Traditional Chinese medicine based integrated health interventions for depression: A systematic review and meta-analysis

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Abstract

Background: Some Traditional Chinese medicine (TCM)-based integrated health interventions have been used for depression, but pooled efficacy remains unknown.

Aims and objectives: This study aimed to systematically evaluate the efficacy of TCM-based integrated health interventions for relieving depression.

Design: Systematic review and meta-analysis.

Methods: A comprehensive literature search was conducted on 17 databases from inception up to June 2022. Randomized controlled trials (RCTs) that examined an integrated health intervention based on TCM theory for depression were included. The risk of bias was assessed using the second version of the Cochrane risk-of-bias tool for randomized trials, and the quality of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation system.

Results: Eighteen RCTs with a total of 1,448 depressed participants were included. Health care providers, mainly nurses (14 studies), implemented TCM-based integrated health interventions. The pooled results showed that TCM-based integrated health interventions had larger effects on reducing depressive symptoms (15 studies; standardized mean difference = −2.05; 95% CI: −2.74, −1.37; p < 0.00001) compared with usual care at posttreatment but showed no significant difference contrasted to cognitive behavioral therapy (two studies, p = 0.31). However, the overall evidence was low.

Conclusions: The meta-analysis results indicated that TCM-based integrated health interventions were effective in reducing depression. However, the results should be interpreted with caution because of the low quality of the included studies. Future RCTs with rigorous designs should be conducted to provide robust evidence of the efficacy of TCM-based integrated health interventions in treating depression.

1. Introduction

Depression is a debilitating mental health problem characterized by depressed mood, loss of interest in normally enjoyable activities, low self-esteem, and suicidal ideation (American Psychiatric Association [APA], 2013). Individuals with depression often suffer from disability, increased mortality, impaired quality of life, considerable productivity loss, and huge economic burden (APA, 2013). As one of the major contributors to the overall global burden of disease, depression affects over 300 million people globally (World Health Organization, 2017), and this number is still rising at a rapid rate. In 2020 alone, 53.2 million new depressive cases were recorded (COVID-19 Mental Disorders Collaborators, 2021).

At present, antidepressants and psychotherapy remain the first line treatments for depression. However, many unhealthy lifestyles and behavior that have been identified as influential in the pathogenesis of depression, such as physical inactivity, poor sleep health, and unhealthy diet, are not sufficiently addressed by current treatments (Sarris et al., 2014). Lifestyle medicine, which adopts lifestyle interventions to treat and manage diseases (Kushner & Sorensen, 2013), has been used to address multiple risk factors for depression and change unhealthy lifestyles related to depression through modified lifestyle components that mainly involve diet, physical activity, stress management, and sleep management (Kushner & Sorensen, 2013). A recent meta-analysis of 50 randomized controlled trials (RCTs) evaluated multicomponent lifestyle medicine interventions (e.g., physical activity, nutritional advice, sleep management, and stress management) for depression (Wong et al., 2021). The finding suggested that multicomponent lifestyle interventions were effective in relieving depressive symptoms when compared to the usual care, especially for those diagnosed with major depression (Wong et al., 2021).

Traditional Chinese medicine (TCM)-based integrated health interventions, which share some similarities with lifestyle medicine interventions, may be a potentially effective alternative for depression. TCM-based integrated health interventions target at educating patients and modifying their lifestyle which include exercise (e.g., *Tai Chi, Qigong*), food therapy, sleep-wake schedule and psychological management based on TCM theories (Deadman, 2005). These lifestyle components are also targeted by lifestyle medicine which provides theoretical evidence of the use of TCM-based integrated health interventions for depression. Since people with depression are more likely to seek complementary and alternative therapies (Ashraf et al., 2021), the TCM-based integrated health interventions may be more acceptable to them, especially for those with Chinese cultural background (Yang et al., 2009; Yung et al., 2016). This may lead to higher adherence and engagement in the application of the interventions.

In recent years, a number of randomized controlled trials (RCTs) on TCM-based integrated health interventions for depression have been performed (Meng et al., 2020; Song & Yuan, 2015; Zhang et al., 2016). However, no systematic review and meta-analysis have summarized the evidence and contents of the TCM-based integrated health interventions for depression. Such information is critical for clinicians and researchers implementing interventions in clinical and research settings.

2. Aims

To fill this research gap, we aimed to synthesize available evidence of TCM-based integrated health interventions for depression and meta-analyze related effect sizes found in RCTs on the basis of available data.

3. Methods

This study was conducted in line with recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements (Page et al., 2021). A review protocol was developed and registered in the International Prospective Register of Systematic Reviews (registration number: CRD42022302264).

3.1 Search strategy

The search included 17 electronic databases: 10 English databases and seven Chinese databases, namely, the Cochrane Common Mental Disorders Group Controlled Trials Register (CCMD-CTR), PubMed, Embase, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations and Theses (PQDT), the Allied and Complementary Medicine Database (AMED), the Cochrane Central Register of Controlled Trials (CENTRAL), the World Health Organization International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), Chinese Biomedical Literature Database (CBM), the China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang, NCL Taiwan Periodical Literature, and National Digital Library of Theses and Dissertations in Taiwan. All the reference lists of RCTs and reviews related to the review topic were searched for the identification of additional studies. The search time of studies was from the inception to June 2022.

Specific Medical Subject Headings Terms, free-text words related to four broad concepts of TCM nursing, TCM health preservation, depression, and RCT, and Boolean operators were explored in each database for the identification of relevant studies. No language filter was used. When the article was presented in a language other than English or Chinese, then language translation was performed or the authors were contacted to obtain an English version. The full search strategies are provided in Appendix A.

3.2 Eligibility criteria

3.2.1 Types of studies

The review included only RCTs. Non-RCTs, uncontrolled trials, case series, case reports, crossover studies, and laboratory studies were excluded.

3.2.2 Types of population

The participants were adults diagnosed with depression according to a standard diagnostic system (e.g., Diagnostic and Statistical Manual of Mental Disorders, DSM; International Classification of Disease, ICD; Chinese Classification of Mental Disorders Version 3, CCMD-3), a cutoff score of validated screening measure or to clinical diagnosis by physicians or clinical psychologists.

3.2.3 Types of interventions

TCM-based integrated health interventions for depression were defined as the use of at least two of the following six components (Gómez-Gómez et al., 2020; Wong et al., 2021): TCM-based depression and/or mental health education, TCM-based exercise, TCM-based food therapy and/or nutritional advice, TCM-based psychological management, TCM-based sleep-wake management, and meridian and collateral management. Studies using single-component TCM-based health interventions were excluded. No restrictions on settings, instructors, intervention modalities, sessions, durations, frequencies, and intervention periods were imposed. The operational definitions of the six components are shown below.

( ) TCM-based depression and/or mental health education

This component refers to any education designed on the basis of TCM theories or philosophies that increases an individual's awareness of depression, enriches his or her depressive knowledge, and influences the attitudes and behavior associated with depression management.

( ) TCM-based exercise

This component refers to any exercise developed on the basis of *Yin-yang* and *Qi* theories, which are characterized by activating the body's muscles, controlling breath, and nourishing the mind or *Shen* through resting meditation (Jiang & Zou, 2013; Sun, 2017), such as *Taichi,* and *Qigong* exercises, including *Baduanjin.*

( ) TCM-based food therapy and/or nutritional advice

This component refers to any food therapy and/or nutritional advice for depression management providing individualized food choice according to TCM theory. The content should be based on an individual's body constitution from the TCM perspective and TCM food therapy and/or nutritional advice principles of *Four Qi* (cold, cool, warm, and hot) and *Five flavors* (sour, sweet, bitter, salty, and pungent) (Sun, 2017).

( ) TCM-based psychological management

This component refers to any psychological care and management or stress and emotion management using TCM theory, such as the control of seven emotions (anger, happiness, pensiveness, sorrow, anxiety, fear, and fright) and five wills (anger, happiness, sorrow, thinking, and fear) (Sun, 2017).

( ) TCM-based sleep-wake management

This component refers to any sleep-wake management advice using TCM theory, such as adjusting the sleep-wake pattern according to the four seasons or planning an optimal bedtime or wake time according to the time being dominated by a particular meridian (Sun, 2017).

( ) Meridian and collateral management

This component refers to any intervention or strategy used to stimulate the body's meridians and acupuncture points to promote health (Sun, 2017), such as acupressure, auricular pressure, and moxibustion.

3.2.4 Types of comparators

The control group can be waitlist, usual care, or a standardized psychological or pharmacological treatment for depression.

3.2.5 Types of outcomes

The primary outcome is depression level as measured by validated questionnaires, such as the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) and the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). Secondary outcomes refer to adverse events.

3.3 Study selection

Two reviewers (JR and JL) independently screened the titles and abstracts of all identified articles according to the eligibility criteria. Citations considered potentially relevant were searched for full texts and assessed according to the inclusion and exclusion criteria. Any disagreement was resolved by discussion between the two reviewers and by consultation with a third senior author (WY).

3.4 Data extraction

A predesigned data collection form adapted from the Cochrane Handbook for Systematic Reviews of Interventions were used for data extraction (Higgins et al., 2022). Extracted details included the author, published year, country, population, recruitment, diagnostic criteria for depression, participants' characteristics, details of intervention and comparator, outcome measures, and follow-up information. Two reviewers (JR and SC) extracted data independently, and any discrepancy was resolved by discussion and consultation with the third reviewer (WY). When data were missing or ambiguous information existed, the original authors were contacted through emails for data supplementation or for clarification with three attempts.

3.5 Risk of bias and quality appraisal

Risk of bias of included studies and overall quality of evidence were evaluated by JR and SC who also discussed with WY if any discrepancy could not be solved between the two reviewers.

The second version of the Cochrane risk of bias tool for randomized trials (RoB 2) was used in measuring the risk of bias in each included RCT (Sterne et al., 2019). The RoB 2 tool involves the evaluation of six domains: bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias. The evaluation of risk of bias for each domain was expressed as "low risk," "high risk," or "some concerns." Then, the overall risk of bias was assigned for each study.

The overall quality of evidence was graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (Goldet & Howick, 2013). The overall GRADE evaluation suggests to which extent an individual can be confident in the effect estimates, and results are presented with four levels of evidence: "very low," "low," "moderate," and "high". "Risk of bias," "inconsistency," "indirectness," "impression," and "publication bias" can decrease the magnitude of effect, and "large magnitude of effect," "all residual confounding," and "dose-response gradient" can rate up the level of certainty in the GRADE evaluation.

3.6 Data analysis

Review Manager software version 5.4 (The Nordic Cochrane Centre, the Cochrane collaboration: Copenhagen, Denmark) was adopted for statistical analysis. The posttreatment values were used for meta-analysis. Standardized mean difference (SMD) with a 95% confidence interval (CI) was used in estimating intervention effects for continuous variables measured by different scales (Higgins et al., 2022). Risk ratio (RR) was expressed with 95% CI for dichotomous outcomes. A two-sided p value of <0.05 indicated statistically significant difference in the overall effect.

The heterogeneity of all the included studies was measured by using Cochran's Q (Chi^2 test) and I-squared statistic (I^2). I^2 values of "0%−40%," "30%−60%," "50%−90%," and "75%−100%" indicated "not important," "moderate heterogeneity," "substantial heterogeneity," and "considerable heterogeneity," respectively (Higgins et al., 2022). In the Chi^2 test, a p value of <0.10 suggested statistically significant heterogeneity in treatment effects. The random-effects model was selected to examine the effects of TCM-based integrated health interventions on depression according to an assumption that the observed estimates of treatment effect can differ across studies because of random sampling error and potential existence of heterogeneity (Higgins et al., 2022).

The results of meta-analyses were presented using forest plots and expressed in SMDs, and their corresponding p values, 95% CI, Chi^2 test results, and I^2 statistics were obtained. In the sensitivity analysis, we excluded one study at a time to examine the robustness and reliability of the pooled results. Moderator analysis using predesigned subgroup analyses was conducted according to different diagnostic criteria for depression, different depression outcome measures, the number of components of TCM-based integrated health interventions, and disease types (Higgins et al., 2022) or when the heterogeneity was moderate, substantial, or considerable.

Comprehensive Meta-Analysis software (version 3.0) was used in measuring publication bias through the visual inspection of funnel plots and Egger's regression test when at least 10 studies were available for meta-analytic comparison (Higgins et al., 2022). In the Egger's regression test, a p value of less than 0.05 indicated statistically significant publication bias. In addition, the "trim and fill" method was used in detecting and adjusting possible publication bias (Duval & Tweedie, 2000).

4. Results

4.1 Study selection

Study selection and inclusion are illustrated in a PRISMA flow chart (Figure 1). The initial pool of 2,185 records were identified by searching 17 databases and other sources. After the titles and abstracts were screened independently, 1,532 articles were excluded, and 40 full-text articles were assessed for eligibility. Finally, 18 RCTs that met the inclusion criteria were included.

4.2 Characteristics of the included studies

4.2.1 Study characteristics

All 18 RCTs included in this review originated from China: 17 published in Chinese from mainland China and one in English from the Hong Kong Special Administrative Region, China (Han et al., 2020). The publication years ranged from 2008 to 2021. The participants were all recruited from hospitals.

The sample sizes of the RCTs varied from 48 to 140, and the total sample size was 1,448. The mean age of the participants was 58.9 years (SD = 6.5), ranging from 37.1 to 72.5 years. The average female percentage was 53.4%. Only two studies provided the disease duration of depression, which had an average of 3.9 years (SD = 7.0) (Han et al., 2020; Yang, 2018).

Depression was diagnosed using the cutoff score of HAMD in four studies (Gao, 2016; Song & Yuan, 2015; Wang, 2019; Zhang et al., 2016), PHQ-9 in one study (Meng et al., 2020), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) in one study (Han et al., 2020), CCMD-3 in one study (Lu et al., 2019), and a combination of HAMD and The Chinese Classification and Diagnostic Criteria of Mental Disorders, Version 2 Revision (CCMD-2R) (Lin et al., 2008) or The criteria of diagnosis and therapeutic effect of diseases and syndromes in TCM (Wang, 2012) or CCMD-3 (Tan et al., 2008; Wu & Li, 2019; Yang, 2018) in five studies. Six studies included clinical diagnosis of depression by physicians or clinical psychologists without specifying the diagnostic systems (Peng et al., 2018; Shao et al., 2018; Sui, 2018; Wang & Wang, 2021; Xin, 2014; Zhang, 2014).

The majority of studies focused on post-stroke depression (11 studies, 61.1%) (Lin et al., 2008; Shao et al., 2018; Song & Yuan, 2015; Sui, 2018; Tan et al., 2008; Wang, 2012, 2019; Wang & Wang, 2021; Wu & Li, 2019; Xin, 2014; Zhang, 2014), and two studies (11.1%) focused on depression (Han et al., 2020; Yang, 2018). The other studies focused on comorbid depression in specific diseases, including leukemia (one study, 5.6%) (Zhang et al., 2016), type 2 diabetes (one study, 5.6%) (Peng et al., 2018), menopause (one study, 5.6%) (Gao, 2016), insomnia (one study, 5.6%) (Meng et al., 2020), and uveitis (one study, 5.6%) (Lu et al., 2019). More than half of the included studies (n = 10, 55.6%) did not provide information about the use of antidepressants. Among studies that provided antidepressant information, only one study reported clearly that all participants were taking antidepressants and their medications were not modified during the study period (Han et al., 2020). The characteristics of the included studies are presented in Table 1.

4.2.2 Characteristics of interventions and comparators

Table 2 presents a summary of the characteristics of TCM-based integrated health interventions. The TCM-based integrated health interventions had an average of three components (from two to four). The components of the TCM-based integrated health interventions in the included studies involved TCM-based psychological management (18 studies, 100%), TCM-based food therapy and/or nutritional advice (14 studies, 77.8%), meridian and collateral management (14 studies, 77.8%), TCM-based sleep-wake management (five studies, 27.8%), TCM-based exercise (three studies, 16.7%), and TCM-based depression and/or mental health education (one study, 5.6%). However, 17 of the included studies did not report how the contents and components of the TCM-based integrated health interventions were selected and established, how intervention protocols were developed, and which theoretical framework was used to support their research design, except the research of Han et al. (2020).

The meridian and collateral management included acupressure in 11 studies (Gao, 2016; Lin et al., 2008; Shao et al., 2018; Song & Yuan, 2015; Sui, 2018; Wang, 2012, 2019; Wang & Wang, 2021; Xin, 2014; Yang, 2018; Zhang et al., 2016) and auricular acupressure in four studies (Lu et al., 2019; Peng et al., 2018; Wu & Li, 2019; Zhang et al., 2016). The modalities of the meridian and collateral management incorporated were nurse-led in seven studies (Lin et al., 2008; Shao et al., 2018; Song & Yuan, 2015; Sui, 2018; Wang, 2019; Wang & Wang, 2021; Xin, 2014) and self-help in four studies (Peng et al., 2018; Wang, 2012; Yang, 2018; Zhang et al., 2016), and no information regarding meridian and collateral management instructors was provided in three studies (Gao, 2016; Lu et al., 2019; Wu & Li, 2019). Three studies adopted TCM-based exercises, including *Shaolin* mind–body exercises (Han et al., 2020), *Baduanjin* (Peng et al., 2018), and *Taichi* (Yang, 2018). Six studies (33.3%) mentioned adopting TCM-based integrated health interventions for depression according to the TCM body constitution theory or TCM pattern differentiation (Lu et al., 2019; Song & Yuan, 2015; Tan et al., 2008; Wang, 2019; Wu & Li, 2019; Yang, 2018), such as liver qi stagnation (　), yin deficiency and fire excess (　), dual deficiency of the heart and spleen (　), and liver depression and spleen deficiency (　).

The TCM-based integrated health interventions were conducted through the Internet (one study, 5.6%) (Meng et al., 2020) or face-to-face sessions at hospital wards (14 studies, 77.8%). Three studies (16.7%) did not report the setting (Han et al., 2020; Peng et al., 2018; Wang, 2012). The instructors of the TCM-based integrated health interventions were nurses in 14 studies (77.8%) (Gao, 2016; Lin et al., 2008; Lu et al., 2019; Peng et al., 2018; Shao et al., 2018; Song & Yuan, 2015; Sui, 2018; Tan et al., 2008; Wang, 2019; Wang & Wang, 2021; Xin, 2014; Yang, 2018; Zhang, 2014; Zhang et al., 2016), nurses and physicians in one study (5.6%) (Wu & Li, 2019), physicians in one study (5.6%) (Meng et al., 2020), and clinical psychologist in one study (5.6%) (Han et al., 2020).

The mean intervention period was 6.5 weeks, and the range was from 2 weeks to 12 weeks. The number of sessions and session duration were only reported by Han et al. (2020), who conducted 90-minute group sessions weekly for 10 weeks. Usual care was selected as the control group in 17 studies (94.4%), including one study that compared a TCM-based integrated health intervention with either usual care or cognitive behavioral therapy (CBT) (Han et al., 2020). Meng et al. (2020) adopted CBT as the sole comparator (5.6%).

Dropout rates were reported in only three studies: 0% in the treatment group and 3.3% in the control group, along with the corresponding reasons (two dropouts: one was admitted to the hospital because of disease aggravation, and the other did not provide a reason) (Meng et al., 2020). Han et al. (2020) reported a 32% dropout rate in the intervention group (eight dropouts because of scheduling difficulties), 32% in the CBT group (eight dropouts because of scheduling difficulties), and 36% in the usual care group (nine dropouts because of scheduling difficulties). Zhang et al. (2016) reported dropout rates of 4.8% (2/42) in the treatment group and 2.4% (1/41) in the control group (three dropouts all due to death).

4.2.3 Outcome measurements

Three instruments were used in measuring the level of depressive symptoms: HAMD (12 studies, 66.7%) (Gao, 2016; Han et al., 2020; Lin et al., 2008; Lu et al., 2019; Sui, 2018; Tan et al., 2008; Wang, 2012, 2019; Xin, 2014; Yang, 2018; Zhang, 2014; Zhang et al., 2016), SDS (five studies, 27.8%) (Peng et al., 2018; Shao et al., 2018; Song & Yuan, 2015; Wang & Wang, 2021; Wu & Li, 2019), and PHQ-9 (one study, 5.6%) (Meng et al., 2020).

4.2.4 Adverse events, adherence, acceptability, fidelity, and perceived usefulness

None of the included studies reported the adverse events, adherence, acceptability, fidelity, and perceived usefulness of TCM-based integrated health interventions.

4.3 Risk of bias assessment

The overall methodological quality of the included studies was poor. Approximately 94.4% (17 studies) were rated as "high risk of bias." The assessment of the risk of bias of each RCT included was presented in Figure 2. Although we made at least three attempts to contact the corresponding authors to clarify unclear or missing data, no additional information was retrieved.

In terms of bias arising from the randomization process, 17 RCTs (94.4%) were graded as "some concerns" and one was evaluated as "low" (Han et al., 2020). Although "randomized" was mentioned in all studies, only five of them (27.8%) reported the methods for sequence generation, such as "random number table" (Meng et al., 2020; Song & Yuan, 2015; Wang, 2019; Zhang et al., 2016) or computer-generated random number list (Han et al., 2020). Only one trial (5.6%) provided information on allocation concealment (Han et al., 2020). As for bias due to deviations from intended interventions, all RCTs were rated as "some concerns" because none provided precise reporting about the blinding of participants or personnel, and no intention-to-treat analyses or modified intention-to-treat analyses were performed when dropouts existed (Han et al., 2020; Meng et al., 2020; Zhang et al., 2016), although the dropout rates did not significantly differ between groups.

On missing outcome data, all trials were considered "low risk of bias," except one study, which was designated as "some concerns" because of the lack of information about whether the missing status in the outcome depended on its true value (Han et al., 2020). The outcome measurements in all the included RCTs were appropriate for depression, and the ascertainment of the outcome coincided between intervention groups, but no details of assessor blinding was provided. In addition, the participant-reported outcome measures for depression (PHQ-9 and SDS) or clinician-reported outcome measures for depression (HAMD) were used, but no information about whether assessors were blinded was provided, except Han et al. (2020), who indicated that the HAMD was measured by psychiatrists who were blinded to group allocation. Therefore, the 17 included studies (94.4%) were evaluated as having a high risk of bias in the outcome measurements. On bias in the selection of the reported results, all included RCTs were graded as "some concerns" because no detailed information on published protocols or registrations and no pre-statistical analysis plan were provided.

4.4 Results of effectiveness of TCM-based integrated health interventions

4.4.1 Depression

At posttreatment, TCM-based integrated health interventions were more effective for depression questionnaire score reduction (HAMD and SDS) than usual care (15 studies, SMD = −2.05, 95% CI [−2.74, −1.37]; $p < 0.00001$; $I^2 = 96\%$; Figure 3). Significant differences between TCM-based integrated health interventions and usual care were found at 1-month (two studies, SMD = −0.96, 95% CI [−1.34, −0.58]; $p < 0.00001$; $I^2 = 0\%$), 2-month (two studies, SMD = −0.99, 95% CI [−1.42, −0.55]; $p < 0.00001$; $I^2 = 23\%$), and 3-month follow-up (one study, SMD = −2.01, 95% CI [−2.64, −1.38]; $p < 0.00001$; Figure 3). No significant difference was observed between TCM-based integrated health interventions and CBT with respect to depressive symptoms reduction (HAMD and PHQ-9; two studies, SMD = −0.29, 95% CI [−0.85, 0.27]; $p = 0.31$; $I^2 = 56\%$; Figure 4).

4.4.2 Moderator analyses

Given the considerable heterogeneity in the meta-analysis comparing TCM-based integrated health interventions and usual care in terms of depressive symptoms at posttreatment ($I^2 = 96\%$), subgroup analysis was conducted (Table 3).

Subgroup analysis based on the outcome measures used, namely, HAMD and SDS or different diagnostic criteria for depression, unexplained considerable heterogeneity still existed. As for the number of intervention components of TCM-based integrated health interventions, three components appeared to be more efficacious than those with two or four components (seven studies, SMD = −3.09, 95% CI [−4.70, −1.47]; $p = 0.0002$; $I^2 = 98\%$). No statistical significance was shown for subgroup difference ($p = 0.08$). Although a subgroup analysis was performed to test whether types of diseases moderated the effect of TCM-based integrated health interventions for depression, the limited number of the other types of illnesses or conditions with depression leads to difficulty in producing meaningful findings.

4.4.3 Sensitive analysis

In terms of depression reduction, the large effect sizes of TCM-based integrated health interventions presented at posttreatment still existed (14 studies, SMD = −1.64, 95% CI [−2.21, −1.08]; $p < 0.00001$; I^2 = 94%) when the study of Wang and Wang (2021) which had the largest effect size, was removed (SMD = −8.33, 95% CI [−9.57, −7.09]).

Similarly, the effect sizes of reducing depressive symptoms at 1-month follow-up (SMD = −0.91, 95% CI [−1.44, −0.38]; p = 0.0008) and 2-month follow-up (SMD = −0.77, 95% CI [−1.30, −0.25]; p = 0.004) were obtained after the study of Zhang (2014), which had the largest effect size, was excluded (SMD = −1.02, 95% CI [−1.56, −0.48] at 1-month follow-up; and SMD = −1.22, 95% CI [−1.77, −0.67] at 2-month follow-up).

4.4.4 Publication bias

The funnel plot analysis of TCM-based integrated health interventions for depression (n = 15) revealed asymmetry (Figure 5) with statistical significance tested by Egger's regression (t = 4.98, df = 13.0, p = 0.0003) when compared with usual care at posttreatment, suggesting potential publication bias. A trim and fill method was performed further and imputed potentially four studies on the left side to yield an adjusted effect size with a larger effect size than the overall effect size of −2.05 measured in 15 studies (19 studies, SMD = −2.71, 95% CI [−3.61, −1.81]; Figure 6).

4.5 Overall quality of evidence

The overall certainty of the body of evidence of TCM-based integrated health interventions for depression was low compared with usual care (Table 4).

5. Discussion

5.1 Summary of main findings

To the best of our knowledge, this study provides the first systematic review and meta-analysis of TCM-based integrated health interventions for depression. The pooled effects indicated the beneficial effects of TCM-based integrated health interventions on the reduction of depressive symptoms with a large effect size (SMD = −2.05, 95% CI [−2.74, −1.37]) compared with usual care at posttreatment. Sensitivity analysis showed that the results were relatively reliable. Nevertheless, the overall quality of evidence was low and should be interpreted cautiously because study quality was poor and no safety information on TCM-based integrated health interventions was provided.

Applying TCM-based integrated health interventions for depression has attracted considerable interest (first appeared in 2008), and more than half (12 of the 18 trials, 66.7%) have been published since 2016. The trend was similar to that of Western lifestyle medicine for depression (Wong et al., 2021). Interest in these lifestyle interventions may be due to the recognition that unhealthy lifestyle and behavior, such as physical inactivity, poor sleep health, and unhealthy diet, may partially increase the risk of depression (Kraus et al., 2019; Sarris et al., 2014). Given that the alteration of behavior is difficult, the application of lifestyle interventions should be considered in the context of long-term sustainability and issues regarding adherence and engagement (Sarris et al., 2014). TCM-based integrated health interventions for depression may have additional benefits when applied to populations that are culturally adapted and when the interventions are well accepted by individuals with Chinese cultural background (Yang et al., 2009; Yung et al., 2016), such as countries in East Asia, where TCM has gained popularity (e.g., Taiwan, Macau, Japan, and South Korea) (Chen et al., 2015) or global TCM believers. This may in turn increase compliance and effectiveness in reducing depression.

Our review found that the majority of the included studies with instructors' information were nurse-led TCM nursing interventions (14 studies); one implemented physician-led TCM health preservation (Meng et al., 2020), and one used clinical psychologist-led integrative lifestyle intervention (Han et al., 2020). TCM nursing education has been established as a compulsory course for undergraduate nursing students for at least 23 colleges and universities in China (Sun, 2017), which provided as the theoretical foundation and practical skills for nurses to adopt TCM nursing as an intervention for depression in clinical practice. Face-to-face modality was adopted by most included trials (77.8%), and one study was delivered through the Internet (Meng et al., 2020). The beneficial effects of the Internet- and mobile-based depression interventions for depressed individuals have been confirmed in a previous systematic review and meta-analysis (Hedges' g = −0.90, 95% CI [−1.07, −0.73]) (Josephine et al., 2017). Apart from the advantages of being cost-effective, safe and convenient without time and place limitations, further studies are required to explore the efficacy of telemedicine, internet, or application-delivered TCM-based integrated health interventions for depression.

5.2 Summary of quality assessment

The research quality of the studies included in this review was low, and nearly all included studies were graded as high risk of bias. Thus, the quality of evidence was low. The three major problems in the 18 RCTs were lack of information or brief reporting without details about randomization and allocation concealment; lack of published protocols, registrations, and/or no pre-statistical analysis plan or limited information; and use of inappropriate statistical methods. Given these issues, we strongly recommend that researchers conducting trials should report sufficient information in accordance with the CONSORT extension for nonpharmacologic trials (Boutron et al., 2017).

Given that TCM-based integrated health interventions belong to complex health behavior interventions, we advocate the adoption of the updated Medical Research Council framework for developing and evaluating complex interventions (Skivington et al., 2021). A suitable theoretical framework, which functions as the foundation of a research and serves as the structure and supports for the rationale of any study, should be used and stated clearly in the articles (Osanloo & Grant, 2014). Moreover, the intervention development should be evidence based, TCM body constitution theory should be applied, and related processes need to be reported clearly in order that they can be repeated by other researchers. All these are essential to the generation of high-quality evidence regarding the use of TCM-based integrated health interventions for depression and promote the understanding of changes in health behavior in depressed individuals.

5.3 Summary of effectiveness of TCM-based integrated health interventions

The pooled effects showed the efficacy of TCM-based integrated health interventions for reducing depressive symptoms at posttreatment and short-term follow-up when compared with usual care. The effect size for depression at posttreatment (SMD = −2.05, 95% CI [−2.74, −1.37]) was larger than the effect sizes of different types of psychological treatments, including life review (Hedges' g = 1.10, 95% CI [0.68, 1.51]), behavioral activation therapy (Hedges' g = 1.05, 95% CI [0.80, 1.30]), and CBT (Hedges' g = 0.73, 95% CI [0.65, 0.80]) (Cuijpers et al., 2020). Owing to the poor quality of the included studies, the effects might be inflated.

Our subgroup analysis found that the largest pooled effect size (SMD = −3.09, 95% CI [−4.70, −1.47]) for depression reduction was observed when three components were adopted, which included TCM-based psychological management, TCM-based food therapy and/or nutritional advice, and meridian and collateral management. This finding was in line with a recent meta-analysis, which showed that the largest effect size was achieved when three lifestyle factors (SMD = −0.27, 95% CI [−0.43, −0.12]) in lifestyle interventions (physical activity, nutrition, and stress management or physical activity, nutrition, and sleep management) were combined for depression treatment when compared with effect sizes generated of two lifestyle factors (SMD= −0.17, 95% CI [−0.30, −0.05]) combined or four lifestyle factors combined for treating depression (SMD = 0.01, 95% CI [−0.12, 0.15]) (Wong et al., 2021).

One possible explanation for the larger effect size might be the combination of the three most effective components, which were the most frequently used in the included studies. Specifically, enhanced effectiveness might have resulted from (1) TCM-based psychological management using music therapy (e.g., five-phase music therapy), which activated a multitude of brain areas, such as the orbitofrontal cortex, dorsolateral prefrontal cortex, and ventromedial prefrontal cortex (Feng et al., 2019; Lin et al., 2017); (2) TCM-based food therapy and/or nutritional advice, such as eating oranges, fingered citron, and tangerine peel, which may have produced an antidepressant-like effect and dispersed stagnated liver qi by regulating neurotransmitters (e.g., gamma-aminobutyric acid), affecting gut microbiome regulation, and increasing the levels of dopamine and serotonin (Ke et al., 2021; Park et al., 2020; Zhang et al., 2019); and (3) meridian and collateral management, including acupressure and auricular acupressure, which may have regulated the functions of hormones and neurotransmitters by stimulating acupoints on the body surface; thus, the disease affecting the corresponding organs can be treated (Rani et al., 2020; Tseng et al., 2021).

Another possible explanation might be related to the optimal number of components. Handling three components simultaneously might be more prone to generate a large effect size because this approach can address modifiable lifestyle risk factors for depression at a time in contrast to interventions with two components. Patients with depression more easily learn and practice an intervention with three components and adhere to it than an intervention with four components or more. The findings of different number of components of TCM-based integrated health interventions on depression may be restricted by the limited number of RCTs available. As such, these findings were inconclusive and should be interpreted with caution. Further exploration on the optimal number of components, content needed, and potential mechanism of how these components function is warranted.

5.4 Strengths and limitations

Our systematic review has several strengths, including the inclusion of Chinese and English databases, and grading the quality of evidence according to the GRADE guideline. However, five limitations should be noted. First, the methodological qualities of the included studies were dissatisfactory and had high risk of bias. Thus, the seemingly positive effects of TCM-based integrated health interventions should be interpreted with caution. Second, most studies included investigated comorbid depression rather depression alone, and no safety information about TCM-based integrated health interventions was reported. Third, only preliminary positive effects of TCM-based integrated health interventions for the treatment of depression at short-term follow-up were generated because only a limited number of related RCTs with long-term follow up are available at present. Fourth, considerable heterogeneity was observed across interventions, including variability in the number of components of TCM-based integrated health interventions and disease types. Although subgroup analyses were performed, the results failed to identify the possible factors that resulted in high heterogeneity. Fifth, publication bias existed, and inputting four studies did not reduce the effect size of TCM-based integrated health interventions for depression after the trim and fill approach was performed. We encourage researchers and publishers to publish studies not only with positive outcomes but also with non-significant or negative findings.

6. Conclusion

The results of this systematic review and meta-analysis suggested that TCM-based integrated health interventions have beneficial effects on the reduction of depressive symptoms at posttreatment. However, owing to the poor methodological quality and high heterogeneity of the studies, the seemingly positive findings need to be interpreted cautiously. RCTs with larger sample sizes, rigorous designs, and reasonable theoretical frameworks should be conducted to confirm the effectiveness of the interventions.

7. Relevance To Clinical Practice And Rsearch

TCM-based integrated health interventions serve as potential effective alternative for individuals worldwide who are suffering from clinical or subthreshold depression. Especially for those who live in the regions that are more culturally bound to TCM, they may have higher preference and adherence for TCM intervention and hence a higher effectiveness.

Nurses could play an important role in designing and providing TCM nursing interventions for the depressed patients. However, due to the limitations of the methodological quality of the included studies, the current evidence may not be enough to support the use of TCM-based integrated health interventions in routine clinical practice. Therefore, further high-quality trials are needed to verify the effects of these TCM-based integrated health interventions for depression. We suggest that these studies should involve individuals with depression at various age groups (e.g., the elderly), from different resources such as hospitals,

communities, or in regions or countries where TCM are deeply rooted, use active control groups as comparators (e.g., psychological therapy), and include long-term follow-up in the future.

Declarations

Competing interests: The authors declare no competing interests.

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Tables

T A B L E 1 Characteristics of the included studies

Author, Year	Country	Population	Recruitment	Mean age, year (range, SD), % female	Diagnostic criteria for depression	Sample size (TG/CG)	Comparator (duration)	Outcome measures	Assessm
Gao, 2016	China	Menopausal depression	Recruited in a hospital	48.71 (46–53,2.92)/100%	HAMD ≥ 18	85 (43/42)	Usual care (6 weeks)	HAMD, clinical efficacy using reduced HAMD score rate, Clinical self-made nursing satisfaction scale	6-week PT
Han et al., 2020	Hong Kong SAR	Major depressive disorder	Recruited from the outpatient clinic at the West Kowloon Psychiatric Centre	Completers: DMBI: 47.06 (NR, 9.54)/88.2% CBT: 46.94 (NR, 6.54)/76.5% Follow-up care: 45.44 (NR, 8.25)/75%	DSM-IV-TR, Chinese-bilingual SCID-I/P version	75 (TG:25/CBT:25/CG FU care: 25)	CG1: Face-to-face CBT (10 sessions, 90 min session/week, 10 weeks); CG2: Regular FU care (10 weeks)	HAMD, BDI-II, EEG	10-week F
Lin et al., 2008	China	Post-stroke depression	Recruited in a hospital	65 (42–78, NR)/31.03%	CCMD-2R, HAMD > 17	58 (30/28)	Usual care	HAMD	8-week PT
Lu et al., 2019	China	Uveitis patients with depression	Recruited in a hospital	NR	CCMD-3	66 (33/33)	Usual care (NR)	HAMD, SF-36	PT
Meng et al., 2020	China	Insomnia patients with depression and anxiety	Sleep disorders clinic in a hospital	47.38 (NR,12.68)/58.33% TG: 45.23 (18–59, 12.76)/55% CG: 49.52 (18–58, 12.34)/61.67%	PHQ-9	120 (60/60)	Internet-delivered CBT for insomnia (8 weeks)	PHQ-9, GAD-7, PSQI	8-week PT
Peng et al., 2018	China	Type 2 diabetes patients with depression	Recruited in a hospital	70.99 (NR, 7.54)/31.11% TG: 70.71 (60–83, 7.53)/28.89% CG:71.27 (60–85, 7.63)/33.33%	Physician diagnosis	90 (45/45)	Usual care (12 weeks)	SDS, DMQLS	6-week DI 12-week F
Shao et al., 2018	China	Post-stroke depression	Recruited in a hospital	60.05 (NR, 3.50)/40.38% TG: 60.3 (NR, 3.3)/38.46% CG: 59.8 (NR, 3.7)/42.31%	Physician diagnosis	104 (52/52)	Usual care (NR)	SDS, Clinical nursing satisfaction	PT
Song & Yuan, 2015	China	Post-stroke depression	Recruited in a hospital	62.8 (NR, 5.70)/39.13% TG: 63.2 (31–79, 6.1)/41.30% CG: 62.4 (31–79, 5.3)/36.96%	HAMD > 8	92 (46/46)	Usual rehabilitation treatment and nursing (2 weeks)	SDS, clinical efficacy based on the extent of depression symptoms relief, clinical nursing satisfaction	2-week PT
Sui, 2018	China	Post-stroke depression	Recruited in a hospital	62.33 (NR, 3.35)/55% TG: 62.31 (NR, 3.35)/52.86% CG: 62.35 (NR, 3.38)/57.14%	Physician diagnosis	140 (70/70)	Usual care	HAMD, ADL	PT
Tan et al., 2008	China	Post-stroke depression	Recruited in a hospital	64.4 (51–76,11.8)/55%	CCMD-3, HAMD ≥ 18	60 (30/30)	Usual care and usual drug therapy in neurology (NR)	HAMD	1-month F 2-month F

Author, Year	Country	Population	Recruitment	Mean age, year (range, SD), % female	Diagnostic criteria for depression	Sample size (TG/CG)	Comparator (duration)	Outcome measures	Assessm...
Wang, 2012	China	Post-stroke depression	Recruited in a hospital	NR (27−55, NR)/53.33%	Criteria of diagnosis and therapeutic effect of diseases and syndromes in Traditional Chinese Medicine, HAMD ≥ 17	60 (30/30)	Usual care	HAMD	8-week PT
Wang, 2019	China	Post-stroke depression	Recruited in a hospital	61.36 (NR, 5.75)/56.25% TG: 60.99 (37−81,6.21)/58.33% CG: 61.73 (39−83,5.35)/54.17%	HAMD > 8	48 (24/24)	Usual care and basic medication treatment usual care (4 weeks)	HAMD HAMA, self-made QOL scale	4-week PT
Wang & Wang, 2021	China	Post-stroke depression	Recruited in a hospital	71.66 (NR, 3.31)/48%	Physician diagnosis	100 (50/50)	Usual care	SDS	4-week PT
Wu & Li, 2019	China	Post-stroke depression	Recruited in a hospital	61.01 (NR, 5.81)/51.67% TG: 62.57 (NR, 6.24)/56.67% CG: 59.45 (NR, 4.98)/46.67%	CCMD-3, HAMD≥20	60 (30/30)	Usual care (NR)	SDS, SAS, WHOQOL-BREF, PSQI	NR
Xin, 2014	China	Post-stroke depression	Medical records	65.5 (53−81, NR)/55%	Physician diagnosis	60 (30/30)	Usual care (4 weeks)	HAMD	1- and 2-week DI, 4-week PT
Yang, 2018	China	Depressive patients	Recruited in a hospital	37.05 (NR, 6.86)/63.33% TG: 36.9 (19−54,7.0)/62.22% CG: 37.2 (17−55,6.8)/64.44%	CCMD-3, HAMD ≥ 20	90 (45/45)	Usual care (8 weeks)	HAMD	2- and 4-week DI, 8-week PT
Zhang, 2014	China	Post-stroke depression	Recruited in a hospital	72.5 (60−78, NR)/NR	Physician diagnosis	60 (30/30)	Usual care (NR)	HAMD, ADL	1-month F 2-month F 3-month F
Zhang et al., 2016	China	Leukemia patients with depressive disorder	Recruited in a hospital	44.81 (NR, 7.27)/36.25% TG: 47.31 (16−67, 6.38)/35% CG: 42.31(18−70, 7.31)/37.5%	HAMD ≥ 21	80 (40/40)	Usual care (4 weeks)	HAMD, Immunologic function	2-week DI week PT

Abbreviations: ADL, Activities of Daily Living; BDI-II, Beck Depression Inventory-II; CBT, Cognitive Behavior Therapy; CCMD-2R, The Chinese Classification and Diagnostic Criteria of Mental Disorders, Version 2 Revision; CCMD-3, The Chinese Classification of Mental Disorders, Version 3; CG, Control Group; DI, During Intervention; DMBI, Dejian Mind-Body Intervention; DMQLS, Diabetes-Mellitus Specific Quality of Life Questionnaire; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision; EEG, Electroencephalography; FU, Follow-up; GAD-7, Generalized Anxiety Disorder-7; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; Hong Kong SAR, Hong Kong Special Administrative Region; NR, Not Reported; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; PT, Posttreatment; QOL, Quality of Life; SAS, Zung Self-Rating Anxiety Scale; SCID-I/P, Statistical Manual of Mental Disorders-IV; SD, Standard Deviation; SDS, Zung Self-Rating Depression Scale; SF-36, 36-item Short Form Survey; TG, Treatment Group; WHOQOL-BREF, the World Health Organization's Quality of Life Instrument, Short Form.

T A B L E 2 Summary of the characteristics of TCM-based integrated health interventions

Author, Year	Setting, Instructor	Content (no. of components)	Regions or points or TCM formula/frequency and duration	Intervention period
Gao, 2016	Inpatient ward, nurses	TCM nursing: TCM-based psychological management (five elements of music), TCM-based food therapy and/or nutritional advice (based on five elements and five flavors), TCM-based sleep-wake management, meridians and collaterals management (4)	Acupressure: Baihui (GV20), Sanyinjiao (SP6), Fengchi (GB20), Hegu (LI4), Taiyang (EX-HN 5), Zusanli (ST36), Yintang (EX-HN 3), Anmian (EX-HN 22), Tianchong (GB9)/2–5 min for each point, twice a day, morning and night	6 weeks
Han et al., 2020	NR, a clinical psychologist	DMBI, an integrative lifestyle intervention for the mind and body: TCM-based psychological management ("listen to their body", "foster self-awareness and self-control"), TCM-based food therapy and/or nutritional advice ("refining the diet"), TCM-based exercise ("practice Shaolin Mind-body exercises", no fixed practicing time until they felt relaxed and warm) (3)	Nil	10 weeks
Lin et al., 2008	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, meridians and collaterals management (2)	Acupressure: Baihui (GV20), Ganshu (BL18), Danshu (BL19), Hegu (LI4), Taichong (LR3)/5 min for each point, twice a day, morning and night Acupuncture (main points): Renzhong (GV26), Neiguan (P6), Taichong (LR3), Shenmen (HT7), Zhigou (TE6)/once a day	8 weeks
Lu et al., 2019	Inpatient wards, nurses	TCM nursing: TCM-based psychological management (music), TCM-based food therapy and/or nutritional advice (e.g., oranges), meridians and collaterals management based on different body constitution-identified TCM syndrome differentiation, TCM-based sleep–wake management (4)	Auricular acupressure: wind-heat in liver meridian: Shenmen (TF4), Liver (CO12), Sympathetic autonomic (AH6a), Forehead (ATI/NR; flaming up of excessive fire of the liver and gallbladder: Shenmen (TF4)/NR Cupping therapy: Dazhui (GV14)/10–15 min per time	NR
Meng et al., 2020	Internet, physicians	TCM health preservation: TCM-based psychological management (200~300 words related emotion regulation sent every 3 days, reading these materials five times a day, and jotting down reading notes), TCM-based food therapy and/or nutritional advice, TCM-based sleep-wake management (3)	Nil	8 weeks
Peng et al., 2018	NR, nurses	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice, meridians and collaterals management, TCM-based exercise (Baduanjin: 3–5 times per week, 45 min each time for 12 weeks) (4)	TCM foot bath: NR/15–30 min every night, 38–40°C Self-help auricular acupressure: NR/3–4 times every day, 3–5 min for each point	12 weeks
Shao et al., 2018	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice (e.g., grapefruit), meridians and collaterals management (3)	Acupressure: Taichong (LR3), Liver (BL18), Gallbladder (BL19), Baihui (GV20)/30 min per day	NR
Song & Yuan, 2015	Inpatient wards, nurses	TCM nursing: TCM-based psychological management (music), TCM-based food therapy and/or nutritional advice (e.g., tangerine peel, oranges, fingered citron), meridians and collaterals management, both based on different body constitution-identified TCM syndrome differentiation (3)	Acupressure: Qi stagnation leading to congestion of phlegm: Tiantu (CV22), Zhaohai (KI6); yin deficiency and fire excess: Taichong (LR3), Shenyu (BL23), Ganyu (BL18), Taixi (KI3); liver qi stagnation: Taixi (KI3) and Taichong (LR3); dual deficiency of the heart and spleen: Neiguan (P6), Sanyinjiao (SP6), Shenting (GV24), Baihui (GV20), Zusanli (ST36)/30 min each time, one time per day	2 weeks
Sui, 2018	Inpatient wards, nurses	TCM nursing: TCM-based psychological management (music), meridians and collaterals management (2)	Acupressure: Taichong (LR3), Hegu (LI4), Gallbladder (Dan shu) (BL19), Ganshu (BL18), Baihui (GV20)/5 min for each point, twice per day	NR
Tan et al., 2008	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice (e.g., oranges), TCM-based sleep-wake management based on different body constitution-identified TCM syndrome differentiation (3)	Nil	NR
Wang, 2012	NR, NR	TCM nursing: TCM-based psychological management (music), TCM-based food therapy and/or nutritional advice, meridians and collaterals management, TCM-based sleep-wake management (4)	Acupressure: Fengchi (GB20), Shenmen (HT7)/30 times for each point per day	8 weeks
Wang, 2019	Inpatient wards, nurses	TCM nursing: TCM-based psychological management (music), TCM-based food therapy and/or nutritional advice (e.g., tangerine peel, oranges, and fingered citron), meridians and collaterals management based on different body constitution-identified TCM syndrome differentiation (3)	Acupressure: Qi stagnation leading to congestion of phlegm: Tiantu (CV22), Zhaohai (KI6); yin deficiency and fire excess: Taichong (LR3), Shenyu (BL23), Ganyu (BL18), Taixi (KI3); dual deficiency of the heart and spleen: Neiguan (P6), Sanyinjiao (SP6), Shenting (GV24), Baihui (GV20), Zusanli (ST36)/30 min each time, once a day	4 weeks

Author, Year	Setting, Instructor	Content (no. of components)	Regions or points or TCM formula/frequency and duration	Intervention period
Wang & Wang, 2021	Inpatient wards, nurses	TCM nursing: TCM-based psychological management (e.g., seven emotions), TCM-based food therapy and/or nutritional advice, meridians and collaterals management (3)	Acupressure: Baihui (GV20), Danshu (BL19), Taichong (LR3)/30 min per day	4 weeks
Wu & Li, 2019	Inpatient wards, health care providers (nurses and physicians)	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice based on different body constitution-identified TCM syndrome differentiation, meridians and collaterals management (3)	TCM acupuncture points: Renzhong (GV26), Baihui (GV20), Quchi (LI11), Neiguan (P6), Waiguan (SJ5), Hegu (LI4), Sanyinjiao (SP6), Zusanli (ST36)/NR

TCM foot bath, moxa-moxibustion, and auricular acupressure: NR/NR | NR |
Xin, 2014	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, meridians and collaterals management (2)	Acupressure: Baihui (GV20), Ganshu (BL18), Danshu (BL19), Neiguan (P6), Hegu (LI4), Taichong (LR3)/30 min per day	4 weeks
Yang, 2018	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice based on different body constitution-identified TCM syndrome differentiation (e.g., tangerine peel, oranges), meridians and collaterals management, TCM-based exercise (Taichi) (4)	Acupressure: Qi stagnation and blood stasis: Zusanli (ST36), Hegu (LI4), Taichong (LR3)/NR	8 weeks
Zhang, 2014	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, TCM-based food therapy and/or nutritional advice (e.g., oranges) (2)	Nil	NR
Zhang et al., 2016	Inpatient wards, nurses	TCM nursing: TCM-based psychological management, meridians and collaterals management, TCM-based depression and/or mental health education (3*30 min/week) (3)	TCM formula for foot bath: radix scutellariae 30 g, caulis sargentodoxae 30g, flos carthami 15 g, radix cyathulae 45 g, herba asari heterotropoidedis 15 g, herba agrimoniae 30 g, radix lithospermi 30 g, with 2,000 ml of water, 41−43°C/30 min every night before bed for 4 weeks

Acupressure: Hegu (LI4), Taichong (LR3), Zusanli (ST36)/each point with massage performed 36 times per time and every night for 4 weeks

Auricular acupressure: main points: Endocrine (CO18), Sympathetic autonomic (AH6a), Shenmen (TF4); adjunct points: heart (CO15), liver (CO12)/each point pressure for 1 min, 3−5 times/day for 2 weeks | 4 weeks |

Abbreviations: DMBI, Dejian Mind-Body Intervention; NR, Not Report; TCM, Traditional Chinese medicine.

T A B L E 3 Statistical summary of the moderator analysis performed using subgroup analysis (TCM-based integrated health interventions for depression versus usual care at posttreatment)

Moderator	Subgroups	No. of studies	No. of TG	No. of CG	Pooled SMD (95% CI)	Test for overall effect (Z)	P value	I^2 (%)	Test for subgroup difference (p value)
Depression measures	HAMD	10	362	358	−1.44 (−1.87, −1.01)	6.60	<0.00001	84	0.07
	SDS	5	223	223	−3.50 (−5.71, −1.29)	3.11	0.002	99	0.07
Diagnostic criteria for depression	Self-reported depression scale	4	153	152	−1.35 (−2.25, −0.45)	2.94	0.003	92	0.17
	Standard diagnostic system	2	50	49	−1.23 (−2.12, −0.34)	2.71	0.007	74	0.17
	Clinical diagnosis	5	247	247	−3.75 (−5.84, −1.66)	3.52	0.0004	98	0.17
	Standard diagnostic system and HAMD	4	135	133	−1.33 (−2.15, −0.52)	3.19	0.001	89	0.17
No. of components	2 components	3	130	128	−1.54 (−2.12, −0.96)	5.20	<0.00001	73	0.08
	3 components	7	259	258	−3.09 (−4.70, −1.47)	3.75	0.0002	98	0.08
	4 components	5	196	195	−1.10 (−1.79, −0.40)	3.08	0.002	90	0.08
Disease type	Post-stroke depression	9	362	360	−2.68 (−3.79, −1.58)	4.77	<0.00001	97	<0.00001
	Depression	2	62	61	−1.42 (−2.68, −0.15)	2.20	0.03	88	<0.00001
	Leukemia depression	1	40	40	−2.18 (−2.74, −1.62)	7.64	<0.00001	NA	<0.00001
	Menopause depression	1	43	42	−0.19 (−0.61, 0.24)	0.85	0.39	NA	<0.00001
	Uveitis depression	1	33	33	−1.66 (−2.22, −1.09)	5.76	<0.00001	NA	<0.00001
	Diabetes depression	1	45	45	−0.49 (−0.91, −0.07)	2.30	0.02	NA	<0.00001

Abbreviations: CG, Control Group; CI, Confidence Interval; HAMD, Hamilton Depression Rating Scale; NA, Not Applicable; SDS, Zung Self-Rating Depression Scale; SMD, Standardized Mean Difference; TCM, Traditional Chinese Medicine; TG, Treatment Group.

T A B L E 4 GRADE assessment on studies of TCM-based integrated health interventions for depression versus usual care

| Certainty assessment | | | | | | | No. of subjects | | Effect | |
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCM-based integrated health interventions for depression	Usual care	Relative (95% CI)	Absolut (95% CI
Depression (at posttreatment)										
15	randomised trials	serious †	serious ‡	not serious	not serious	none	585	581	–	SMD **2.05 lower** (2.74 lower to 1.37 lower)
Depression (1-month follow-up)										
2	randomised trials	serious †	not serious	not serious	serious ¶	none	60	60	–	SMD **0.96 lower** (1.34 lower to 0.58 lower)
Depression (2-month follow-up)										
2	randomised trials	serious †	not serious	not serious	serious ¶	none	60	60	–	SMD **0.99 lower** (1.42 lower to 0.55 lower)
Depression (3-month follow-up)										
1	randomised trials	serious †	not serious	not serious	serious ¶	none	30	30	–	SMD **2.01 lower** (2.64 lower to 1.38 lower)

Note. CI = Confidence Interval; SMD = Standardized Mean Difference; TCM = Traditional Chinese Medicine.

† = serious due to crucial limitations for one criterion or some limitations for multiple criteria.

‡ = serious inconsistency because of considerable heterogeneity (I^2 = 96%) and *p* value (chi-square test) < 0.10.

§ = GRADE working group grades of evidence:

High quality = further research is very unlikely to change our confidence in the estimate of effect; Moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality = we are very uncertain about the estimate.

¶ = serious imprecision because of the small sample size (less than 400 participants)

Appendix

Appendix A is not available with this version

Figures

Identification

Records identified through database searching (n = 2183)

PubMed (n = 213), Embase (n = 192), PsycINFO (n = 18), CINAHL (n = 44), PQDT (n = 103), AMED (n = 1), CENTRAL (n = 42), CCMD-CTR (n = 0), ICTRP (n = 0), ClinicalTrials.gov (n = 0), ChiCTR (n = 5), CBM (n = 50), CNKI (n = 316), VIP (n = 275), Wanfang (n = 913), NCL Taiwan Periodical Literature (n = 1), National Digital Library of Theses and Dissertations in Taiwan (n = 10)

Additional records identified through other sources (n = 2)

Screening

Records after duplicates removed (n = 1572)

Records screened (n = 1572)

Records excluded (n = 1532)

- Irrelevant studies (n = 1472)
- Review articles (n = 51)
- Case reports (n = 7)
- Survey study (n = 2)

Eligibility

Full-text articles assessed for eligibility (n = 40)

Full-text articles excluded, with reasons (n = 22)

- Not participants with depression (n = 2)
- Ineligible outcome measures (n = 4)
- Study protocol (n = 1)
- Ineligible interventions (n = 15)

Included

Studies included in qualitative synthesis (n = 18)

Studies included in quantitative analysis (meta-analysis) (n = 18)

Figure 1

The PRISMA flow chart of study selection process

Figure 2

Assessment of the risk of bias of each randomized controlled trial

Study or Subgroup	TCM-based integrated health interventions Mean	SD	Total	Usual care Mean	SD	Total	Weight	Std. Mean Difference IV. Random, 95% CI	Year
1.1.1 posttreatment									
Lin et al., 2008	11.68	2.29	30	15.56	1.74	28	6.7%	-1.87 [-2.50, -1.25]	2008
Wang, 2012	5.9	1.4	30	7.5	1.3	30	6.8%	-1.17 [-1.72, -0.62]	2012
Xin, 2014	9.3	4.2	30	17.4	4.6	30	6.7%	-1.82 [-2.42, -1.21]	2014
Song & Yuan, 2015	41.58	5.22	46	49.16	6.03	46	6.9%	-1.33 [-1.79, -0.88]	2015
Gao, 2016	12.89	5.41	43	14.09	7.32	42	6.9%	-0.19 [-0.61, 0.24]	2016
Zhang et al., 2016	15.42	6.17	40	28.11	5.34	40	6.8%	-2.18 [-2.74, -1.62]	2016
Peng et al., 2018	51.52	8.71	45	55.93	9.03	45	6.9%	-0.49 [-0.91, -0.07]	2018
Sui, 2018	8.61	2.92	70	11.96	3.32	70	7.0%	-1.07 [-1.42, -0.71]	2018
Yang, 2018	7.39	2.21	45	13.31	3.42	45	6.8%	-2.04 [-2.55, -1.53]	2018
Shao et al., 2018	31.3	2.8	52	53.6	3.1	52	6.0%	-7.49 [-8.60, -6.39]	2018
Lu et al., 2019	8.13	1.61	33	12.42	3.24	33	6.8%	-1.66 [-2.22, -1.09]	2019
Wang, 2019	17.15	4.87	24	25.52	4.39	24	6.6%	-1.78 [-2.45, -1.10]	2019
Wu & Li, 2019	46.67	3.7	30	48	5.56	30	6.8%	-0.28 [-0.79, 0.23]	2019
Han et al., 2020	6.5	4.31	17	9.75	4.16	16	6.6%	-0.75 [-1.46, -0.04]	2020
Wang & Wang, 2021	31.16	1.02	50	50.25	3.05	50	5.8%	-8.33 [-9.57, -7.09]	2021
Subtotal (95% CI)			585			581	100.0%	-2.05 [-2.74, -1.37]	

Heterogeneity: Tau² = 1.72; Chi² = 330.15, df = 14 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.87 (P < 0.00001)

1.1.2 1-month follow-up									
Tan et al., 2008	12.6	2.5	30	15.1	2.9	30	50.6%	-0.91 [-1.44, -0.38]	2008
Zhang, 2014	12.34	4.261	30	17.25	5.21	30	49.4%	-1.02 [-1.56, -0.48]	2014
Subtotal (95% CI)			60			60	100.0%	-0.96 [-1.34, -0.58]	

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 4.98 (P < 0.00001)

1.1.3 2-month follow-up									
Tan et al., 2008	8.8	1.7	30	10.3	2.1	30	52.0%	-0.77 [-1.30, -0.25]	2008
Zhang, 2014	10.75	3.262	30	15.48	4.32	30	48.0%	-1.22 [-1.77, -0.67]	2014
Subtotal (95% CI)			60			60	100.0%	-0.99 [-1.42, -0.55]	

Heterogeneity: Tau² = 0.02; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 4.45 (P < 0.00001)

1.1.4 3-month follow-up									
Zhang, 2014	7.26	2.242	30	13.28	3.53	30	100.0%	-2.01 [-2.64, -1.38]	2014
Subtotal (95% CI)			30			30	100.0%	-2.01 [-2.64, -1.38]	

Heterogeneity: Not applicable
Test for overall effect: Z = 6.27 (P < 0.00001)

Favours TCM-based integrated health interventions   Favours usual care

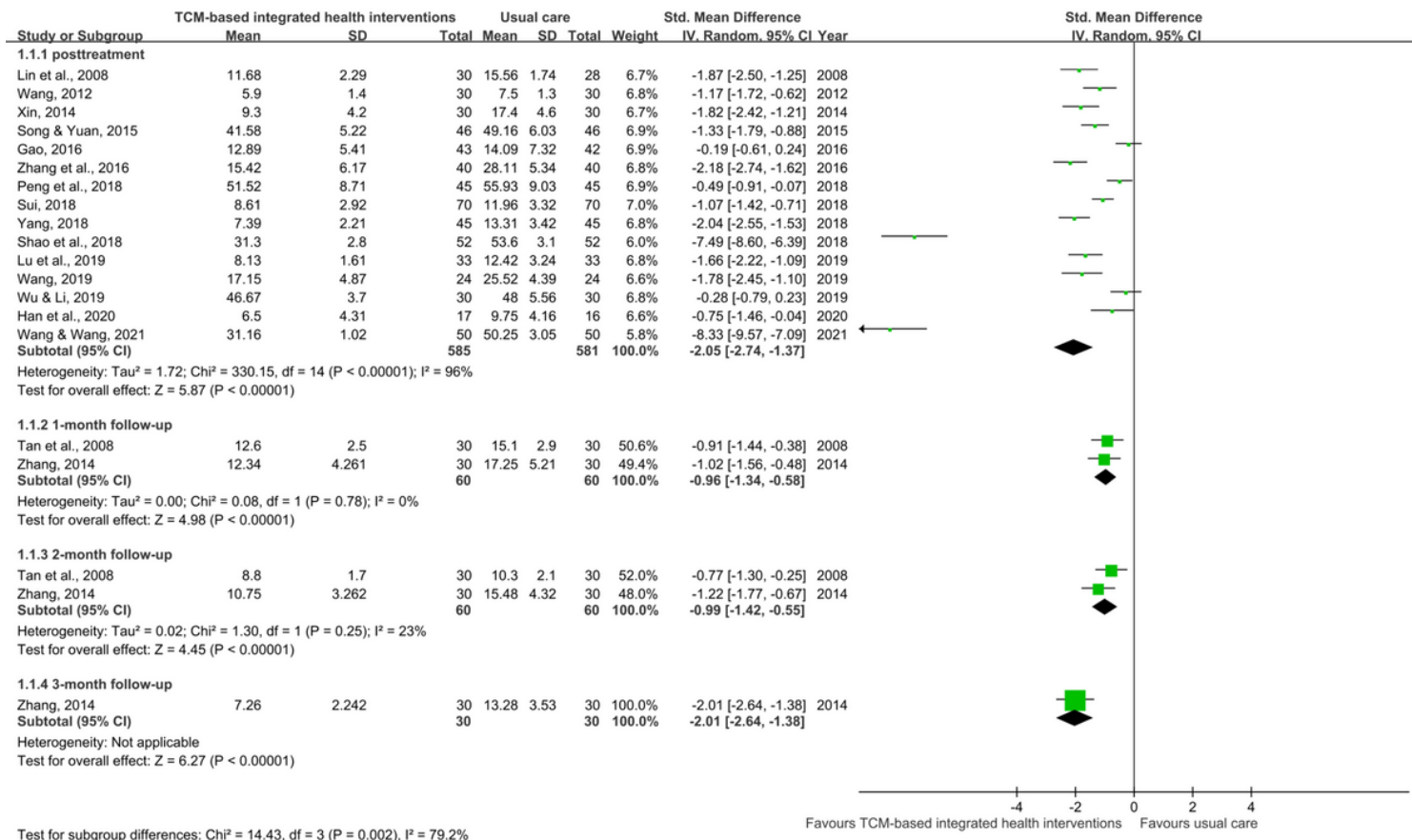Test for subgroup differences: Chi² = 14.43, df = 3 (P = 0.002), I² = 79.2%

Figure 3

Forest plot for TCM-based integrated health interventions versus usual care on depression

Study or Subgroup	TCM-based integrated health interventions Mean	SD	Total	Cognitive behavioral therapy Mean	SD	Total	Weight	Std. Mean Difference IV. Random, 95% CI	Year
Meng et al., 2020	2.48	1.43	60	3.34	1.88	58	61.9%	-0.51 [-0.88, -0.15]	2020
Han et al., 2020	6.5	4.31	17	6.13	5.11	17	38.1%	0.08 [-0.60, 0.75]	2020
Total (95% CI)			77			75	100.0%	-0.29 [-0.85, 0.27]	

Heterogeneity: Tau² = 0.10; Chi² = 2.27, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 1.01 (P = 0.31)

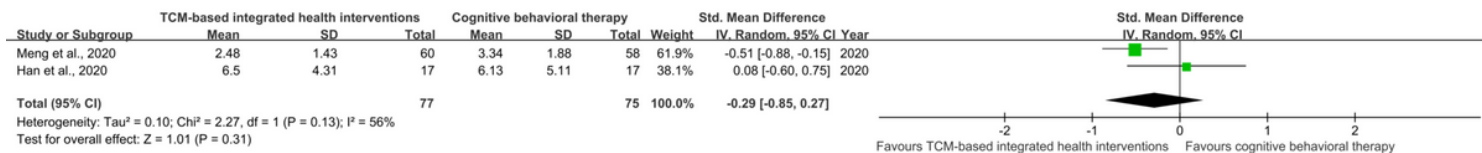Favours TCM-based integrated health interventions   Favours cognitive behavioral therapy

Figure 4

Forest plot for TCM-based integrated health interventions versus cognitive behavioral therapy on depression
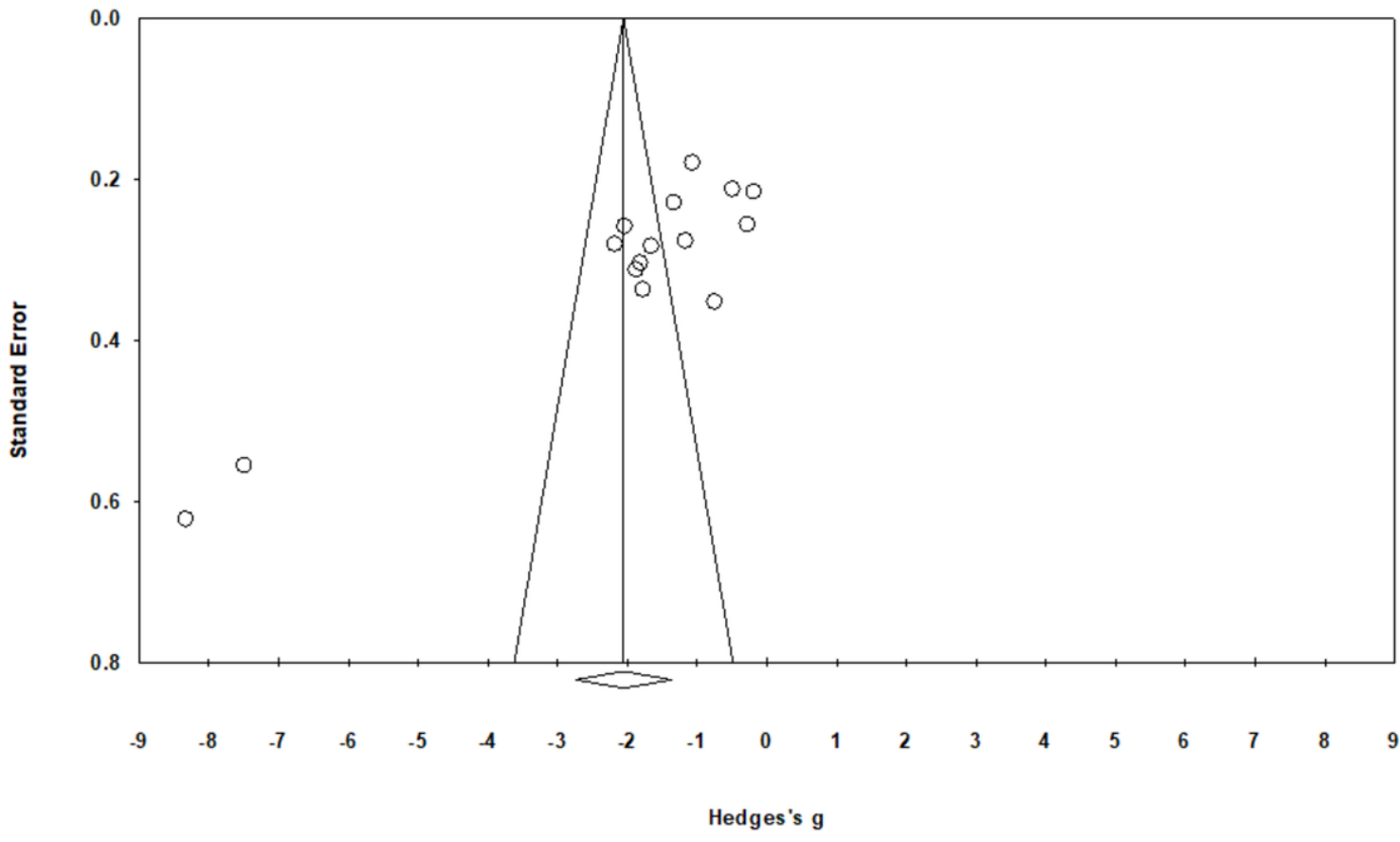
Figure 5

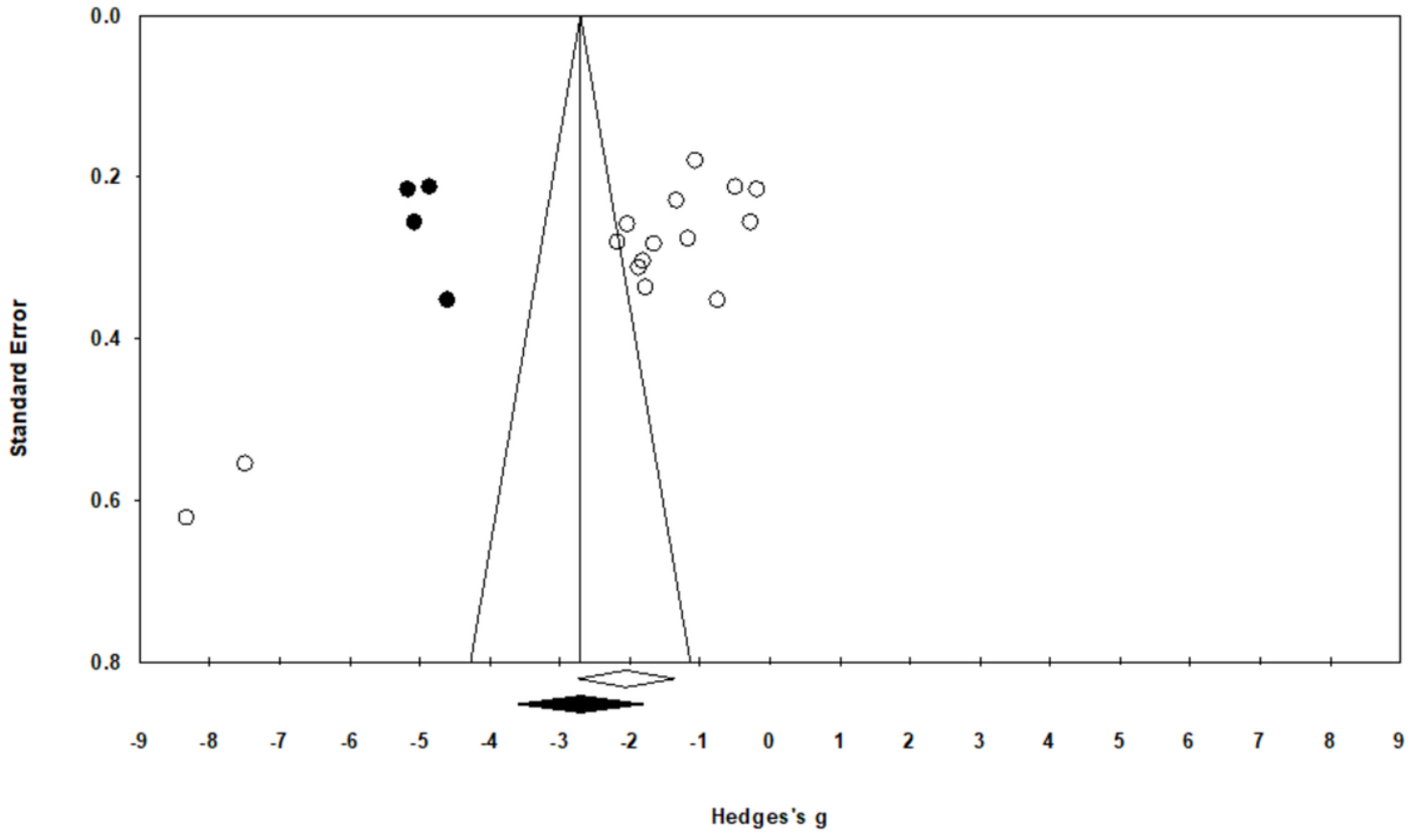Funnel plot of TCM-based integrated health interventions for depression

Figure 6

Funnel plot of TCM-based integrated health interventions adjusted for publication bias; Open circles refer to original studies, and solid circles refer to "filled" studies