treatment to inform clinical decision-making and thus excluded treatments that were a combination of acupressure or two or more Traditional East Asian Medicine (TEAM) interventions.

4.2.2 Effects and mechanisms of laser acupuncture and electroacupuncture

In addition to reducing BW, BMI, and WC, acupuncture regulates the endocrine system, promotes digestion, and attenuates oxidative stress and obesity-related peptides and inflammatory markers (57). Laboratory evidence indicates that acupuncture

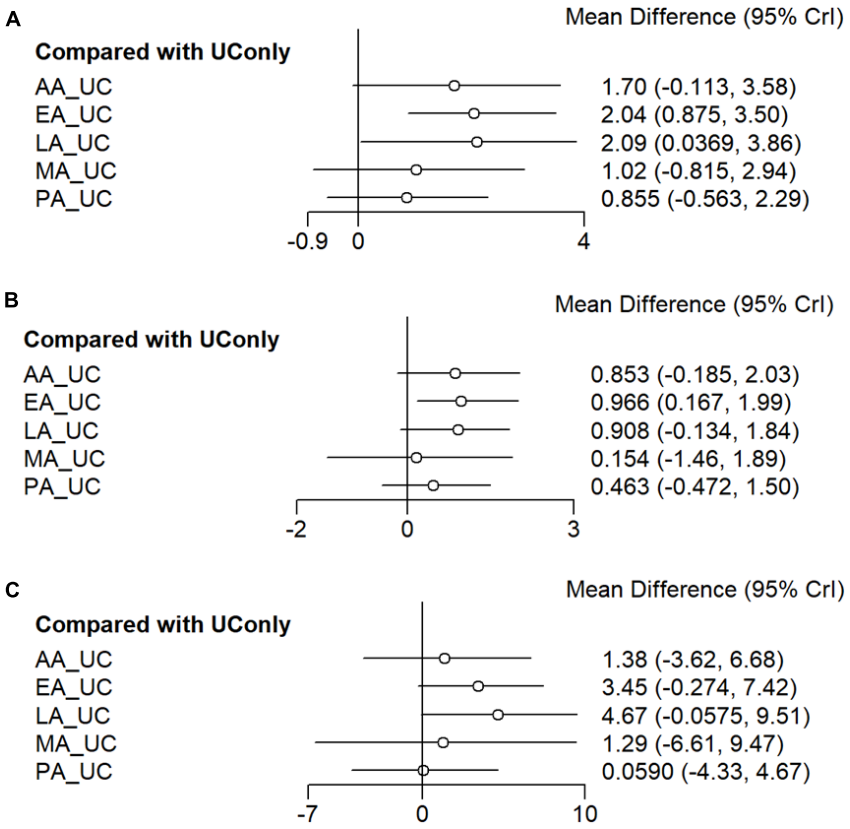

FIGURE 3
Network meta-analysis forest plot. **(A)** Body weight. **(B)** Body mass index. **(C)** Waist circumference. Network meta-analysis forest plot of primary and secondary outcomes. The forest plot was based on a random-effects model. This indicates the mean difference and 95% confidence interval for the effectiveness of the different acupuncture modalities versus usual care. The random-effects model was used to account for variability between studies. AA, auricular acupuncture; BW, body weight; BMI, body mass index; EA, electroacupuncture; LA, laser acupuncture; MA, manual acupuncture; PA, placebo acupuncture; UC, usual care; WC, waist circumference.

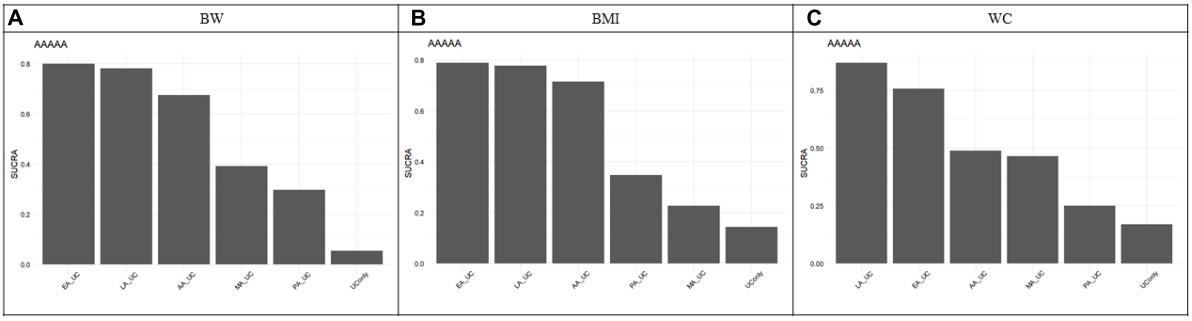

FIGURE 4
Surface Under the Cumulative Ranking Curve (SUCRA). **(A)** Body weight. **(B)** Body mass index. **(C)** Waist circumference. SUCRA showed the probability of each acupuncture modality being the best treatment for body weight, body mass index, and waist circumference. EA showed the highest SUCRA value for BW reduction (0.80), suggesting that it was the most effective modality. The SUCRA values vary from 0 to 1, where 1 indicates that the treatment might be the best and 0 indicates the worst. The probability of being the best treatment for reducing BW was highest for EA (0.8006), LA (0.7830), AA (0.6737), MA (0.3911), PA (0.2962), and UC alone (0.0553), BMI was highest for EA (0.8035), LA (0.7373), AA (0.7176), PA (0.3616), MA (0.2517), and UC alone (0.1284), WC was highest for LA (0.8685), EA (0.7577), AA (0.4891), MA (0.4648), PA (0.2501), and UC alone (0.1698). AA, auricular acupuncture; BW, body weight; BMI, body mass index; EA, electroacupuncture; LA, laser acupuncture; MA, manual acupuncture; PA, placebo acupuncture; SUCRA, surface under the cumulative ranking curve; UC, usual care; WC, waist circumference.

regulates lipid metabolism, modulates inflammatory responses, and promotes the browning of white adipose tissue. Furthermore, acupuncture has been demonstrated to suppress appetite by regulating appetite regulatory hormones and downstream signaling pathway (58). EA exerts antinociceptive and anti-inflammatory effects by regulating the balance of neural-immune–endocrine interactions. EA modulates immune cells, inflammatory cytokines, and peripheral nociceptors at the peripheral level and involves

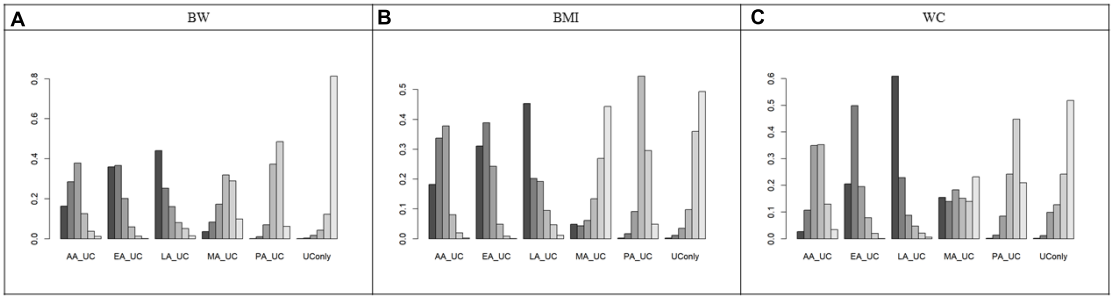

FIGURE 5
Rank plot. **(A)** Body weight **(B)** Body mass index **(C)** Waist circumference. Rank plot showing the probability of each acupuncture modality being the best treatment for body weight, body mass index, and waist circumference. AA, auricular acupuncture; BW, body weight; BMI, body mass index; EA, electroacupuncture; LA, laser acupuncture; MA, manual acupuncture; PA, placebo acupuncture; UC, usual care; WC, waist circumference.

spinal nociceptive neurons and glial cells at the central level (59). EA and MA have been demonstrated to reduce abnormal 5-hydroxytryptamine and corticotropin-releasing hormone concentrations in patients with irritable bowel syndrome. Additionally, EA and MA have been shown to improve intestinal motility and sensitivity by regulating the peptides of the brain-gut axis, such as substance P, vasoactive intestinal peptide, and neuropeptide Y, in the large intestine (60). Consequently, the mechanisms of acupuncture treatment for obesity have been elucidated in considerable detail, which is beneficial for selecting appropriate acupuncture modalities according to the target symptoms of obese patients in clinical practice.

4.2.3 Effectiveness of acupuncture for obesity-related conditions

Acupuncture is used to treat a variety of obesity-related conditions, and its effectiveness has been previously investigated. Recent studies have suggested that major depressive disorder (MDD) and obesity are interrelated in areas such as genetics, immunology, and endocrinology (61). Zhichao et al. (62) compared the effects of several acupuncture treatments and Western medications [selective serotonin reuptake inhibitors (SSRIs), noradrenergic, and specific serotonergic antidepressants] on MDD with NMA. The findings indicated that EA, MA, and Western medications significantly reduced MDD. The combination of EA and SSRIs demonstrated the greatest effect. Polycystic ovary syndrome (PCOS) is closely associated with body weight and BMI, with obesity representing a prominent phenotype in women with PCOS (63). Pan et al. (64) conducted RCTs comparing MA and PA combined with personalized herbal medicine in women with PCOS. The results demonstrated that the MA group exhibited a significantly greater reduction in PCOS scores than those in the PA group.

4.3 Implications for further study and clinical practice

The results of this study demonstrated that EA and LA were the most effective treatments for obesity, with no significant difference in safety compared with that in UC alone, which is consistent with previous studies (65). However, while EA is widely used in clinical practice, LA is not. Based on the results of the current study, it is possible to consider the active use of LA for the treatment of obesity in clinical practice. The acupuncture treatment methods employed in the studies included in the systematic review differed, and there may have been variations in their effectiveness. However, this aspect was not examined in the current study. Future studies should compare the effectiveness of slightly modified acupuncture methods in different clinical settings to determine whether they influence the outcomes of obesity treatment. Furthermore, since the effectiveness of obesity treatment may vary depending on the initial weight of the study participants, it is necessary to apply methodologies such as meta-regression analysis to examine the effectiveness of acupuncture treatment according to obesity level. In this study, only acupuncture was used for isolation. Future studies should investigate the potential synergistic effects of combining two or more TEAM treatments. Furthermore, although this study focused on BW, BMI, and WC outcomes, other indicators of obesity, such as inflammation, blood pressure, and blood glucose levels, should also be studied.

4.4 Strengths and limitations

This study included patients with simple and complex obesity; therefore, the results are generalizable because the patient population is similar to the obese patients encountered in clinical practice. In addition, this approach has the advantage of not combining different clinical outcomes and expressing MD results for each clinical outcome. Nevertheless, certain limitations should be noted. Although an extensive search was conducted using five English-language databases, the number of included studies was limited, and publication bias may have occurred, necessitating a cautious interpretation of the results. Another limitation is that despite some dropouts occurring, most included studies did not clearly state whether they used intention-to-treat (ITT) or per-protocol (PP) in their statistical analysis. This could introduce bias and affect the generalizability of the results. Future studies should clearly define the statistical analysis methods, specifying ITT as the primary outcome analysis and PP for sensitivity analysis, and present the results accordingly to enhance the reliability of the findings. Additionally, the overall number of reported adverse events in the included studies was relatively small,

and some studies did not report on adverse events. Therefore, further observational studies are needed to track the incidence of adverse events in acupuncture treatment for obesity. Furthermore, the number of acupuncture sessions and treatment duration in the included studies were insufficient to examine the long-term effects of acupuncture. Most studies lasted between six and 12 weeks. Future clinical studies on acupuncture for obesity should include longer follow-up periods to better understand the long-term effects and ensure interpretive robustness of the results.

5 Conclusion

A systematic review and network meta-analysis were conducted to compare various acupuncture modalities for the treatment of patients with obesity and overweight. The analysis was conducted on 14 RCTs that included 868 participants. The PMA findings demonstrated that the combination of EA and UC was associated with a significantly greater reduction in both BW and BMI than that in UC alone. The probability of each modality being the optimal treatment was evaluated using SUCRA; EA was observed to be the most efficacious treatment for BW and BMI, whereas LA was the most efficacious treatment for WC. Based on the results of this study, it is possible to consider the active use of EA and LA for the treatment of obesity in clinical practice.

Data availability statement

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

Author contributions

YK: Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. H-iP: Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. HC: Conceptualization, Methodology, Project administration, Writing – review & editing. HJ: Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. JL: Conceptualization, Funding acquisition, Methodology, Software, Supervision, Writing – review & 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1446515/full#supplementary-material

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Comprehensive review of Korean Medicine registries 2015–2023

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Background: Despite the increasing popularity of Korean Medicine (KM), its scientific evidence faces scrutiny. Instead of randomized controlled trials, registries are favored to capture the real world of KM practice due to the difficulties associated with proper control and the holistic nature of the KM approach. This review aimed to examine the KM registries in detail, identify the scope and focus of studies within this field, and assess the research trends.

Methods: We conducted a comprehensive analysis of KM registries listed in trial registration platforms, covering records from their inception until the end of 2023. The selection criteria aimed to include studies focusing on various interventions related to KM, with data extraction focusing on study characteristics and outcomes measured. The analysis utilized descriptive statistics to summarize the findings.

Results: We identified a steady increase in registry studies (2015, one; 2023, seven). Musculoskeletal disorders were most studied (28%), aligning with patients' demand. The involvement of 112 primary clinics and Quality of Life (QOL) as the predominant outcome in 14 (66.7%) registries demonstrates the positive impact on patient well-being and the critical role that primary clinics play in KM practice.

Conclusion: Our findings indicate a heightened interest and commitment to evidence-based KM practices. Future Registries should be implemented on a large scale, incorporating long-term follow-up encompassing primary clinics. This approach would enable a comprehensive evaluation of the effectiveness and safety of KM interventions, as well as offer valuable insights into the influence of KM on chronic conditions and QOL.

KEYWORDS

Korean Medicine, registry, evidence-based, review, research trends

1 Introduction

Korean Medicine (KM), which is an integral part of East Asian traditional medicine, is characterized by a holistic approach that focuses on balancing the vital energy of the entire body (1). It encompasses a range of practices, including herbal medicine, acupuncture, and mind–body therapies. Formed under the influence of ancient Chinese medicine, KM has evolved in tandem with Traditional Chinese Medicine, with both systems influencing each other over centuries (2). However, unlike Chinese medicine facilities, most KM facilities are primary clinics, which impedes the conduct of large-scale controlled clinical trials (3) due to limited personnel and resources.

Accordingly, most related studies have been small-scale studies, such as case series, which may not offer the comprehensive data required for scientific validation (3). Moreover, randomized controlled trials (RCTs) may not be ideally suited to evaluate the holistic and individualized characteristics of KM modalities (4, 5) since they involve complex, tailored treatments aimed primarily at restoring body balance. This focus on the restoration of homeostasis, dynamics, and vitality approaches the individual as an integrated whole, rather than merely targeting isolated pathological entities (6). Consequently, there is a need to establish new research methodologies that align with KM characteristics and allow assessment of the clinical effectiveness and safety of KM as well as facilitate the exploration of KM theories through large-scale data analysis.

Clinical registries are structured systems used to collect, manage, and analyze health-related data for a specific population, condition, or treatment (7, 8). These registries are designed to systematically gather detailed medical information from patients over time, providing a rich resource for understanding disease progression, treatment outcomes, and patient safety (9). Unlike RCTs, clinical registries capture data in real-world settings, offering insights into how treatments perform in diverse and everyday clinical scenarios (10). These data can include patient demographics, diagnostic information, details of treatments received, and outcomes of those treatments (2020) (9). By harnessing the power of large datasets, clinical registries facilitate observational studies and post-marketing studies, which contributes toward elucidation of healthcare interventions (11). This approach is particularly suited for KM settings where large-scale RCTs are less feasible.

Accordingly, this study aimed to explore the current status of clinical KM registries. Specifically, this study aimed to analyze information from ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), and the Clinical Research Information Service (CRIS) in order to gain insights into the methodologies and demographics involved in KM research. Our objective was to review the past registration status of Korean Medicine in registries in order to guide future research.

2 Methods

2.1 Database sources

We comprehensively utilized KM registry information from the ClinicalTrials.gov, ICTRP, and CRIS, covering the period from their inception to the end of 2023. These databases were selected due to their comprehensive coverage of clinical studies in KM, which yielded a broad and representative sample of KM research.

2.2 Data collection and selection criteria

This study included registry studies focusing on KM interventions such as herbal medicine, acupuncture (including electroacupuncture, pharmacopuncture, and thread embedding), moxibustion, massage, and mind–body therapies. Searches were conducted in both Korean and English, using keywords like Korean Medicine, herbal medicine, acupuncture, registry, and Korea, in order to capture a diverse collection of KM practices. Our inclusive approach did not restrict disease conditions, age, or sex of participants. We excluded duplicate studies across the databases, non-registry-based studies, and studies conducted outside South Korea in order to focus on native KM practices. The analysis did not impose a predefined definition for endpoint outcomes, which allowed the inclusion of a wide array of outcome measures reported in KM studies.

2.3 Data extraction

We utilized a data extraction form to systematically gather essential information from each included KM registry such as study registration number, registration and ethics approval dates, public and scientific titles, sponsor organization and study site, study status, primary sponsor, study design, actual start and completion dates, sample size, intervention measures, inclusion and exclusion criteria, participant demographics (age, sex, health condition), and primary and secondary outcomes. Missing data were supplemented from study descriptions or marked as Not Reported (N/R) when unavailable.

2.4 Analysis methodology

For the analysis of coded data within our study, we employed Microsoft Excel (Version 2108), leveraging its capabilities to systematically organize and assess the collected information. We focused on categorical data, which are expressed as absolute numbers (n) and relative percentages (%).

3 Results

3.1 Search results

Figure 1 shows the publication retrieval process. From an initial 1,088 identified records, 336 were removed due to duplication and 731 were excluded for not being relevant to KM registries, including 484 non-registry-based studies, 216 studies conducted outside South Korea, and 31 studies not related to Korean Medicine. Consequently, we selected 21 eligible studies on KM registries. Supplementary Table S1 provides the detailed characteristics of the selected KM registry studies.

3.2 Registration trends of the KM registries

The included KM registries were registered between 2015 and 2023, with a trend of a steady increase from one in 2015 to seven in 2023 (Figure 2). The first registry study, which was registered on March 30, 2015, was an observational multicenter study trial titled "Korean medicine registry for low back pain-prospective observational multicenter study" (KCT0001427, NCT02418286), and it was sponsored by Gil Korean Medicine Hospital, Gachon University. The organization that conducted the highest number of registry studies during this period was Kyung Hee University ($n = 7$), followed by Korea Institute of Oriental Medicine ($n = 3$) and Pusan National University ($n = 3$).

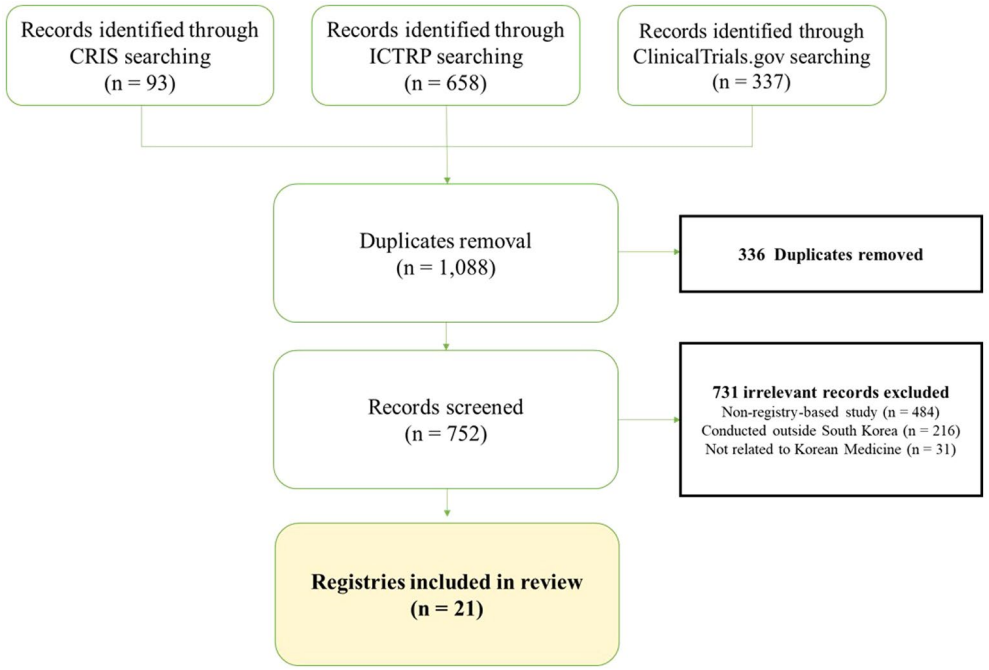

FIGURE 1
PRISMA flowchart of the selection process for Korean Medicine registries.

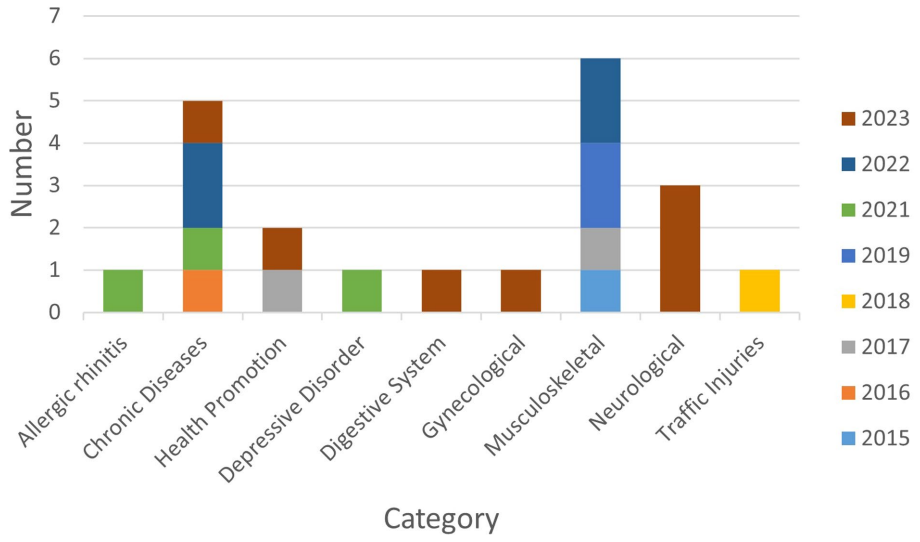

FIGURE 2
Categorization and annual distribution of Korean Medicine registries.

3.3 Prevalence of conditions in KM registries

Musculoskeletal disorders were the most studied condition with six registries (28%), followed by chronic diseases with five registries (24%). Regarding chronic diseases, neoplasms and obesities were studied in two registries (9%) each, while essential hypertension was studied in one (5%). Neurological conditions were studied in three registries (14%), including two studies (9%) on stroke and one (5%) on facial palsy. Two (9%) registries focused on health promotion, while there was one (5%) registry each on the respiratory disorders, gynecological disorders, depressive disorder, traffic injuries, and digestive disorders (Figure 2).

3.4 Characteristics of the KM registries

Ethics approval was granted in 95.2% of KM registries, with the remaining registries having an unclear status. Hospitals were the

predominant sponsor organizations (61.9%), followed by universities (19.0%), research institutions (14.3%), and a primary clinic (4.8%). Registries typically focused on specific diseases or conditions (52.4%), treatment methods (28.6%), and patient groups (19.0%). The sample sizes varied, with most studies (33.3%) including 100–199 participants. Large cohort studies with 200–499 and ≥ 1,000 participants were equally represented (23.8% each), while smaller studies with <100 and 500–999 participants were less frequent (9.5% each). Completed studies comprised 66.7% of the registries, with the remaining registries (33.3%) still recruiting. Most studies were multi-center, with 52.4 and 28.6% of the studies involving <10 and ≥ 10 centers, respectively, highlighting a preference for collaborative research efforts across sites. Single-center studies accounted for 19.0% of the registries. Among the participating institutions, there were 112 primary clinics and 68 hospitals, indicating the active participation of various healthcare settings in advancing KM research. Among the 21 included registries, 10 published their protocol, with only one registry (KCT0006625) publishing both the protocol and the results (12, 13) (Table 1; Supplementary Table S1).

TABLE 1 Characteristics of the KM registries.

Item	Detail	Record [*n* (%)]
Ethics approval	Yes	20 (95.2)
	Unclear	1 (4.8)
Sponsor organization	Hospital	13 (61.9)
	University	4 (19.0)
	Research institution	3 (14.3)
	Primary clinic	1 (4.8)
Types of registries	Disease/Condition	16 (76.2)
	Treatment method	8 (38.1)
	Patient group	5 (23.8)
Sample size	< 100	2 (9.5)
	100–199	7 (33.3)
	200–499	5 (23.8)
	500–999	2 (9.5)
	≥ 1,000	5 (23.8)
Recruitment status	Completed	14 (66.7)
	Recruiting	7 (33.3)
Participating site	Single-center	4 (19.0)
	- Hospital	3 (14.3)
	- Primary clinic	1 (4.8)
	Multi-center (< 10)	11 (52.4)
	- Hospital	10 (47.6)
	- Combined	1 (4.8)
	Multi-center (≥ 10)	6 (28.6)
	- Hospital	1 (4.8)
	- Primary clinic	5 (23.8)
Publication	Yes	10 (47.6)
	No	11 (52.4)

3.5 Outcomes measured in KM registries

The most frequently assessed outcome was quality of life [14 (66.7%)] registries, underscoring the impact of KM treatments on patient well-being. Subsequently, adverse events were monitored in 12 (57.1%) registries to ensure safety of KM interventions. Disease-specific outcomes, including the Shoulder Pain and Disability Index, Body Mass Index, Total Nasal Symptom Score, the House-Brackmann scale, and stroke evaluation metrics, were tracked in 10 (47.6%) registries to evaluate treatment efficacy across various conditions. Other measured outcomes included the Numeric Rating Scale score for pain [6 (28.6%) registries], patient satisfaction [5 (23.8%) registries], the Oswestry Disability Index for back pain disability and Concomitant Drug use [4 (19.0%) registries], and the Patient Global Impression of Change and KM Pattern Identification [3 (14%) registries each] (Figure 3; Supplementary Table S1).

4 Discussion

We conducted a comprehensive review of KM registries listed in ClinicalTrials.gov, the ICTRP, and the CRIS from inception up to the year 2023. The analysis revealed a consistent increase in the number of KM registry studies (one in 2015 to seven in 2023). This upward trajectory highlights the growing interest in registry research within the KM community and illustrates the expanding commitment to documenting and validating the efficacy and safety of KM practices through clinical registries. This trend is especially significant given the unique challenges of conducting large-scale studies in KM clinical settings, which often operate within resource-constrained environments (14, 15). The increase in registry studies serves as an adaptive strategy for comprehensive collection of KM data, which enhances the evidence base within the constraints of traditional clinical settings.

This review of KM registries showed that musculoskeletal disorders were most extensively studied condition. This is consistent with the findings of a 2022 survey indicating that 74.8% of patients sought KM treatments specifically for musculoskeletal issues (16), and thus emphasizes the significant role of KM in addressing these ailments. Furthermore, the diversity in research topics extends beyond musculoskeletal disorders, covering a wide spectrum of health conditions ranging from neurological and respiratory to metabolic diseases (12, 17, 18). This highlights the broad applicability and versatility of KM, showcasing its potential to address diverse health challenges.

Our findings indicated a strong ethical commitment in KM research, with 95.2% of the studies receiving ethics approval. In registry studies, ethics approval is essential for safeguarding participant welfare, ensuring data integrity, and maintaining public trust in the research process (2018) (19). In our review, hospitals were the leading sponsor organizations (61.9%), with universities and research institutions also providing significant support, which highlights the wide-ranging backing for KM research. Moreover, the registries primarily focused on specific diseases or conditions (76.2%), treatment methods (38.1%), and patient demographics (23.8%), which demonstrates the diversity of studies within the KM field. Moreover, majority of the studies were multi-center studies, emphasizing

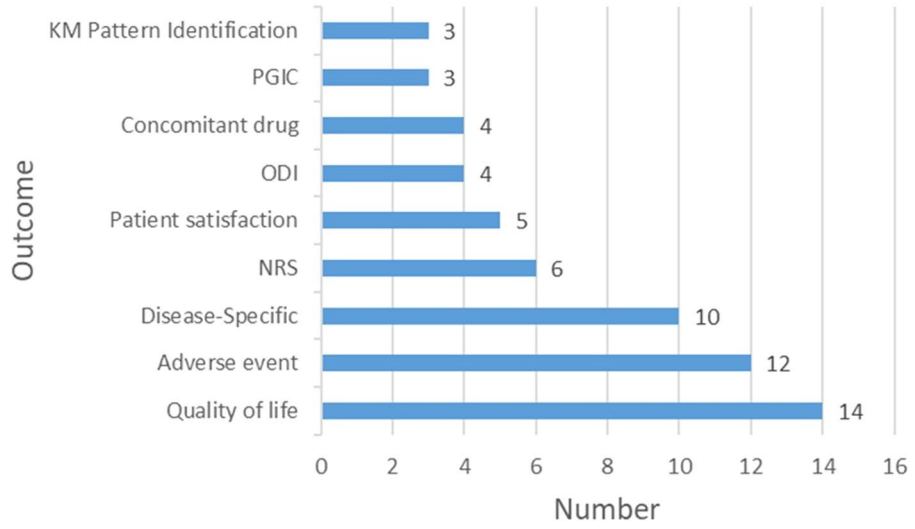

FIGURE 3
Outcome measures in Korean Medicine registries. KM, Korean Medicine; PGIC, Patient global impression of change; ODI: Oswestry disability index; NRS: Numeric rating scale.

collaboration and comprehensive research. Furthermore, 112 primary clinics and 68 hospitals participated in registries, highlighting the essential role of primary clinics in KM research. This is consistent with the fact that >85% of KM institutions operate as primary care clinics (3, 16), which underscores the extensive involvement of various healthcare environments in KM studies.

In KM registries, quality of life emerged as the primary outcome [14 (66.7%) registries], highlighting the positive effects of KM treatments on well-being. Subsequently, 12 (57.1%) registries tracked adverse events, emphasizing the commitment to the safety of KM practices. This is consistent with previous findings indicating that KM treatments contribute to enhancing the quality of life and are recognized as safe therapeutic options (20–23). Disease-specific outcomes, along with metrics such as pain and patient satisfaction, illustrate a broad approach for evaluating the efficacy of KM. However, the limited inclusion of KM Pattern Identification (only three registries) and the overall scarcity of unique characteristics of KM suggest that the research may not fully capture or utilize the unique aspects associated with KM. This gap could restrict the selection of suitable participants and accurate evaluation of the efficacy of KM, which May lead to overlooking of its holistic and individualized nature. This highlights the necessity for future research to comprehensively integrate and elaborate on the distinct principles and practices of KM.

In this review, only one KM registry study (KCT0006625) published both its protocol and results, indicating a significant transparency gap in KM research (12, 13). This issue impedes identification of publication bias and selective reporting, and thus challenges the integrity and assessment of KM findings (24). It is important to improve publication practices of KM in order to ensure transparency, uphold ethical standards in clinical research, build trust, and maintain the relevance of research findings. Publishing both study protocols and outcomes is key to validating research credibility. Future efforts should aim to broaden the scope of research, improve the sharing of findings, and foster collaborations that will deepen the understanding and application of KM in addressing a wide range of health challenges.

To address these critical issues, we propose several recommendations. Large-scale studies are warranted to comprehensively evaluate the effectiveness and safety of KM treatments, as well as to elucidate underlying KM theories. Given that >85% of KM care is delivered in primary clinics (3, 16), their inclusion in studies is vital for capturing real-world practices. Establishing incentive systems, including certifying clinics that use standardized electronic medical records for registry contributions, can significantly enhance data collection, and thus facilitate comprehensive research representation of KM (25). Furthermore, developing a registry for treatment methods that accommodates the unique diagnostic terminologies of KM, alongside long-term observation of patients, will provide insights into the impact of KM on chronic conditions and quality of life (26, 27). Research should not only focus on data collection but also aim to improve patient care through measurement-based care approaches, offering patients tangible benefits from their participation (28). Finally, the development and widespread adoption of a user-friendly, comprehensive electronic medical record system that is tailored to the specific needs of KM will support retrospective and prospective data collection, and thus ultimately advance the integration of KM into the broader healthcare landscape.

5 Conclusion

Our comprehensive review highlights the growth and potential of KM research in South Korea, emphasizing the need for greater transparency and integration of its unique attributes. The increasing number of registry studies signals a shift toward evidence-based practices. However, there remain challenges, including the limited inclusion of unique characteristics of KM and gaps in publishing protocols and results. Addressing these issues is crucial for advancing the credibility and utility of KM in healthcare. Future efforts should

focus on enhancing publication standards, deepening research into holistic principles, fostering its role in integrative medicine, and improving patient care.

Data availability statement

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

Author contributions

S-DK: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. SC: Supervision, Writing – review & editing. SK: Conceptualization, Project administration, Supervision, Writing – review & 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1412053/full#supplementary-material

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Integrative nursing interventions: knowledge, attitudes and practice in home nursing services in Germany—a quantitative and qualitative online survey

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Introduction: Integrative nursing interventions (INI) play a significant role in healthcare, particularly in the prevention and treatment of chronic diseases. Integrating evidence-based INI into healthcare aligns with global initiatives such as the WHO's Decade of Healthy Aging 2020–2030. Many INI are low-threshold practices, empowering patients to independently manage health. However, the extent to which INI are used by home-care nursing-services (HNS) remains largely unknown. This study aims to explore the field of INI in German HNS regarding nurses' use of INI as well as attitudes, subjective knowledge, and information needs on the subject.

Methods: A cross-sectional anonymous online survey with 29 Likert scale items and two open-ended questions was conducted between April 2023 and July 2023. The survey targeted nurse managers of HNS in Baden-Württemberg, Germany. Descriptive analysis was performed for quantitative data, while content analysis according to Kuckartz was applied to analyze open-ended text responses.

Results: In total, $n = 68$ out of $n = 1{,}331$ HNS took part in the survey yielding a response rate of 5.1%. Their overall attitude toward INI was clearly positive (10-point Likert scale M ± SD: 8.37 ± 2.22). The average self-assessed knowledge level about INI was moderate (M ± SD: 5.39 ± 2.76). Almost half of the participants (45.6%) declared to incorporate INI in patient care. Most participants (84.2%) lacked employees with additional qualifications in INI. The INI used most were medicinal herbal teas (61%), compresses (57%), and aromatherapy (48%). Acupressure showed the greatest disparity between actual use in participating HNS (4.3%) and interest in further education (61%). The most common symptoms for which INI are used are pain, respiratory problems, anxiety, and palliative care. The main challenges reported for the use of INI in HNS are financial aspects, qualification and limited resources (staff and time).

Discussion: This exploratory study provides the first insights into nurses' attitudes, self-assessed knowledge, and utilization of INI in German HNS. Overall response rate was low (5.1%), therefore, the results should be interpreted with caution. Urgent action is needed to address financial aspects and further education on INI, to promote integration of INI in HNS to the best possible extent.

KEYWORDS

integrative nursing, self-care, home nursing service, Naturheilkunde, non-pharmacological interventions, primary health care

1 Introduction

Integrative nursing interventions (INI) play a significant role in global healthcare, particularly for the prevention and treatment of chronic disease (1, 2). This recognition is endorsed by the World Health Organization (WHO) (3, 4). Integrating evidence-based INI into healthcare aligns with global initiatives such as the WHO's Decade of Healthy Aging 2020–2030 (5, 6).

Nurses are approached by their patients for INI and increasingly apply them as complementary interventions during standard patient care (7). One reason for this is that they are considered low-threshold, safe interventions that can be learned by patients and their relatives (8–11). Kligler et al. discovered that employing"effective educational strategies that encourage patient engagement in symptom self-management and strategies that improve whole-person wellbeing" are considered profession-specific nursing competencies in the field of Integrative Health (12).

To date, there is no clearly defined terminology for interventions considered complementary to biomedical practice and nursing (1). Terms like "Integrative Medicine" (IM), "Integrative Nursing" (IN) or "Complementary and Integrative Health" (CIH) are used to refer to evidence-based approaches to implementing these interventions in health care (1, 13–15). In German-speaking countries, the term "Naturheilkunde" is commonly used in the context of CIH, especially for nursing interventions of German Traditional European Medicine (TEM) (16, 17). For consistency in terminology, the term "complementary and integrative health" (CIH) will be used throughout this study, even when referring to studies that use the term "complementary and alternative medicine" (CAM) or "complementary and integrative medicine." The term "integrative nursing interventions" (INI) will be used to describe CIH interventions that are applicable to nursing practice.

INI encompasses therapies such as wraps, compresses, aromatherapy, and acupressure, therefore, taking a holistic approach to healthcare by addressing physical, psychological, social, and spiritual dimensions (18–20). Many INI facilitate self-care practices, empowering patients to manage their health independently, either with guidance from healthcare professionals or autonomously (21). As a result INI are an important resource for self-care, with patients' confidence in their ability to care for themselves being a strong predictor of physical and emotional quality of life (22). Numerous studies have shown the effective promotion of (older) people's self-care skills by professional caregivers (7, 23–28).

Self-care skills can be helpful for people in need of long-term care. In Germany, more than 80 percent of people in need of long-term care are cared for at home, with more than half (51.3%) being cared for by family caregivers and with around a third (36%) being supported by home nursing services (HNS). HNS play an increasingly important role in supporting family caregivers (29). Furthermore, INI such as acupuncture/acupressure and phytotherapy have accumulated evidence from randomized controlled trials and meta-analyses that supports their efficacy and relevance in clinical practice (30, 31). The German S3 guideline for complementary methods in oncology underscores the growing recognition of these interventions (32).

For external applications, which are the main INI, there is a growing body of evidence for their efficacy. For example, studies have shown the effectiveness of topical herbal medicines for treating psoriasis (33), hot abdominal compresses for increasing liver blood flow (34), yarrow liver compresses for reducing fatigue in cancer patients (35), cabbage leaf wraps for osteoarthritis of the knee (36), and footbaths with mustard, ginger, or warm water alone for improving heat distribution (37). However, there is a lack of studies of external applications, therefore expert consensus provides the best available evidence in these cases (16).

The strong patient preference for INI also plays an important role in evidence-based healthcare (38, 39). Studies show a high level of acceptance of INI and CIH among patients (8, 15, 21, 40–42). In Europe 25.9% of the general population reported using CIH, with two to four times higher usage among those with health problems compared to those in good health (43). In Switzerland, around a third of the total population report using CIH, while in Germany the figure ranges from 40 to 62% (44–46). Patients use INI and CIH for various reasons, among them expecting benefits in treating their diseases and alleviating the side effects of conventional therapy (9, 47, 48).

In Germany, the growing demand for INI is contrasted by the lack of formalized training for these skills. Although there are many INI education and training options available, they vary widely in eligibility requirements, length, content, evidence base, certification, and cost. An evidence-based formalized education on CIH and INI is also important for patient safety, as asserted by the WHO in 2013, which emphasized that the knowledge and qualifications of practitioners directly impact patient safety (4).

Nurses are often very open to CIH (49), particularly in oncology, where they see CIH as an opportunity to provide more individualized care to patients. Nurses report that CIH enables them to expand their nursing practice, feel more satisfied with their work and have an effective tool for empowerment (50). Data from a survey of health care professionals at the four university hospitals in Baden-Württemberg show a high level of acceptance of CIH and INI among nurses, even higher than that of medical staff (15). Similarly, a survey of members of the German Society for Palliative Medicine found a high acceptance of CIH and INI (92%) and noted differences between healthcare professions (51). CIH is already widely used in general practice in Germany where approximately 60% of family doctors use CIH procedures such as phytotherapy, acupuncture, and neural therapy (52).

For the German-speaking primary care setting, no INI data from nurses working in HNS could be found in the literature. Therefore, this study aims to gain initial insights into the perspectives of nurses in HNS in Germany on the use of INI, their attitudes, knowledge, and the need for information on the topic of INI.

2 Methods

2.1 Research questions

To gain insights into the field of INI in German HNS regarding nurses' use of INI as well as their attitudes, current knowledge and perceived need for continuing education on the subject the following research questions were specifically addressed:

1 Status quo in daily care: To what extent are INI offered in HNS in Baden-Württemberg?
2 Attitudes and knowledge of providers: What are the attitudes and knowledge of nurses working in HNS toward INI?
3 Spectrum: Which INI are specifically used by HNS nurses to prevent or treat a patient's symptoms and health complaints?
4 Interest in training: What skills and information do HNS nurses need regarding INI?
5 Enablers and barriers: What are the enablers and barriers to the use of INI in HNS?

2.2 Study design

We conducted an explorative cross-sectional online survey between April and July 2023 using Unipark software (Questback GmbH). The survey was anonymous and addressed the nurse managers of all 1,331 HNS in the federal state of Baden-Württemberg, Germany. According to the Ethics Committee of the University Hospital and Faculty of Medicine of Tübingen, and in accordance with the German Federal Law § 3 Abs. 6 BDSG/LDSG BW, no formal ethics approval is required for the collection of anonymous data. Therefore, the Ethics Committee of the University Hospital and Faculty of Medicine Tübingen did not provide a consultation. The study was conducted in accordance with local legislation and institutional requirements. The participants gave their written informed consent to participate in this study. To ensure anonymity, no IP addresses were recorded and no cookies were used. The survey targeted nurses with leadership roles in the HNS, as they can provide comprehensive information on the use of INI and the challenges involved, including the economic perspective.

To date, no suitable validated questionnaire has been found in the literature. Therefore, we developed a questionnaire based on our research questions. As a basis, we used a questionnaire recently distributed to healthcare professionals at university hospitals in Germany (15), and a questionnaire used in a nationwide survey of general practitioners in Germany (52).

We then adapted it to the context of HNS. The questions adopted from the previous questionnaires pertain to general attitudes toward INI, attitudes toward INI in HNS, knowledge of INI, and training needs (research questions 2 and 4). The questionnaire underwent a two-stage pretest. Initially, it was pretested by a group of eight healthcare professionals in a methods workshop. Subsequently, it was cognitively pretested by five nurses of the target group with the think aloud method (53) for content completeness, clarity, and duration of the survey. The nurses are part of the author's research network. All hold managerial positions and have work experience in HNS, with three having additional qualifications in INI. After pretesting, the questionnaire was adapted accordingly.

The final version of the questionnaire contained 29 Likert scale questions (for research questions 1, 2, and 4) and two open-ended questions (for research questions 3 and 5).

The 29 Likert scale questions are divided into six sections covering attitudes, practice of INI in HNS, knowledge and information needs, socio-demographic data, characteristics of HNS and challenges. The scales include 5- and 10-point endpoint Likert scales, e.g., on general attitudes toward INI (10 = "very favorable") or motivation to use INI in HNS (5 = "I fully agree"), as well as multiple-choice and single-choice questions.

In addition, a list of nine INI was used to assess the methods used in HNS, the additional qualification of participants and nurses, and the need for continuing education. These nine items were derived from previous studies (7, 10, 54). Due to the exploratory nature of the study, two additional questions were open-ended (reason for using INI in HNS, challenges associated with using INI in HNS) and six questions allowed for free-text responses in the "other" field (e.g., reasons for not using, reimbursement options, INI used).

2.3 Recruitment of participants

The survey was conducted as a full survey. However, there is no publicly available directory of all HNS in Germany. Since all services are organized through providers, they were asked to distribute the survey link to their members starting in April 2023. Of 11 providers contacted, three declined to distribute the link, citing restrictions on external links due to data security issues. Therefore, a list was manually compiled based on the AOK-Pflegenavigator (as of May 7th, 2023), an online database of a large health insurance company that lists all HNS. The survey link was then distributed to all 1,331 listed HNS in the state of Baden-Württemberg, Germany, in June 2023. For previously contacted HNS, this email served as the initial reminder, followed by reminders sent to all 29 email addresses that send out-of-office notifications. The survey was completed after 12 weeks in July 2023, 2 weeks after the last recorded end of leave date according to participants' out-of-office notifications.

As an incentive to participate in the survey, a free online training course on evidence-based INI in HNS (90 min) was offered to all staff at the participating HNS.

2.4 Analyzed data

All questionnaires that received an answer "yes" or "no" to the only mandatory question "Do you use INI in your home nursing service?" were included in the analysis with variable n due to missing data. The number of responses to each item was variable due to missing data. Cases were excluded only if the duration was implausible (e.g., survey time < 1 min, $n = 6$). Several plausibility checks were performed, e.g., to ensure that no service participated twice [e.g., plausibility of number of staff (number of variable (v)101), organization (v164), location (v100)] or to control for a non-response bias.

Two variables were recoded for analysis. "Year of exam" (v_78) was recoded to "Years since exam" (v_78_new), HNS provider (v_164 v_165) was recoded to provider status (private, non-profit, public; v_164 v165_new).

2.5 Analysis

IBM SPSS Statistics 28 was used for descriptive statistical analysis. Results are presented as absolute frequencies and percentages or as mean ± standard deviation (SD).

All written responses to the two open-ended questions were analyzed using content analysis following Kuckartz's approach, to generate major categories and their corresponding subcategories (55). Responses to the six questions that allowed free-text responses in the "other" field were analyzed descriptively.

Two investigators developed a first coding system of thematic categories. Through consensus, initial codes were refined to create a coherent system of categories. The emergent themes from the content analysis were then discussed with the other data of the survey.

Participants' quotes were translated from German into English and are presented along with their pseudonyms to highlight the findings in this article.

Data reporting in this article follows the standard of the consensus-based Checklist for Reporting of Survey Studies (CROSS) (56).

3 Results

3.1 Response rate

The survey link was sent to $n = 1{,}331$ HNS. The overall response rate was 5.1% ($n = 68$).

3.2 Sociodemographic characteristics of participants

Sociodemographic data are summarized in Table 1. Not all 68 participants answered all the questions. The gender question was answered by 57 participants and of which four fifths (80.7%, $n = 46$) identified as female. The majority (91.2%, $n = 52$) had a working capacity of 75 to 100% (part time employment measure where 100% would be considered full time employment).

The mean age of the participants was 49.5 years (SD = 11.9), and they had an average of 25.7 years (SD = 12.7) of experience since graduating from nursing school. Almost all respondents (96.5, $n = 57$) were involved in direct patient care. The majority of respondents/nurses (86.4%, $n = 57$) use INI personally.

TABLE 1 Demographic categories.

Demographic categories	N	%
Gender ($n = 57$ respondents)		
Female	46	80.7
Male	11	19.3
Nursing qualification ($n = 59$)[1]		
Registered nurse (3 year qualification with state exam)	53	89.8
Postgraduate bachelor degree in nursing science	11	18.6
Other postgraduate academic qualification[2]	5	8.5
Leadership position ($n = 59$)		
Head of nursing service	38	64.4
Deputy head of nursing service	12	20.3
Management	14	23.7
Other[3]	8	13.6
No leadership position	1	1.7
Involved in direct patient care ($n = 57$)		
Yes	55	96.5
No	2	3.5
Personal use of INI ($n = 66$)		
Yes	57	86.4
No	9	13.6
Percentage of work[4] ($n = 57$)		
< 50%	2	3.5
50–75%	3	5.3
75–100%	52	91.2
	Mean	SD
Age, in years ($n = 56$)	49.46	11.91
Years since exam $n = 54$	25.69	12.73

Demographic categories with frequency (N) and valid percentage (%).
[1]Nursing education in Germany is predominantly vocational, with few bachelor's degree programs. Some nurses also pursue a bachelor's or master's degree in nursing science.
[2]e.g., public health, palliative care MAS.
[3]Other (e.g. quality management, continuing education and training, clinical supervisor).
[4]Where 100% corresponds to full-time employment.

3.3 INI in HNS

3.3.1 Use of INI and patient demand for INI

The question "Do you use INI in HNS" was the only mandatory question, meaning that all $n = 68$ participants provided an answer. Slightly more than half (54%, $n = 37$) of the HNS do not use INI, while 46% ($n = 31$) do. Patients' demand for INI (question: "I myself am explicitly asked about INI by patients") was answered by $n = 57$ participants, whereby 63.2% ($n = 36$) with "never or rarely (about once every 6 months)" and 15.8% ($n = 9$) with "very often (several times a week)" or "frequently (about once per week)."

3.3.2 General attitude toward INI

The general attitude of the responding nurse managers ($n = 65$) toward INI (question: "What is your general attitude toward INI") was clearly positive ($M \pm SD$: 8.37 ± 2.219; Likert scale: 1 = "very unfavorable," 10 = "very favorable").

3.3.3 Characteristics of HNS

The majority of HNS (84.2%, $n = 48$) did not have staff with additional qualification in INI.

All HNS in Germany have a provider that has one of the following statuses: private/for-profit, non-profit (e.g., charitable and religious associations), or public (municipalities, municipal associations). When asked about the type of provider, nearly two-thirds of participants (27/44 = 61.4%) indicated a private provider, one-third

TABLE 2 Characteristics of HNS.

	N	%
Provider ($n = 44$)[1]		
Private/ for-profit	27	61.4
Non-profit	15	34.1
public	2	4.5
Use of INI in the HNS ($n = 68$)		
Yes	31	45.6
No	37	54.4
Additional qualification INI (leadership) ($n = 57$)		
Yes	8	14.0
No	49	86.0
Employees with additional INI qualification ($n = 57$)		
Yes	9	15.8
No	48	84.2
Location of HNS ($n = 55$)		
Big city > 100.000 inhabitants	8	14.5
Small town 15.000 bis 100.000 inhabitants	22	40.0
Rural area < 15.000 inhabitants	25	45.5
	Mean	SD
Number of employees $n = 55$	38.25	55.25

Characteristics of home nursing services with frequency (n) and valid percentage (%).[1]HNS in Germany have a provider that holds one of the following statuses: private/for-profit, non-profit (e.g. charitable and religious associations), or public (municipalities, municipal associations).

TABLE 3 Motivation to use INI in HNS (scale 1-5).

	Mean	SD
Own basic nursing attitude ($n = 20$)	4.50	.827
Positive experiences with INI in professional activities ($n = 21$)	4.14	1.014
Key experience ($n = 21$)	3.71	1.347
Expanding the repertoire of nursing interventions ($n = 19$)	3.63	1.674
Enthusiasm for INI ($n = 20$)	4.15	1.089
Financial aspects ($n = 18$)	2.94	1.552
Retention of employees ($n = 19$)	3.05	1.615
Good placebo ($n = 19$)	2.00	1.333
Conviction of the effectiveness of INI ($n = 21$)	4.52	.750

non-profit provider (15/44 = 34.1%), and (2/44 = 4.5%) a public provider. See Table 2 for more information.

3.3.4 Motivation to use INI in HNS

Assessment of nine motives for using INI (question: "What motivates you to use INI in HNS?") was obtained using a 5-point Likert scale (5 = "I strongly agree"). The strongest motivators were: Belief in the efficacy of INI (M ± SD: 4.52 ± 0.750), Own basic nursing attitude (M ± SD: 4.50 ± 0.827), Enthusiasm for INI (M ± SD: 4.15 ± 1.089) and Positive experiences with INI in professional activities (M ± SD: 4.14 ± 1.014). See Table 3 for a complete overview.

3.3.5 INI methods used in HNS, additional qualification, interest in training

Table 4 provides an overview of the methods of INI which are used by HNS, the additional qualifications of participants/nurses, and the number of participants who indicated an interest in training.

The most commonly provided INI (question: "Which of the following methods do you use in your HNS?") is herbal tea (60.9%, $n = 14$), the most frequently requested topic for training [question: "Of the INI mentioned, which one would you like to know more about (e.g., as part of a training course)"] is aromatherapy (64.4%, $n = 38$). For acupressure, the difference between use in home-care (4.3%, $n = 1$) and perceived need for training (61%, $n = 36$) is greatest.

Compresses used included ginger compresses on the chest or kidneys and curd compresses on the joints or chest. Herbal teas used included thyme internally for cough and thyme externally for MRSA disinfection. See Supplementary Table 1 for a complete overview of specific methods.

3.3.6 Symptoms for which INI are used

Twenty nurses responded to the open-ended question for "For which diagnoses or nursing diagnoses do you use INI with your clients?" Two nurses stated that INI can be used for all types of health problems, depending on the nurses' competencies and knowledge. The others ($n = 18$) reported a total of $n = 51$ health problems, which were grouped into 12 symptoms and nursing diagnoses. The results were pain ($n = 8$), respiratory problems ($n = 6$), anxiety/restlessness ($n = 6$), palliative care/oncology ($n = 6$), acute injury ($n = 6$), skin problems ($n = 5$), gastrointestinal problems ($n = 6$), depression/mood disorders ($n = 4$), cystitis ($n = 2$), sleep problems ($n = 2$), fever ($n = 2$), dementia ($n = 1$). See Supplementary Table 2 for a complete overview of symptoms.

3.3.7 Reimbursement options

The multiple response question "What are the current options for reimbursement INI?" was answered by $n = 59$ participants. Approximately half (53%, $n = 31$) of the respondents indicated that they were not aware of any official reimbursement options. However, almost the same percentage said they were aware of options, specifically a privately paid service (59%, $n = 35$) and a fee-based service (9%, $n = 5$).

3.3.8 Reasons for non-use (barriers)

Of the $n = 37$ nurses who do not use INI in the HNS, 76% ($n = 28$) use INI personally. The reasons given for not using INI in the HNS were "No way to bill for the service" ($n = 26$, 70.3%), "No staff with knowledge of INI" ($n = 23$, 62.2%), "No resources" ($n = 7$, 18.9%), "I do not believe in INI" ($n = 2$, 5.4%), and "other" ($n = 7$, 18.9%). The following five reasons were listed under "other": "Little interest from staff," "I'm not yet very familiar with INI," "Consultation with doctors necessary, who often do not think much of INI," "No doctor's prescription," "No demand from patients."

3.3.9 Relevance in nursing education

The relevance of INI in their nursing education (question: "How relevant were INI in your nursing education?") was rated (by $n = 56$

TABLE 4 INI methods used, additional qualification, further training.*

	INI used by HNS ($n = 23$)		Additional qualification of participants ($n = 8$)		Additional qualification of nursing staff ($n = 9$)		Participants interest for further training ($n = 59$)	
Methods INI	n	%	n	%	n	%	n	%
Acupressure	1	4.3	0	0	0	0	36	61.0
Anthrop. NC[a]	6	26.1	3	37.5	4	44.4	24	40.7
Aromatherapy	11	47.8	1	12.5	3	33.3	38	64.4
Compresses	13	56.5	2	25.0	5	55.5	35	59.3
Kneipp[b]	1	4.3	0	0	1	11.1	20	33.9
Rhythm.E.[c]	6	26.1	3	37.5	3	33.3	30	50.8
Inhalation	3	13.0	0	0	0	0	21	35.6
Reflexology	1	4.3	1	12.5	1	0	32	54.2
Tea[d]	14	60.9	0	0	2	22.2	27	45.8
Others	7[e]	30.4	3[f]	37.5	0	0	3[g]	5.1

INI methods provided, additional qualification, training needs with frequency (n) and valid percentage (%). *multiple choice.
[a]Anthroposophic nursing care.
[b]Kneipp-therapy.
[c]Rhythmical embrocation according to Wegmann/Hauschka.
[d]Medicinal herbal tea.
[e]e.g., hand massage, see Supplementary Table 1.
[f]Naturopathic practitioner, homeopathy, innerwise coach.
[g]e.g., seitai, Japanese method, embrocation.

participants) as rather low (M ± SD: 3.41 ± 2.418; scale: 1 = "not at all," 10 = "very important").

3.3.10 Knowledge and need for information on INI

The personal level of knowledge about INI (question: "How well do you feel informed about INI overall?") was assessed (by $n = 57$ participants) as rather average (M ± SD: 5.39 ± 2.757; scale: 1 = "very bad," 10 = "very good").

3.3.11 Comparison between INI user and non-user

Comparison of responses from nurse managers of HNS using INI (users) and those that do not (non-user) reveals differences in several variables, as shown in Table 5.

3.3.12 Challenges of using INI in HNS

The open-ended question regarding the challenges of INI in home nursing ("What challenges have you encountered in your experience with INI in HNS") was answered by $n = 45$ participants. In the open-ended final question ("Do you have any comments about this study?"), $n = 20$ participants provided comments, three of which included remarks about opportunities and barriers. These three comments were included in the analysis. The answers were given in keywords and rarely in complete sentences, whereby the maximum number of characters was not used by any participant.

The data-driven content analysis revealed that not only challenges but also opportunities were mentioned. Seven major categories were identified: Financial aspects ($n = 29$ statements), Qualification ($n = 17$ statements), Limited resources (workforce and time; $n = 12$ statements), Patient and Family empowerment ($n = 7$ statements), Policy and health care system ($n = 6$ statements), Interprofessional collaboration ($n = 5$ statements), Patient interest ($n = 4$ statements). Both the challenges and the opportunities were very similar in content between nurse managers of HNS user (U) and HNS non-user (NU). All of the responses can be found in Supplementary Tables 3, 4.

3.4 Financial aspects

Most comments focused on financial aspects of INI ($n = 29$), with $n = 25$ expressing concern about the lack of reimbursement options. Four comments focused on patient financing. On one hand, there are patients who are willing to cover the costs ('Costs (usually) willingly borne by patients when they feel the impact' [U30]), while on the other hand, for many patients, it is not feasible to pay privately out of pocket ('The question is almost always one of coverage, as clients already have high costs and do not want to incur additional costs, even for their own health.' [U22]). The dilemma between perceived need for INI and the lack of funding leads to 'sneaking' services in funded services. [U21].

3.4.1 Qualification

In second place ($n = 17$ comments) were various aspects of qualification, with the most common concern ($n = 11$ out of $n = 17$ statements) being a lack of knowledge about INI among staff. Further training was also discussed from a financial perspective, with one participant noting, "At the moment, systematic further training and education of nursing staff is too expensive and time-consuming" [NU36]. It was suggested that INI should be integrated into nursing education.

3.4.2 Limited resources (staff and time)

In total, $n = 12$ comments were made about the time required for INI. While it was generally noted that there is not enough time, it

TABLE 5 Comparison INI user/ non-user.

Question	Total	INI user	Non-user
	Mean ± SD	Mean ± SD	Mean ± SD
Age	49.46 ± 11.91 (n = 56)	52.33 ± 10.032 (n = 21)	47.74 ± 12.733 (n = 35)
Time passed since passing nursing exam?	25.69 ± 12.73 (n = 54)	27.38 ± 11.042 (n = 21)	24.61 ± 13.756 (n = 33)
General attitude toward INI	8.37 ± 0.219 (n = 65)	9.34 ± 1.045 (n = 29)	7.58 ± 2.590 (n = 36)
Overall, how well do you feel informed about INI?[1]	5.39 ± 2.757 (n = 57)	7.05 ± 2.376 (n = 21)	4.42 ± 2.511 (n = 36)
How relevant were INI to your nursing education?[1]	3.41 ± 2.418 (n = 56)	4.38 ± 2.906 (n = 21)	2.83 ± 1.886 (n = 35)
I myself am explicitly asked about INI by patients.[2]	3.84 ± 1.192 (n = 57)	3.29 ± 1.347 (n = 21)	4.17 ± 0.971 (n = 36)
Counseling on INI is one of the tasks of nursing home-care.[2]	3.33 ± 1.215 (n = 57)	3.86 ± 1.062 (n = 21)	3.03 ± 1.207 (n = 36)
Application of INI is one of the tasks of nursing home-care[2]	3.44 ± 1.254 (n = 57)	4.05 ± 1.161 (n = 21)	3.08 ± 1.180 (n = 36)
I tend to take a positive view of my colleagues' attitude toward INI.[2]	3.70 ± 1.077 (n = 56)	3.95 ± 1.024 (n = 21)	3.54 ± 1.094 (n = 35)
HNS that use INIs are particularly attractive to nurses.[2]	3.19 ± 1.217 (n = 57)	3.38 ± 1.161 (n = 21)	3.08 ± 1.251 (n = 36)
	Percentage		
Personal application (yes/no)	Yes: 86.4% (n = 57)	100% (n = 29)	76% (n = 28)
	No: 13.6% (n = 9)	–	24.3% (n = 9)
Nursing staff with additional qualification in INI (yes/no)	Yes: 15.8% (n = 9)	33.3% (n = 7)	5.6% (n = 2)
	No: 84.2% (n = 48)	66.7% (n = 14)	94.4% (n = 34)

SD, Standard deviation.[1]Scale 1–10.
[2]Scale 1–5.

was also acknowledged that INI require a significant amount of time.

3.4.3 Patient and family caregiver education

There were n = 7 comments regarding the importance of patient and family caregiver education. These statements emphasized the need to provide information about the applications themselves and their mechanisms ("More information is needed to encourage people, especially about the potentially more complex nature and longer onset of effects" [U34]).

3.4.4 Policy and health care system

N = 6 comments were attributed to policy and health care system. Physicians and health insurance companies should address the issue of INI and promote its implementation in HNS. Clarity was called for regarding the activities for which nurses are responsible ("Clear agreement on what can also be done without a doctor's prescription" [NU32]).

3.4.5 Interprofessional collaboration

Within the category of interprofessional collaboration (n = 5 comments), one aspect mentioned was the lack of acceptance of INI by physicians ("Few doctors are open to this kind of healing, dismissing it with the words: 'If you believe in it' "[U60]). The assumption of tasks by nurses was seen as a relief for doctors ("Also, in the context of the shortage of doctors, INI could provide some relief, as it can certainly accompany and manage some symptoms in the early stages of an illness" [NU47]).

3.4.6 Patient interest

N = 4 comments were made regarding patient interest, two of which focused on the age of the patients ("A question of acceptance by the older population" [U22] and "Only patients who have had contact with INI in the past can be won over in old age" [U87]).

4 Discussion

To the best of our knowledge, this study provides the first quantitative and qualitative insights into the attitudes, knowledge, and use of INI among nurses working in HNS. With a response rate of only 5.1 percent, the results should be interpreted with caution. The low response rate is probably due to a lack of time (the resource 'time' is extremely scarce) and because research in the HNS setting is still very uncommon.

The general attitude of the participating nurses toward INI was clearly positive, with almost half of the them stating that they use INI in patient care. The most commonly addressed symptoms are pain, respiratory problems, anxiety, and palliative care. The main challenges reported are financial aspects, qualification and limited resources such as time and staff.

The overall positive attitude toward INI is consistent with the results of a survey conducted at German university hospitals by Hesmert et al., where midwifes and nurses expressed a higher favorability toward CIH compared to physicians and other healthcare professionals (15). In our study, the general attitude toward INI was more favorable among those participants who used INI in HNS compared to those who did not.

Motivators for using INI include the belief in the efficacy of INI, one's own basic nursing attitude, enthusiasm for INI procedures, and positive experiences. This is consistent with data from a study conducted in Switzerland by Aveni et al. which found that personal experience is an important factor for healthcare professionals when forming their opinions and applying CIH (31).

The strong interest of nurses in INI aligns with the literature (57, 58). In our study, aromatherapy was the most frequently requested topic for further training, followed by acupressure. Similar, in the study of university hospitals by Hesmert et al. acupuncture/acupressure was the most frequently requested topic (15).

The need for systematic further education was clearly identified by the qualitative analysis of the survey. Lack of knowledge among staff and lack of training opportunities were identified as the second most common challenge regarding INI in HNS. Participants expressed that knowledge and skills in INI should be provided both during education and through increased opportunities for further training, seeing this as a prerequisite for the implementation of INI in HNS. Hall et al. also state that nurses still have very limited education in this area and lack professional frameworks to support them (50). Resources like the Integrative Nursing Handbook for Teachers in Nursing (INES) (59), and the Competency Catalog for Postgraduate Education in Medical Education developed by Valentini et al. (60) could address this need for qualification.

INI are used for a wide range of conditions, depending on nurses' competencies and knowledge. The assessment of different indications is consistent with the literature, e.g., for pain (36). The specified INI also showed high concordance with those reported by patients as self-administered in a study conducted in primary care practices (9).

The lack of a specific billing code for direct reimbursement of INI suggests that professionals' statements regarding its use are based on professional judgment rather than financial incentives. The survey results indicate that the INI can currently only be funded as a privately paid service. Funding was the most frequently cited challenge related to INI in HNS according to the analysis of the open-ended responses.

A potential advantage of INI in HNS is that they are often cost-effective and that INI applications can be learned by patients who can then apply them independently as directed by nurses. There is a reimbursement/billing code for nursing instructions. When nurses educate patients and family caregivers then this code could be used for billing purposes. The importance of patient and family caregiver education was supported by the qualitative analysis of the statements made in the survey responses in our study.

Interprofessional collaboration (IP) emerged as an issue as a result of the qualitative analysis of the survey. Despite a prevailing negative view among participants, discussions also highlighted opportunities supported by existing literature. Matthys et al. suggest that physician-nurse collaboration can positively impact several patient outcomes and pathologies, including hospital length of stay, blood pressure, and patient satisfaction. This is particularly relevant for patients with chronic conditions or those in need of longterm-care (61). Joos also considers close collaboration between nurses with additional qualification in INI and primary care physicians to be an important factor in the implementation of CIH and INI in patient care (62).

4.1 Limitations

The results should be interpreted with caution because of several important limitations. First, the questionnaire was not validated because, to our knowledge, this is the first study in this area in the German-speaking countries and no validated questionnaire has been published. Therefore, we needed to develop a new instrument. We discussed the questionnaire in our interprofessional team and research network and conducted pre-tests. Another limitation is the low response rate of 5.1%, which, however, is not uncommon in HNS research. Recent work in online monitoring of nursing staff in Baden-Württemberg, Germany, reported a response rate of 8.9% among HNS (63). However, a selection bias is highly probable. To mitigate this, the survey invitation email was worded neutrally. The structural characteristics of the providers of the realized sample closely matched the provider structure of the entire population of nursing facilities in Germany (64).

It is possible that the survey link was distributed beyond the intended list of HNS, as there was no personalized access. While multiple participation by participants was generally possible, it was considered unlikely given the need to provide false demographic information.

Lastly, qualitative data were collected exclusively through two open-ended questions which usually lead to short, condensed responses. More complex content which might emerge in an interview was likely missed.

5 Conclusion

By exploring the challenges and factors that facilitate or hinder the use of INI, this study provides a broad overview and a starting point for further research. Insights into the perspective of nurses working in HNS on INI in their work context were gained. This should be explored further through qualitative interviews. With demographic changes leading to an increase in the number of people needing care, it is increasingly important to empower patients for self-care. INI are good, low-threshold, and safe methods for self-care. Therefore, it is important that they are taught in nursing education and training, that they are reimbursed, and that they are used in an interprofessional primary care setting. The structures within the German healthcare system urgently need to be adapted in order to initiate this development.

Data availability statement

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

Ethics statement

According to the Ethics Committee of the University Hospital and Faculty of Medicine of Tübingen, and in accordance with the German Federal Law § 3 Abs. 6 BDSG/LDSG BW, no formal ethics approval is required for the collection of data. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their informed consent to participate in this study prior to participation in the survey. The participants provided their consent for publication prior to participation in the survey.

Author contributions

RS: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing, Investigation. CK: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. CM: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. JV: Writing – original draft, Writing – review & editing. SJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & 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.

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Supplementary material

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Exploring the association between phytopharmaceutical use and antibiotic prescriptions in upper respiratory infections: results from a German cohort study evaluating the impact of naturopathy qualifications of general practitioners using routine data

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Background: Antibiotic resistance is a significant global health threat, exacerbated by inappropriate prescribing practices, particularly for upper respiratory infections that are predominantly viral. Complementary and Integrative Medicine (CIM), including the use of phytopharmaceuticals, offers a potential strategy to reduce antibiotic prescriptions.

Objective: This study aimed to describe the impact of General Practitioners' (GPs) naturopathy (NP) qualifications and phytopharmaceutical prescriptions on the rate of antibiotic prescribing for upper respiratory infections (RTI).

Methods: We conducted a retrospective cohort study using routine data from the CONTinuous morbidity registration Epidemiologic NeTwork (CONTENT), which includes over 200,000 patients across four federal states in Germany. The study included data from $n = 36$ GPs who recorded at least one ICD-10 diagnosis of RTI. Antibiotic and phytopharmaceutical prescriptions were identified and analyzed through mixed-effects logistic regression models to explore the influence of GPs' naturopathy qualifications and phytopharmaceutical use on antibiotic prescribing patterns.

Results: The study included 40,344 patients managed by 36 GPs. Prescriptions of phytopharmaceuticals significantly reduced the likelihood of antibiotic use (OR 0.48, 95% CI 0.45–0.52). Additionally, holding a naturopathy qualification was associated with lower rates of antibiotic prescriptions (OR 0.73, 95% CI 0.69–0.78). The interaction between naturopathy qualification and phytopharmaceutical prescriptions also showed a significant effect (OR 1.43, 95% CI 1.27–1.62). Patient's year of birth influenced prescribing patterns indicating a reduction of antibiotic prescriptions for younger patients, while patients' gender did not reveal a significant effect.

Conclusion: Prescriptions of phytopharmaceuticals were significantly associated with a decrease antibiotic prescriptions among GPs, especially when combined with naturopathy qualifications. Training in naturopathic approaches could enhance antibiotic stewardship efforts in primary care settings, suggesting that broader integration of CIM elements into medical training could be beneficial in mitigating antibiotic resistance.

KEYWORDS

antibiotic resistance, phytopharmaceuticals, phytotherapeutica, complementary and integrative medicine, naturopathy, upper respiratory infections, cohort study, primary care

1 Introduction

Antibiotic resistance has emerged as a significant and escalating concern in recent years. The World Health Organization declared antibiotic resistance in the Global antimicrobial resistance (AMR) and use report of 2021 as one of the top 10 global public health threats facing humanity (1). AMR develops not only in the context of human medicine but also as a result of antimicrobial consumption in animals, which has enabled large-scale breeding for meat production (2). In 2019, almost 1.3 million deaths worldwide were attributed to multi-resistant pathogens (3), which alone cost the health systems in the EU/EEA an additional approximately 1.1 billion euros per year (4). In Europe alone, approximately 33,000 deaths occur annually as a result of infections caused by antibiotic-resistant bacteria (5). Alarmingly, up to 50% of antibiotic prescriptions in humans are estimated to be not indicated (6). According to the German Antibiotic Resistance Strategy 2030 (DART 2030), about 85% of antibiotics are prescribed in outpatient settings, underscoring the importance of reinforcing appropriate antibiotic usage (7). Antibiotic Stewardship (ABS) is emphasized as an essential strategy for optimizing antibiotic use and mitigating the escalating challenge of antimicrobial resistance according to DART 2023 (7). By focusing on precise diagnostics, timely and appropriate antibiotic selection, and clear guidance on treatment specifics, ABS contributes significantly to responsible antibiotic management in both inpatient and outpatient settings (7). Emphasizing education and behavior reflection among healthcare professionals, including physicians, dentists, and veterinarians, is key to ingraining responsible antibiotic practices (7).

In cases of acute upper RTI, antibiotics are prescribed in 25–41% of instances, despite the majority of these infections being caused by viral pathogens (8, 9). Consequently, antibiotic prescriptions often are inappropriate and ineffective. Further, only half of these prescriptions align with clinical recommendations (10). Notably, general practitioners account for 85% of antibiotic prescriptions (7), which is unsurprising given that acute lower and upper RTI rank among the most common reasons for visits to general practices (11). Consequently, general practitioners represent a crucial starting point for potentially reducing overall antibiotic usage as well as reducing non-indicated antibiotic prescriptions and mitigating associated issues such as antibiotic resistance (12).

One approach to reducing unnecessary antibiotic prescriptions could involve strategies from Complementary and Integrative Medicine (CIM) (13), particularly the use of phytopharmaceuticals, which have been associated with a decrease in antibiotic use (14). Phytopharmaceuticals are defined as medicinal products derived from plant materials (including extracts, tinctures, and compounds) used for therapeutic purposes. Phytopharmaceuticals, unlike traditional herbal remedies such as teas or decoctions, are typically standardized to ensure consistent potency and efficacy (15, 16). When treating acute upper RTI, phytopharmacological substances have undergone extensive investigation in experimental studies, with numerous compounds demonstrating efficacy (17–23). Additionally, patients treated with phytopharmaceuticals experienced a significantly reduced risk of prolonged sick leave (14). In a retrospective cohort study by Martin et al. Pelargonium sidoides root and thyme extract were found to be particularly effective in adult GP patients, while pediatric patients benefited most from Pelargonium sidoides root extract in combination with thyme and ivy extract, as well as thyme and primrose root extract (14).

Despite patients often expecting antibiotics prescriptions (24), phytopharmaceuticals may offer in many cases a preferable alternative that could potentially contribute to reducing antibiotic-resistant bacteria and associated infections. GPs with additional qualifications in naturopathy are known to prescribe more phytopharmaceuticals in general compared to GPs without such qualifications (25). The term "naturopathy" has different meanings in various contexts and countries. For the purposes of this publication, naturopathy refers to the additional qualification in CIM for physicians awarded by the German Medical Association. Upon completing their postgraduate education, physicians in Germany have the opportunity to pursue structured additional qualifications in the field of CIM, which are conferred by the medical association (26). These include Acupuncture, Homeopathy, Manual Medicine/Chirotherapy, Medical Balneology and Climatology, Naturopathy, and Physical Therapy (26). Furthermore, it is important to note that obtaining an additional qualification in Naturopathy (NP) requires 3 months of training under a certified physician, 80 h of case-seminar supervision, and 160 h in a seminar program, totaling 240 h of advanced education (26). This training encompasses various facets of naturopathy including phytotherapy, balneotherapy, massage, manual diagnostics, nutritional medicine, regulative therapy, physical therapy, and neural therapy. Notably, phytotherapy (including phytopharmaceuticals) is a key component among these NP approaches, underscoring the significance of herbal treatments in this field of medicine (26).

Thus, the objective of this study is to examine whether GPs holding an additional qualification in naturopathy prescribe fewer

antibiotics for acute upper RTI compared to those without this qualification. Additionally, we aim to assess which antibiotics and/or phytopharmaceuticals are commonly prescribed for upper RTI and whether phytopharmaceutical usage correlates with reduced antibiotic prescriptions.

2 Materials and methods

This study is a retrospective cohort analysis using routine data from general practices within the German healthcare system. The STROSA 2 checklist was applied to this manuscript (27).

2.1 Data source

Data were obtained from the CONTinuous morbidity registration Epidemiologic NeTwork (CONTENT), a comprehensive general practice research network in Germany (28). CONTENT facilitates the continuous, episodic recording of primary care data, incorporating information from over 200,000 patients and upwards of 4 million patient encounters. The network spans rural, suburban, and urban areas across four federal states in Germany: Baden-Württemberg, Bavaria, Lower Saxony, and Rhineland-Palatinate. The dataset comprises routine claims data from General Practitioners (GPs) as typically gathered within the German healthcare framework. The CONTENT Register was developed and put into operation by the Department of General Medicine and Health Services Research at the University Hospital Heidelberg.

For this study, the CONTENT research network was expanded between April 2009 and March 2015 to include 11 GP practices with additional naturopathic qualifications. This meant that a total of 41 GP practices, 11 of which had additional naturopathic qualifications, were included in the study period. As phytopharmaceuticals are over-the-counter medications that are often recommended but not formally prescribed by GPs, GPs were specifically instructed prior to the start of the CONTENT registry to prescribe each phytopharmaceutical on a prescription (and not just give a verbal recommendation, as is often done in clinical practice) to ensure that the data also accurately reflected the prescribing of phytopharmaceuticals (25).

2.2 Legal basis

The data provision took place before the EU-GDPR. At the time of data collection, the medical professional code of Baden-Württemberg (§15, Para. 3) applied: As a basic principle, only anonymized data are transmitted. For each patient, the CONTENT EPR contains a case number, the patient's year of birth, and the patient's gender but not the name or address. Thus, it is not possible to determine a patient's identity, and the implementation of extensive data security mechanisms is not needed. Moreover, the German Data Protection Act allows the transmission of anonymized patient data for scientific purposes without the explicit permission of patients.

The Ethics Committee of the University Hospital Heidelberg has dealt extensively with the CONTENT project concerning ethical and data protection aspects and, after a consenting assessment, issued a positive vote (442/2005).

2.3 Data protection

The data processing of the Department of General Medicine and Health Services Research at the University Hospital Heidelberg is carried out with systems that are approved, implemented, maintained, and secured by the Center for Digitalization and Information Technology (ZDI) of the University Hospital Heidelberg. The ZDI is a certified institution that either carries out the necessary technical and organizational measures for data processing in accordance with the EU General Data Protection Regulation itself or enables these measures.

2.4 Data flow

Encrypted exports (https) were initiated quarterly by the general practitioner from each individual practice. The quarterly exports were received on a central server behind a firewall. These data were then imported quarterly into the central CONTENT database, which is inaccessible from the outside.

2.5 Eligibility criteria

The study included data from GPs contributing their routine data to CONTENT between January 1, 2010, and December 31, 2014. This encompassed data on 53,572 patients who had at least one ICD-10 diagnosis starting with "J." Diagnoses related to upper RTI, as per the ICD-10 codes, were selected and are detailed in Appendix 1. Exclusions were made for diagnoses where antibiotic prescriptions are generally not indicated (e.g., J09) or in cases of chronic conditions such as COPD. The study required the join of diagnosis and prescription data, both of which were derived from secondary sources.

Initially, all antibiotic prescriptions were identified using the Anatomical Therapeutic Chemical (ATC) classification system. Subsequently, two physicians evaluated these prescriptions to determine their appropriateness for the use in upper RTI, excluding any that were deemed not suitable (e.g., Antibiotics that are either not approved for treating respiratory infections, not recommended by guidelines, or exclusively administered intravenously). Phytopharmaceuticals were also classified using the ATC Code, specifically searching for the term "pflanzl" within the chemical substance subgroup. Following this step, two physicians reviewed the phytopharmaceuticals identified, selecting those appropriate for treating upper RTI according to according to the currently valid clinical guidelines. Prescriptions were considered relevant if prescribed within a maximum of 14 days following the diagnosis.

2.6 Outcome and predictor variables

The study's primary outcomes were antibiotic prescriptions for an ICD-10 J-Diagnosis. The outcome was binary coded (0/1). Predictor variables included the additional qualifications of general practitioners (GPs), specifically their certification in naturopathy and phytopharmaceutical prescriptions. Patient's year of birth (YOB) and patient's gender were also considered as predictor variables. YOB was included as a continuous variable and was scaled to address

convergence issues to ensure the identifiability and proper calculation of the general linear mixed model. The unit for YOB was expressed as the standard deviation (SD) of the overall age distribution.

2.7 Data preprocessing and statistical analysis

Data preprocessing and analysis were performed using R version 4.3.2 (29), utilizing the tidyverse package (30) for data preprocessing and the gtsummary (31) package for generating descriptive tables.

Mixed-effects logistic regression models were constructed, building upon simpler models. These included a model with only an intercept, a model incorporating patient's year of birth (YOB) and patient's gender as covariates, a model integrating the aforementioned predictors alongside the additional NP qualification and phytopharmaceutical prescriptions, and a full model encompassing all explanatory variables along with the interaction of phytopharmaceutical prescriptions and the additional qualification in naturopathy. A random effect for patients was introduced to address data clustering (multiple observations per patient). The analysis was conducted using the R package glmmtmb (32), with result tables produced utilizing the sjPlot (33) package. Overdispersion statistics were derived with the DHARMa (34) package.

3 Results

3.1 Sample description

The cohort comprised 36 GPs, with 11 (27%) possessing additional qualifications in NP and 25 (73%) without the additional NP qualification. Applying the eligibility criteria, resulted in $N = 40,344$ Patients and $N = 81,057$ diagnoses included. An overview of patient demographic can be found in Table 1. Patients year of birth ranged from 1903 to 2014 and 57.2% of the participants were female. The most frequently prescribed phytopharmaceuticals and antibiotics can be found in Tables 2, 3. An overview of the 10 most coded ICD-10 diagnosis can be found in Table 4.

3.2 Generalized linear mixed model

3.2.1 Summary results

Overdispersion statistics can be found in Appendix 2. They were visually checked as significance is a known problem considering the large numbers of measurements. There were no relevant discrepancies discovered. The variance of the random effect ranged between 1.82 and 1.76, the random effect was statistically significant further indicating underlying heterogeneity between the individuals (Table 5). The Model with the best Akaike information criterion (AIC) (101290) was Model 4; including all predictors as well as the interaction term of the NP qualification and phytopharmaceutical prescriptions. An overview of all models and predictors can be found in Table 5.

3.2.2 Patient's year of birth and patient's gender

Patient's year of birth (YOB) was consistently identified as a significant predictor across all models, with odds ratios (ORs) remaining stable at 0.82 (95% CI: 0.80–0.84). Accordingly, antibiotic prescriptions decreased with an odds ratio (OR) of 0.82 for each increase in the scaled variable "year of birth" (where one unit equals 20.1 years), suggesting that younger individuals were less likely to receive antibiotics. Patient's gender, however, did not show a significant impact in Models 0–4, with ORs close to 1 across all models (OR: 1.03–1.04; 95% CI: 0.99–1.08).

3.2.3 NP qualification

The inclusion of additional qualifications in NP as a variable revealed a notable impact across all models where it was included. ORs ranged from 0.76 to 0.73 (95% CI: 0.69–0.82), indicating a reduction on antibiotic prescription rates.

3.2.4 Phytopharmaceutical prescriptions

Phytopharmaceutical prescriptions emerged as another significant predictor, with ORs between 0.53 and 0.48 (95% CI: 0.45–0.56), pointing to a reduction on antibiotic prescriptions.

3.2.5 Interaction: phytopharmaceutical prescriptions and NP qualification

The interaction between phytopharmaceutical prescriptions and an additional NP showed a significant effect, leading to a stratified analysis based on the presence of naturopathy qualifications (Table 6). For GPs with NP qualifications, the OR for phytopharmaceutical prescriptions was 0.69 (95% CI: 0.62–0.76). For GPs without an additional NP qualification, the OR was 0.48 (95% CI: 0.45–0.52). Both predictors revealed a significant effect within their respective models (Figure 1).

3.2.6 *Post hoc* analysis: differences in prescriptions stratified for NP qualification

To further investigate the effect of the identified significant interaction of NP qualification and phytopharmaceutical prescriptions a *post hoc* analysis was conducted. Hereby the primary outcome was re-structured to also describe simultaneous prescriptions of antibiotics and phytopharmaceuticals. A Pearson's Chi Square test revealed differences in

TABLE 1 Sociodemographic characteristics of the patients.

Patient demographics	No NP qualification, $N = 29,947$[1]	NP qualification, $N = 10,397$[1]	Total $N = 40,344$[1]
Year of birth	1972 (20.2)	1973 (19.8)	1972 (20.1)
Gender (female)	17,061 (57.0)	6,028 (58.0)	23,089 (57.2)
Type of health insurance			
Satutory	26,991 (90.1%)	9,603 (92.4)	36,594 (90.7)
Private	2,956 (9.9%)	794 (7.6%)	3,750 (9.3)

[1]Mean (SD); n (%).

TABLE 2 Ten most frequently prescribed phytopharmaceuticals.

10 most frequently prescribed phytopharmaceuticals	$N = 19,317^1$
Sinupret®	5,358 (27.7)
Gelomyrtol®	3,491 (18.1)
Bronchipret®	1991 (10.3)
Prospan®	1888 (9.8)
Bronchicum®	1794 (9.3)
Umckaloabo®	1,529 (7.9)
Bronchoforton®	1,049 (5.4)
Muc Sabona®	789 (4.1)
Angocin®	714 (3.7)
Imupret®	714 (3.7)

[1]n (%).

TABLE 3 Ten most frequently prescribed antibiotics.

10 most frequently prescribed antibiotics	$N = 56,102^1$
Amoxicillin with or without Beta-Lactase-Inhibitors	11,127 (19.8)
Clarithromycin	8,794 (15.7)
Cefuroxime	7,844 (14.0)
Ciprofloxacin	5,666 (10.1)
Cefpodoxime	5,331 (9.5)
Azithromycin	5,062 (9.0)
Levofloxacin	4,114 (7.3)
Phenoxymethylpenicillin	3,186 (5.7)
Doxycycline	2,604 (4.6)
Roxithromycin	2,374 (4.2)

[1]n (%).

the prescription patterns between GPs with and without NP qualification considering prescriptions of antibiotics, phytopharmaceuticals, both types of medication or no prescriptions. GPs with a qualification in NP prescribed less antibiotics, more phytopharmaceuticals, more frequently a combination of both types of medication and more frequently no medication compared to GPs without a NP qualification (Table 7).

4 Discussion

4.1 Main results

The recent study explored how the variables—patient's year of birth, patient's gender, phytopharmaceutical prescriptions, NP qualification, and the combined impact of phytopharmaceutical prescriptions and NP qualification—affect antibiotic prescriptions for upper RTI. As expected all predictors besides patient's gender significantly influenced antibiotic prescription rates. Phytopharmaceutical prescriptions led to the most substantial decrease in antibiotic use, followed by having a qualification in NP and then by patient's year of birth. The concurrent prescription of phytopharmaceuticals along with holding a NP qualification had a notable impact, leading to a reduction in antibiotic prescriptions among GPs possessing an NP qualification while simultaneously prescribing phytopharmaceuticals. Surprisingly, GPs without additional qualification in NP who prescribed phytopharmaceuticals, prescribed even less antibiotics.

In the subsequent paragraph the influence of the significant predictors on antibiotic prescriptions will be discussed.

4.2 Patient's year of birth and patient's gender

While year of birth was consistently identified as a predictor, with older patients likely receiving more antibiotics, patient's gender did not significantly influence prescription patterns. The age-related trends might be attributed to a higher co-morbidities and frailty and is in line with other recent findings (35). However, the lack of significant impact of patient's gender suggests that prescriptive decisions are more strongly influenced by clinical factors and individual qualifications rather than patient gender (36).

4.3 Phytopharmaceutical prescription

Consistent with findings from other studies (12), phytopharmaceutical prescriptions have been found to significantly reduce antibiotic use in treating upper RTI. The effects demonstrated in recent literature also seem applicable to the context of GPs in Germany, suggesting a broader relevance and potential for phytopharmaceuticals in clinical practice consisting of two steps. Firstly, unnecessary antibiotic prescriptions, often administered for upper RTIs which are predominantly viral (37), are not indicated. This action can reduce adverse effects for patients and help mitigate the development of antibiotic resistance. Secondly, evidence-based phytopharmaceuticals should be more widely utilized to alleviate symptoms. Additional research already highlights the effectiveness of phytopharmaceuticals (17–23). In light of our data, it appears that phytopharmaceuticals contribute to the decrease in antibiotic prescriptions for upper RTI. Additional training for physicians in outpatient settings on phytopharmaceuticals could further help reduce unnecessary antibiotic prescriptions.

4.4 NP qualification

To our knowledge, this is the first study to investigate the impact of additional qualifications in NP on antibiotic prescriptions in upper RTI. As anticipated, possessing an additional certification in NP was associated with reduced antibiotic prescriptions in general practice settings in Germany. These GPs' broader training and awareness in complementary and integrative medicine, including phytotherapy as part of their NP qualification, likely predisposes them to favor non-antibiotic treatments. Similar results were found by van der Werf et al. for NHS England GP practices employing GPs with additional CIM training had

TABLE 4 Ten most frequently coded ICD-10 diagnosis, with the frequency and percentages of prescribed antibiotics and phytopharmaceuticals.

10 most frequently coded ICD-10 Diagnosis		No NP qualification	NP qualification	*N* = 77,610
J06.9	Acute upper respiratory infection, unspecified	28,089 (48.3)	9,951 (43.5)	38,040 (49.0)
	Prescribed antibiotics	3,925 (14)	2,684 (27)	
	Prescribed phytopharmaceuticals	5,842 (21)	1,758 (18)	
J02.9	Acute pharyngitis, unspecified	11,961 (20.6)	3,032 (13.3)	14,993 (19.3)
	Prescribed antibiotics	8,201 (69)	1,116 (37)	
	Prescribed phytopharmaceuticals	869 (7.3)	381 (13)	
J20.9	Acute bronchitis, unspecified	7,868 (13.5)	2,335 (10.2)	10,203 (13.1)
	Prescribed antibiotics	4,058 (52)	1,053 (45)	
	Prescribed phytopharmaceuticals	1,175 (15)	476 (20)	
J03.9	Acute tonsillitis, unspecified	4,504 (7.8)	1,340 (5.9)	5,844 (7.5)
	Prescribed antibiotics	3,359 (75.0)	1,005 (75.0)	
	Prescribed phytopharmaceuticals	156 (3.5)	117 (8.7)	
J04.0	Acute laryngitis	1,609 (2.8)	882 (3.9)	2,491 (3.2)
	Prescribed antibiotics	413 (26)	278 (32)	
	Prescribed phytopharmaceuticals	110 (6.8)	145 (16)	
J06.0	Acute laryngopharyngitis	1,564 (2.7)	68 (0.3)	1,632 (2.1)
	Prescribed antibiotics	808 (52.0)	29 (43.0)	
	Prescribed phytopharmaceuticals	112 (7.2)	16 (24.0)	
J06.8	Other acute upper respiratory infections of multiple sites	770 (1.3)	602 (2.6)	1,372 (1.8)
	Prescribed antibiotics	355 (46.0)	103 (17.0)	
	Prescribed phytopharmaceuticals	116 (15.0)	150 (25.0)	
J04.2	Acute laryngotracheitis	573 (1.0)	480 (2.1)	1,053 (1.4)
	Prescribed antibiotics	323 (56.0)	136 (28.0)	
	Prescribed phytopharmaceuticals	110 (19.0)	72 (15.0)	
J01.1	Acute frontal sinusitis, unspecified	93 (0.2)	927 (4.0)	1,020 (1.3)
	Prescribed antibiotics	37 (40.0)	228 (25.0)	
	Prescribed phytopharmaceuticals	40 (43.0)	259 (28.0)	
J01.9	Acute sinusitis, unspecified	701 (1.2)	261 (1.1)	962 (1.2)
	Prescribed antibiotics	438 (62.0)	104 (40.0)	
	Prescribed phytopharmaceuticals	185 (26.0)	86 (33.0)	

lower antibiotic prescribing rates for RTI compared with GPs without additional CIM training. In contrast to this study, we included GPs with a specific qualification in naturopathy, whereas van der Werf et al. included GPs with a wider range of different specializations in CIM (acupuncture, anthroposophic medicine, homeopathy), making the results and implications somewhat difficult to compare, as CIM GPs may have adopted different strategies to decrease antibotic prescribing (38). Nevertheless, both of these findings emphasize the potential benefits of incorporating naturopathic (and/or CIM) training or modules into medical education to enhance multiple therapeutic options for their own prescribing practice. This finding therefore highlights the potential benefits of further training in CIM, suggesting that early integration of CIM-specific competencies in undergraduate as well as in postgraduate training could be particularly beneficial for GPs (39, 40). Valentini et al. (40) identified 16 competencies for postgraduate training of general practitioners (GPs) within the German healthcare system. Among these, competency 7 emphasizes the ability to use common phytotherapeutics and supplements for frequent consultation issues, such as pain, fever, and uncomplicated infections, thus providing a suitable framework for additional training.

4.5 Interaction of phytopharmaceutical prescriptions and NP qualification

The observed outcome of combining an additional NP qualification with the prescription of phytopharmaceuticals did not align with our expectations. Surprisingly, GPs lacking an additional

TABLE 5 Model parameters for Models 0–4.

	Intercept-only model			Model 1			Model 2			Model 3			Model 4		
Predictors	Odds ratios	CI	*p*	Odds ratios	CI	*p*	Odds ratios	CI	*p*	Odds ratios	CI	*p*	Odds ratios	CI	*p*
Intercept	0.47	0.46–0.49	<0.001	0.46	0.44–0.48	<0.001	0.49	0.47–0.51	<0.001	0.54	0.52–0.56	<0.001	0.55	0.53–0.57	<0.001
Gender (female)				1.03	0.98–1.08	0.205	1.03	0.99–1.08	0.146	1.03	0.99–1.08	0.150	1.04	0.99–1.08	0.141
Year of birth scaled				0.82	0.80–0.84	<0.001	0.82	0.80–0.84	<0.001	0.82	0.80–0.84	<0.001	0.82	0.80–0.84	<0.001
NP qualification (yes)							0.76	0.72–0.80	<0.001	0.78	0.74–0.82	<0.001	0.73	0.69–0.78	<0.001
Phytopharmaceutical (yes)										0.53	0.50–0.56	<0.001	0.48	0.45–0.51	<0.001
Interaction phytopharmaceutical (yes) and NP qualification (yes)													1.43	1.27–1.62	<0.001
Random effects															
σ^2	3.29			3.29			3.29			3.29			3.29		
τ_{00}	1.82 $_{cid}$			1.80 $_{cid}$			1.80 $_{cid}$			1.76 $_{cid}$			1.76 $_{cid}$		
ICC	0.36			0.35			0.35			0.35			0.35		
N	40,344 $_{cid}$			40,344 $_{cid}$			40,344 $_{cid}$			40,344 $_{cid}$			40,344 $_{cid}$		
Observations	81,057			81,057			81,057			81,057			81,057		
AIC	102239.572			101941.078			101841.618			101321.117			101290.370		

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TABLE 6 Stratified *post hoc* analysis for NP qualification.

	Model NP qualification			Model no NP qualification		
Predictors	Odds ratios	CI	*p*	Odds ratios	CI	*p*
Intercept	0.35	0.33–0.39	<0.001	0.57	0.54–0.59	<0.001
Gender (female)	1.21	1.10–1.33	<0.001	0.98	0.93–1.04	0.566
Year of birth scaled	0.83	0.79–0.87	<0.001	0.82	0.80–0.84	<0.001
Phytopharmaceutical prescription	0.69	0.62–0.76	<0.001	0.48	0.45–0.52	<0.001
Random effects						
σ^2	3.29			3.29		
τ_{00}	2.02 $_{cid}$			1.69 $_{cid}$		
ICC	0.38			0.34		
N	10,397 $_{cid}$			29,947 $_{cid}$		
Observations	20,590			60,467		
AIC	25171.864			76104.223		

TABLE 7 *Post hoc* analysis—prescriptions stratified for NP qualification.

Qualification in naturopathy	No, *N* = 60,467[1]	Yes, *N* = 20,590[1]	*p*-value[2]
Prescriptions			<0.001
Antibiotics	21,161 (35%)	6,090 (30%)	
Phytopharmaceutical	6,557 (11%)	2,573 (12%)	
Both	2,427 (4.0%)	1,018 (4.9%)	
Nothing	30,322 (50%)	10,909 (53%)	

[1]n (%).
[2]Pearson's Chi-squared test.

NP title showed a greater reduction in antibiotic prescriptions when they also prescribed phytopharmaceuticals.

This discrepancy may arise from GPs with an NP qualification tending to co-prescribe antibiotics and phytopharmaceuticals more frequently than GPs without an additional NP qualification. In contrast, GPs without an additional NP qualification seem to prefer an "either/or" approach, choosing more often to prescribe either antibiotics alone or substitute them with phytopharmaceuticals, rather than combining the two. To explore this hypothesis further, a stratified *post hoc* analysis was conducted. The analysis revealed that GPs with NP qualifications co-prescribed both types of medication in 5% of cases, compared to 4% for GPs without the qualification, underscore this hypothesis. Another reason that may explain the interaction between phytopharmaceutical prescriptions and the additional qualification is that prescribing antibiotics and phytopharmaceuticals is a two-step process. First, non-indicated antibiotic prescriptions must be reduced. In the second step, phytopharmaceutical prescriptions should be increased when indicated to help with symptom relief.

Additionally, we could not account for the use of home remedies, such as inhalation or rinses with, e.g., sodium chloride solutions, which may also have an impact on reducing symptoms. In addition to home remedies, factors such as professional networks and collaborations with laboratories routinely providing information on local resistance data are recognized for their role in shaping antibiotic prescribing behaviors. These elements might also affect how phytopharmaceutical prescriptions and naturopathic practitioner qualifications interact, varying with regional conditions (41). Additional evidence from qualitative studies investigating these different aspects, as well as the motives for antibiotic and phytopharmaceutical prescriptions, are necessary to understand this interaction in depth.

4.6 Clinical and policy implications

These findings have significant implications for clinical practice and health policy. Encouraging the integration of NP training and the use of phytopharmaceuticals could be a part of a feasible strategy to reduce antibiotic prescriptions, particularly in the context of upper RTI where overprescription is common. In Germany, some phytopharmaceuticals are already included in clinical guidelines for GPs, suggesting their broader implementation in treating upper RTIs as an evidence-based strategy (42, 43). Additionally, our research supports ongoing education for healthcare professionals on the risks of antibiotic resistance and the benefits of complementary therapies. The over-prescription of antibiotics, often driven by perceived patient pressure and the fear of disease complications as noted by Altiner et al. (12) highlights the need for improved patient education regarding upper RTIs (44). Home remedies, for instance, could serve as effective tools for patients managing self-limiting conditions. According to a 2014 study, a significant number of patients use home remedies to manage symptoms of colds, with 97%

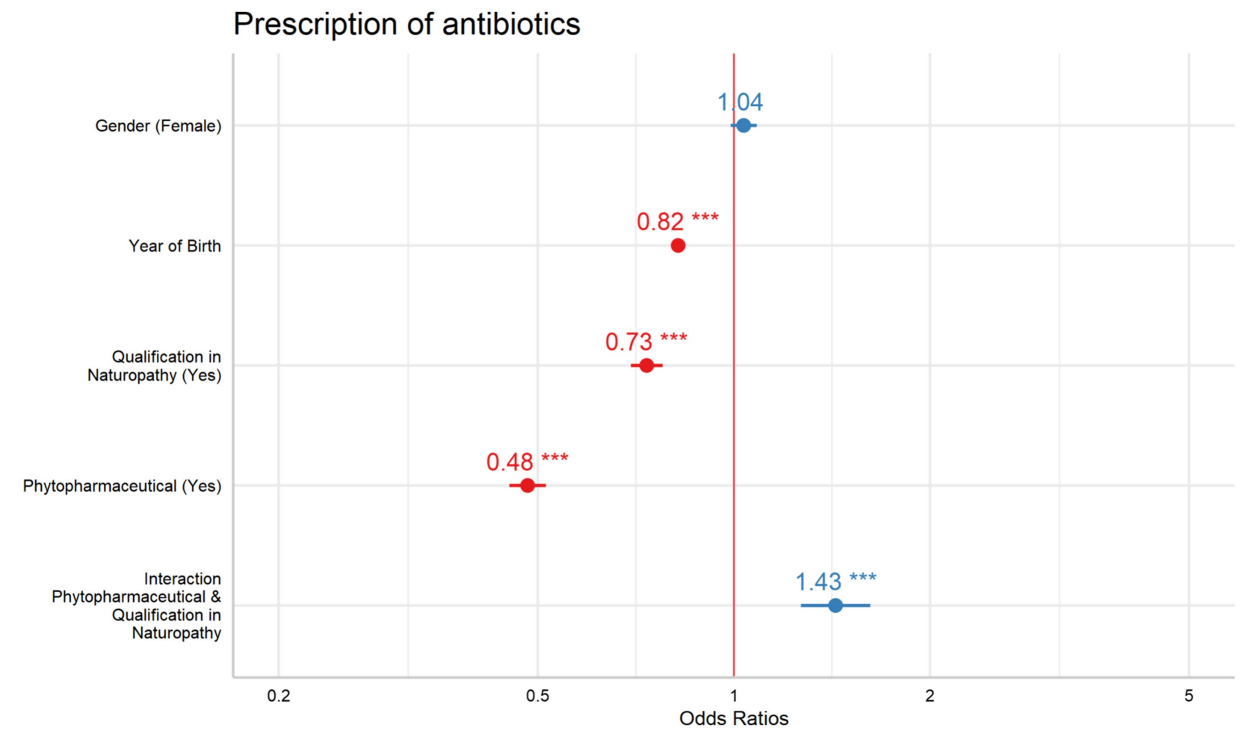

FIGURE 1
Odds ratios and confidence intervals for model 4.

reporting improved well-being and reduced symptoms (45). The most commonly used home remedies include hot steam inhalation, hot lemon drinks, and honey (45). These remedies also play a role in patients' own symptom management for minor health complaints, indicating that those who use home remedies take a more active interest and role in their health (45). GPs should promote the use of home remedies for managing symptoms. A comprehensive study from Germany revealed promising outcomes and produced informational materials that were well-received by both doctors and patients. Information leaflets offer an accessible approach that can help align patient expectations about medication use and increase self-efficacy, while also enhancing the visibility and use of home remedies for symptom relief (46).

Health policymakers should consider incentivizing the reimbursement for evidence-based phytopharmaceuticals for specific indications like RTIs. Currently, patients in Germany must pay for these treatments out-of-pocket, whereas antibiotic treatments are covered by statutory health insurance. Addressing this disparity could help reduce unnecessary antibiotic prescriptions.

4.7 Strengths, limitations, and future research

A major strength of this study is its large patient sample size and the utilization of data from general practice settings, which enhances the applicability of the findings. An additional strength of this study lies in the systematic documentation of phytopharmaceuticals facilitated by the structured training of GPs. Phytopharmaceuticals are often recommended by physicians without formal prescriptions, so patients typically acquire them over-the-counter based on this advice, a practice not reflected in existing routine datasets.

The data analyzed in this study comprehensively represents the full spectrum of prescribed phytopharmaceuticals. However, the study has several limitations. It focuses generally on antibiotic prescriptions without determining whether they were indicated or not, as it was not possible to assess the adequacy of antibiotic prescriptions with the presented data. However, the study is subject to several limitations. It primarily examines antibiotic prescriptions without determining whether they were warranted, as the data provided did not allow for an assessment of the appropriateness of these prescriptions. Nonetheless, other studies have suggested that upper respiratory tract infections (RTIs) are seldom caused by bacterial pathogens. For instance, a 2019 study investigating upper RTIs found that only 11.6% of cases were attributable solely to bacterial infections (37). Additionally, the analysis included only a limited set of covariates and did not account for comorbidities. Although prior analyses suggest similar morbidity levels across practices (25), the sample may not be fully representative of the entire German population. In addition, the data presented is from the period 2010–2014 and could not be updated due to limited access to more recent records; however, it is unlikely that prescribing practices have changed significantly so it can be assumed that the results are still valid today. The retrospective design and reliance on routine data further necessitate a cautious interpretation of the results. Future research should aim to prospectively validate these findings and explore how naturopathy training specifically influences prescription behaviors. Expanding the study to include diverse geographic regions and healthcare systems would also improve the generalizability of the results.

5 Conclusion

This study illustrates the beneficial role of phytopharmaceuticals and naturopathy qualifications in reducing antibiotic prescriptions among GPs in upper RTI. It highlights the importance of complementary approaches and specialized training in fighting the global challenge of antibiotic resistance. Encouraging broader adoption of these practices could significantly contribute to more sustainable healthcare practices and better patient outcomes in the face of escalating antimicrobial resistance.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the author on reasonable request in anonymised form in accordance with the institutional regulations and the General Data Protection Regulation.

Ethics statement

The studies involving humans were approved by the Ethics Committee University of Heidelberg (442/2005). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

A-JW: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. GL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. SJ: Conceptualization, Resources, Supervision, Validation, Writing – review & editing. BM: Conceptualization, Writing – review & editing. JV: Data curation, Supervision, Validation, Writing – review & 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1440632/full#supplementary-material

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