Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Insufficient Evidence to Recommend *Shu Mian Capsule* in Managing Depression With or Without Comorbid Insomnia: A Systematic Review With Meta-Analysis and Trial Sequential Analysis

Fei-Yi Zhao[1–3,*], Peijie Xu[4,*], Gerard A Kennedy[2,*], Xiaochao Jin[5,6], Yan-Mei Wang[3], Wen-Jing Zhang[3], Li-Ping Yue[1], Yuen-Shan Ho[7], Qiang-Qiang Fu[8], Russell Conduit[2]

[1]Department of Nursing, School of International Medical Technology, Shanghai Sanda University, Shanghai, 201209, People's Republic of China; [2]School of Health and Biomedical Sciences, RMIT University, Bundoora, Melbourne, VIC, 3083, Australia; [3]Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 200071, People's Republic of China; [4]School of Computing Technologies, RMIT University, Melbourne, VIC, 3000, Australia; [5]Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China; [6]Shanghai Jiaotong University School of Nursing, Shanghai, People's Republic of China; [7]School of Nursing, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, People's Republic of China; [8]Yangpu Hospital, School of Medicine, Tongji University, Shanghai, 200090, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuen-Shan Ho, School of Nursing, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, People's Republic of China, Tel +852 2766-6410, Fax +852 2364-9663, Email janice.ys.ho@polyu.edu.hk; Qiang-Qiang Fu, Yangpu Hospital, School of Medicine, Tongji University, Shanghai, 200090, People's Republic of China, Tel + 86 021-6569 0520, Fax + 86 021-6569 6249, Email qiangqiang.fu@tongji.edu.cn

Aim: This systematic review with trial sequential analysis (TSA) aims to evaluate the efficacy and safety of Shu Mian Capsule (SMC), a commercial Chinese polyherbal preparation, for managing depression with or without comorbid insomnia.

Methods: Controlled clinical trials assessing SMC against waitlist control, placebo or active controls, or as an adjunct treatment were searched across seven databases. Risk of bias and evidence quality were assessed using Cochrane criteria and GRADE framework, respectively.

Results: Fourteen studies were analyzed, involving 1207 participants. Trials comparing SMC with placebo or standard antidepressive treatments were limited. In depressed patients without comorbid insomnia, combining SMC with antidepressants reduced the incidence of antidepressants-induced sleep disorders (from 12.2% to 3.8%) but did not significantly lower Hamilton Rating Scale for Depression (HAM-D) scores compared to antidepressants alone [SMD = −0.09, 95% CI (−0.32, 0.14), $p = 0.45$]. In depressed patients with comorbid insomnia, the combination of SMC and psychotropic drugs significantly reduced HAM-D [SMD = −1.29, 95% CI (−1.96, −0.62), $p < 0.01$] and Pittsburgh Sleep Quality Index scores [SMD = −1.53, 95% CI (−1.95, −1.11), $p < 0.01$], and exhibited a lower incidence of various drug-related adverse effects compared to psychotropic drugs alone. TSA validated the sample size adequacy; nevertheless, the methodological quality of supporting studies varied from very low to low due to substantial bias risk. Additionally, 92.9% of trials lacked follow-ups.

Conclusion: The effectiveness of SMC as an alternative to conventional antidepressive treatment is unclear. For depressed patients with comorbid insomnia, adding SMC to standard care demonstrates augmented efficacy and improved safety, though the supporting evidence is methodologically limited. Further rigorous trials are warranted to confirm SMC's short-term efficacy and explore its medium- to long-term effects as either an alternative or complementary therapy. Current evidence precludes recommendations for the administration of SMC in depression.

Keywords: Chinese patent medicine, commercial Chinese polyherbal preparation, Chinese medicine, herbal medicine, depressive disorder, major depressive disorder, sleep quality

Received: 7 October 2024
Accepted: 22 January 2025
Published: 31 January 2025

Background

Depression is the leading global contributor to disability, as identified by the World Health Organization, affecting approximately 322 million people and accounting for 7.5% of all years lived with disability.[1] It impairs cognitive function, behavior, and overall quality of life,[2] and contributes to the development of chronic diseases such as cancer, diabetes, coronary artery disease, and stroke.[3] Up to 15% of individuals with depression ultimately commit suicide.[4] Depression's impact extends beyond health, reducing workplace productivity and increasing absenteeism.[5] In the US, depressed employees lose over 27 workdays annually, resulting in a $36.6 billion economic loss.[5] From 2010 to 2018, the incremental economic burden of depression among US adults rose by 37.9%, from $236.6 billion to $326.2 billion.[6] In China, depression similarly drives higher economic burden, with total healthcare costs increasing by 3.1% to 85.0%, and annual productivity losses by 1.6% to 90.1%.[7] The burden of depression in Switzerland and South Korea was estimated to be about €8 billion[8] and $4,049 million,[9] respectively, per year. Interpersonal functioning is also compromised,[10] often leading to family instability, separation, or divorce.[5] Additionally, dysfunctional interactions between depressed mothers and their children are extensively documented.[10]

Herbs and dietary supplements are especially prevalent among individuals with psychiatric disorders.[11] A national survey in the US revealed that 53.6% of those with depression utilized Complementary and Alternative Medicine (CAM), including herbal remedies, over the past year to alleviate symptoms.[12] During the COVID-19 lockdown in Mexico, severe anxiety and depression affected 20.8% to 48% of the population, with self-medication using medicinal plants reaching 61.9%.[13] Concurrent use of CAM is also widespread among patients on prescription medications.[11] Furthermore, physicians are showing growing interest in traditional herbs as a promising alternative for managing depression.[14]

Commercial Chinese polyherbal preparations (CCPP) are defined as Chinese medicinal products formulated according to Traditional Chinese Medicine (TCM) principles and manufactured through standardized preparation techniques into various forms, including solutions, concentrated extract granules, ointments, pills, powders, capsules, or tablets.[15,16] Shu Mian Capsule (SMC; Chinese character: 舒眠膠囊; Manufacturer: DaLong Pharmaceutical Co., Ltd.; FDA Approval No. Z20000105) is a CCPP listed among 1,311 CCPPs in the latest National Medical Insurance Catalogue in China (Drug Code: ZA10C-452; Drug Catalog Search: https://www.gov.cn/). It is composed of six botanical drugs (*Ziziphi Spinosae Semen, Bupleuri Radix, Paeoniae Radix Alba, Albiziae Flos, Silktree Albizia Bark, Silktree Albizia Bark, Junci Medulla*) and two animal-derived drugs (*Bombyx Batryticatus, Cicadae Periostracum*).[17] All species have been taxonomically validated, with full species names, authorities, and families provided in Appendix 1. According to the National Medical Products Administration, China (https://www.nmpa.gov.cn/) and the drug package insert, SMC is indicated for soothing the Liver and relieving depression, as well as calming the Mind and tranquilizing the Spirit.[18] SMC is recommended for treating depression, irritability, feelings of chest tightness, and/or insomnia characterized by vivid dreams.

Two randomized controlled trials (RCTs) examined the adjunctive antidepressive effects of SMC, yielding conflicting results.[19,20] One RCT demonstrated that combining SMC with Paroxetine significantly reduced the 24-item Hamilton Rating Scale for Depression (HAM-D_{24}) scores compared to Paroxetine alone.[19] Conversely, another RCT reported no significant difference in HAM-D_{24} score reduction between Paroxetine and the combination therapy.[20] Notably, both trials utilized the same dosage and treatment duration for SMC.[19,20] Conflicting results were also observed in two RCTs examining the effects of combining SMC with Sertraline in depressed patients. Chen et al[21] found that eight weeks of Sertraline combined with SMC did not lead to a greater reduction in HAM-D_{17} scores compared to eight weeks of Sertraline alone. In contrast, Zhu et al[22] reported that, with the same dose and treatment duration, adding SMC to Sertraline significantly reduced HAM-D_{17} scores. Additionally, while some systematic reviews have investigated SMC's effects on sleep disorders,[17,23] none currently address its use in depression. These discrepancies in clinical outcomes and the research gap prompted us to conduct this systematic review to appraise the efficacy and safety of SMC in treating depression, aiding clinicians in making evidence-based treatment decisions.

Approximately 75% of patients with depression experience comorbid insomnia, typically characterized by difficulties in falling asleep, maintaining sleep, or both.[24] A large-scale study in the UK involving 8,580 participants demonstrated that insomnia incidence among depressed patients increases with age.[25] Given that a prior systematic review indicated

SMC as a potentially effective and safe treatment for insomnia,[17] we did not exclude studies addressing depression with comorbid insomnia in this review. This inclusion would enhance our understanding of SMC's specific applicability.

Materials and Methods

Study Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement guidelines.[26] A prospective protocol was registered in PROSPERO (Identifier: CRD42023472237).

Eligibility Criteria

Eligible studies had to fulfill the following PICOS framework criteria.

Participant (P)

Studies included patients clinically diagnosed with depression as per established diagnostic criteria (Appendix 2.1), irrespective of comorbid insomnia. Trials lacking standardized diagnostic guidelines were excluded, even if they identified participants as having depression or provided brief descriptions of depressive symptoms. Studies involving patients with other comorbid psychiatric or physical illnesses, except insomnia, were excluded. Secondary depression from conditions such as stroke, diabetes, or cancer was not considered.

Intervention (I)

Interventions were limited to SMC, administered either alone or in conjunction with standard care per clinical guidelines,[27] including antidepressants and/or psychotherapy (eg, psychodynamic therapy, cognitive-behavioral therapy). Olanzapine, Aripiprazole, and Quetiapine were also considered standard care, being FDA-approved for depression treatment.[28] While some antidepressant trials suggest concomitant benzodiazepine use correlates with poorer outcomes,[29] others indicate its efficacy as monotherapy for depression, particularly in anxious cases.[30] Historically, benzodiazepines were still considered viable monotherapy options after modern antidepressants emerged.[31] Similarly, a systematic review found that incorporating *Z*-drugs into antidepressive regimens can enhance efficacy.[32] Despite ongoing debate, hypnotic use in depressed patients is common.[33] Given that this review included studies on depression with comorbid insomnia, the intervention group could use the same antidepressants, antipsychotics, and/or hypnotics as the control group alongside SMC. Trials with inconsistencies in this aspect were excluded.

Comparator (C)

Comparators were limited to waitlist control, placebo-SMC, or standard care.

Outcome (O)

The primary outcome was scores from validated depression scales, such as the HAM-D, Self-Rating Depression Scale (SDS), or Beck Depression Inventory, without restrictions on the HAM-D version for study inclusion. Studies failing to report global scores from any validated depression scale were excluded, even if they reported partial items or clinical efficacy rates based on scale scores. Secondary outcomes included clinical efficacy rate, sleep symptoms, quality of life (QoL), and adverse effects (AEs).

Study (S)

Formally published RCTs and non-randomized controlled clinical trials (NRCTs) with parallel designs were included, regardless of language or date restrictions.

Search Strategy and Data Extraction

The search strategy entailed a comprehensive search of three English databases (MEDLINE via PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) and four Chinese databases (SinoMed, Wanfang, China National Knowledge Infrastructure, and Chongqing VIP) until September 2024. Relevant search terms related to SMC, depression, and clinical trials were used, as detailed in Appendix 2.2, with no language restrictions. Articles published in journals and

conference proceedings were considered. Additional trials and gray literatures were identified from the reference lists of included studies and relevant reviews, as well as from the US ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform Search Portal. Two reviewers (QQ-F and PJ-X) performed the search independently.

EndNote 21 was used to organize retrieved articles and remove duplicates. Titles and abstracts were initially screened to exclude irrelevant studies, with full texts reviewed as necessary. Two investigators (XC-J and LP-Y) independently selected eligible trials and reached a consensus on inclusion.

A predesigned data sheet was utilized to extract the following data from each included trial: first author's name, publication date, study type, grouping methods, sample size per group, duration of depression, diagnostic system, participant characteristics (including TCM syndrome patterns), intervention protocols (ie, dosage, frequency, treatment duration), control prescriptions, outcome measures, results, follow-ups, and AEs.

Evaluation of Risk of Bias in Individual Studies

Two investigators (YM-W and WJ-Z) independently appraised the quality of the included studies following the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.5 (https://training.cochrane.org/handbook). The methodological quality of RCTs and NRCTs was evaluated using the Revised Cochrane Risk of Bias Tool for Randomized Trials (ROB 2.0)[34] and the Cochrane Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I),[35] respectively. A substantial agreement was achieved (Kappa = 0.79), with discrepancies resolved through discussion and consensus, arbitrated by a third assessor (FY-Z).

Data Analysis

All studies were analyzed qualitatively. Outcomes measured in at least three trials were combined for quantitative meta-analysis using *R* 4.3.3 with the "meta" package (version 7.0–0). Categorical variables (eg, clinical efficacy rate) were pooled using the Mantel–Haenszel method, while continuous variables (eg, depression or sleep questionnaires/scales) were pooled using the inverse variance method. Heterogeneity was assessed with the *Chi*-squared test and quantified by I^2 statistic. Following Tufanaru et al,[36] a random-effects model was employed as the default to generalize conclusions beyond the included studies and made results more conservative. The fixed-effects model was applied only when $I^2 = 0$ (no heterogeneity existed). Similarly, to enhance external applicability, standardized mean difference (SMD) was used to estimate the effect size of continuous variables, as it is preferred over mean difference (MD) for generalizability.[37] Odds ratio (OR), rather than relative risk (RR), was used for categorical variables due to the inclusion of NRCTs.[38] Trial sequential analysis (TSA) assessed primary outcomes (ie, depression scale scores; and, if patients had comorbid insomnia, sleep scale scores as well) to determine whether sample sizes were adequate for statistically significant results, with a two-tailed type I error rate of 5% and 80% power using TSA 0.9.5.10 Beta software.

In cases of significant clinical heterogeneity, subgroup analyses were performed based on study types (RCT or NRCT), patients' comorbid conditions (with or without comorbid insomnia), treatment duration (≥8 weeks or <8 weeks), and comparators (psychotherapy or psychiatric medications). Meta-regression and sensitivity analysis were conducted when sufficient studies ($n \geq 10$) were available to identify heterogeneity sources and verify result robustness. For meta-regression, publication year, sample size, study types, comorbid condition, treatment duration, and standard care used in control were considered as covariates.

Using STATA 18.0, a funnel plot was generated for outcomes measured in at least ten trials, and linear regression analysis (Egger's test) was conducted to detect potential publication bias. When significant bias was identified, the Trim and Fill method was employed to correct for it.

Assessment on the Certainty of Evidence

The overall quality of evidence from the meta-synthesis was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework.[39] This framework assigns a GRADE rating from "High" to "Very Low" based on five variables: risk of bias (RoBs), inconsistency, indirectness, imprecision, and publication bias, reflecting the certainty of the reported evidence.

Results Analysis

The initial database search yielded 117 potentially eligible citations. Following the removal of duplicates and full-text screening, 12 RCTs and two NRCTs with 1,207 participants met the predefined criteria (Figure 1). Details of the excluded studies and their specific exclusion reasons were provided in Appendix 3.

Description of Studies

Among the 14 trials (Appendix 4), four included participants diagnosed with depression alone,[21,40–42] while the remaining ten involved depressed participants with comorbid insomnia.[19,20,22,43–49] Of these trials, only one compared SMC to psychotropic drugs, while 13 evaluated SMC combined with psychotropic drugs against psychotropic drugs

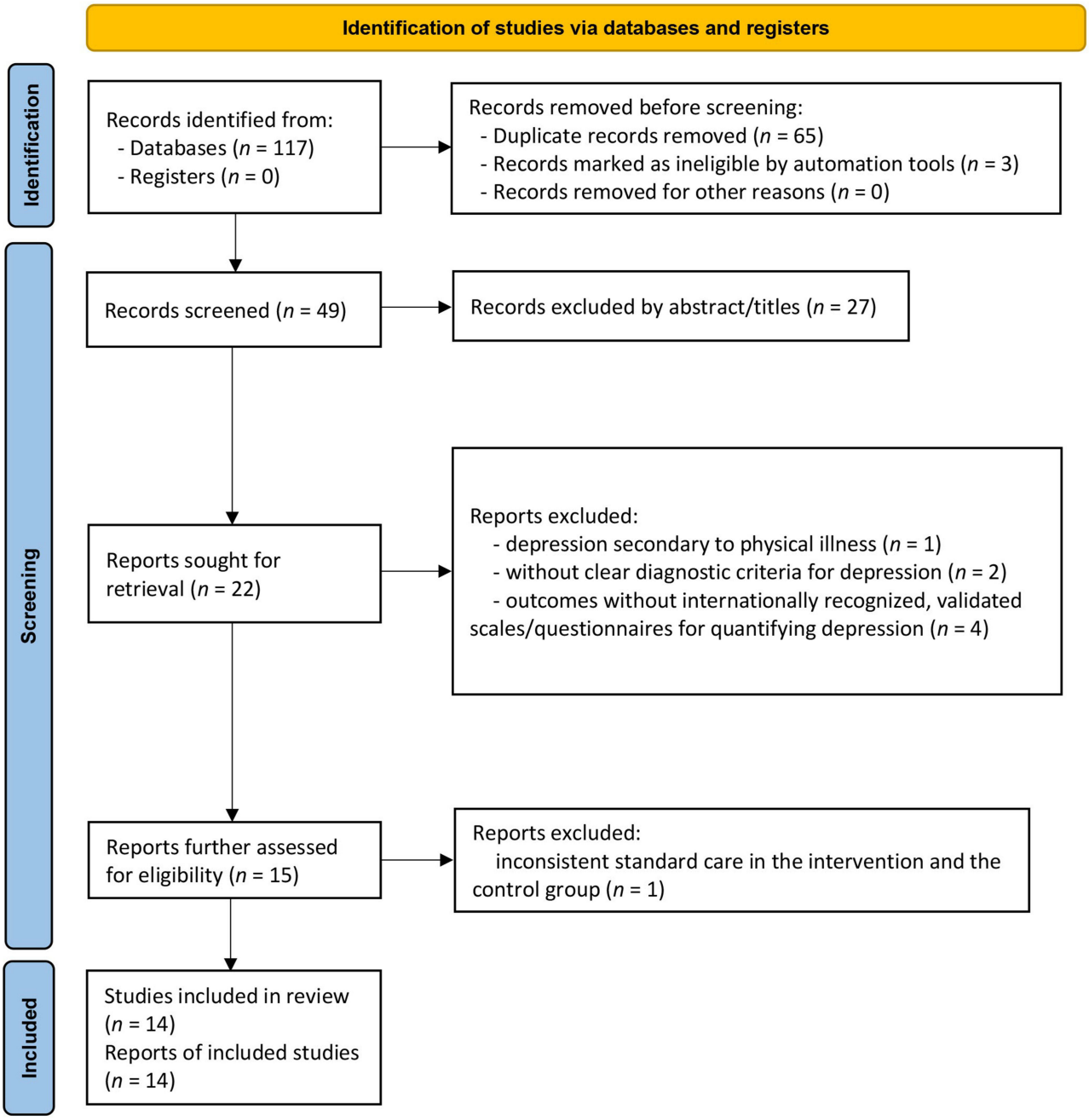

Figure 1 Flow Diagram of the Study Selection.

https://doi.org/10.2147/NDT.S499574

alone. None included psychotherapy, placebo-SMC, or waitlist control. Two trials[43,46] utilized hypnotics as active controls, one trial[45] used Olanzapine (a second-generation antipsychotic agent), and the others used antidepressants (eg, Sertraline, Paroxetine, Escitalopram, Venlafaxine, Mirtazapine).

All trials employed either the HAM-D_{17} or HAM-D_{24} as primary outcome measures, with one study additionally incorporating the SDS to assess patients' self-reported depressive symptoms. Nine trials utilized the Pittsburgh Sleep Quality Index (PSQI) scale or polysomnography to evaluate sleep changes during pharmacological treatment. Five trials assessed QoL changes at pre- and post-treatment using the World Health Organization Quality of Life-BREF scale or the Quality of Life Index (QoLI). Furthermore, nine trials compared clinical efficacy rates across interventions, albeit with varying grading criteria (Appendix 5).

In all 14 included trials, the SMC was sourced from the same pharmaceutical company, with a consistent batch number, as detailed in the "Background" section. The composition of each botanical drug in the SMC aligns with the specifications required by the National Medical Products Administration, China. All trials followed the recommended dosage from the drug package insert, administering 1.2g of SMC twice daily (once after dinner and once before bedtime). This uniformity in source, composition, and dosage allows for consistency and comparability of prescriptions across trials, ensuring homogeneity for the meta-synthesis.

Except for two trials,[42,48] all others reported AEs. Most trials compared the safety of SMC combined with psychiatric drugs against psychiatric drugs alone, with reported AEs during these interventions listed in Appendix 6. Overall, SMC was found to be safe and appears to mitigate some AEs associated with psychiatric medications. AEs from antipsychotics in depressed patients included dizziness, dry mouth, gastrointestinal symptoms (eg, loss of appetite, nausea, diarrhea, constipation), and weight gain. However, with the addition of SMC to the antipsychotic regimen, no dizziness (8.6% vs 0%) or gastrointestinal symptoms (8.6% vs 0%) were reported. The incidence of dry mouth remained unchanged (2.9% vs 2.9%), while weight gain significantly decreased (from 8.6% to 2.9%). When compared to hypnotics alone, the addition of SMC resulted in lower incidences of fatigue and daytime drowsiness (24.4% vs 2.0%). Adding SMC to antidepressants led to a slight increase in blurred vision incidence (from 0% to 1.8%) and a significant decrease in sleep disturbances (from 12.2% to 3.8%). Other symptoms, including dizziness, fatigue, daytime drowsiness, dry mouth, gastrointestinal issues, sexual dysfunction, sweating, edema, and weight gain, showed no significant changes.

Assessment of Risk of Bias (RoB) in Individual Studies

Assessing RCTs Quality: ROB 2.0 Shows Moderate to High RoB

Of the 12 RCTs, while all claimed to use randomized groupings, only four explicitly detailed the method (random number table).[19,20,47,48] None described whether allocation concealment methods, such as sealed blinding codes, were implemented. As a result, all RCTs were judged to have "some concerns" in the "randomization process" domain of the ROB 2.0 tool. Eleven trials comparing psychotropic drugs alone versus their combination with SMC were rated as high risk for "deviations from intended interventions" due to the lack of placebo controls, which unblinded participants and implementers, potentially affecting outcomes. While blinding the intervention was challenging, blinding the outcome assessors was feasible, yet none of the trials provided relevant information on this, raising further concerns in the "outcome measurement" domain. Similarly, the remaining trial,[43] which compared psychiatric drugs to SMC, was judged to have concerns in these two domains as well due to the lack of clarity about blinding procedures.

One study[20] raised concerns in the "missing outcome data" domain due to a 2.7% dropout rate, with these cases excluded from the analysis. All other studies showed low risk in this domain due to no participant withdrawals. One RCT[41] had concerns in the "selective reporting outcome" domain, reporting only global scores of the Treatment Emergent Symptom Scale (used to track drug-related AEs)[50] without detailing specific AEs. Three trials were rated as high risk in this domain: two[42,48] did not provide information on drug-related AEs, and two[20,48] reported only on the clinical efficacy rate of treatments for comorbid insomnia without addressing efficacy rate for depression outcomes.

Overall, except for one trial rated as having "some concerns", all were classified as having a high RoB (Figure 2A and B).

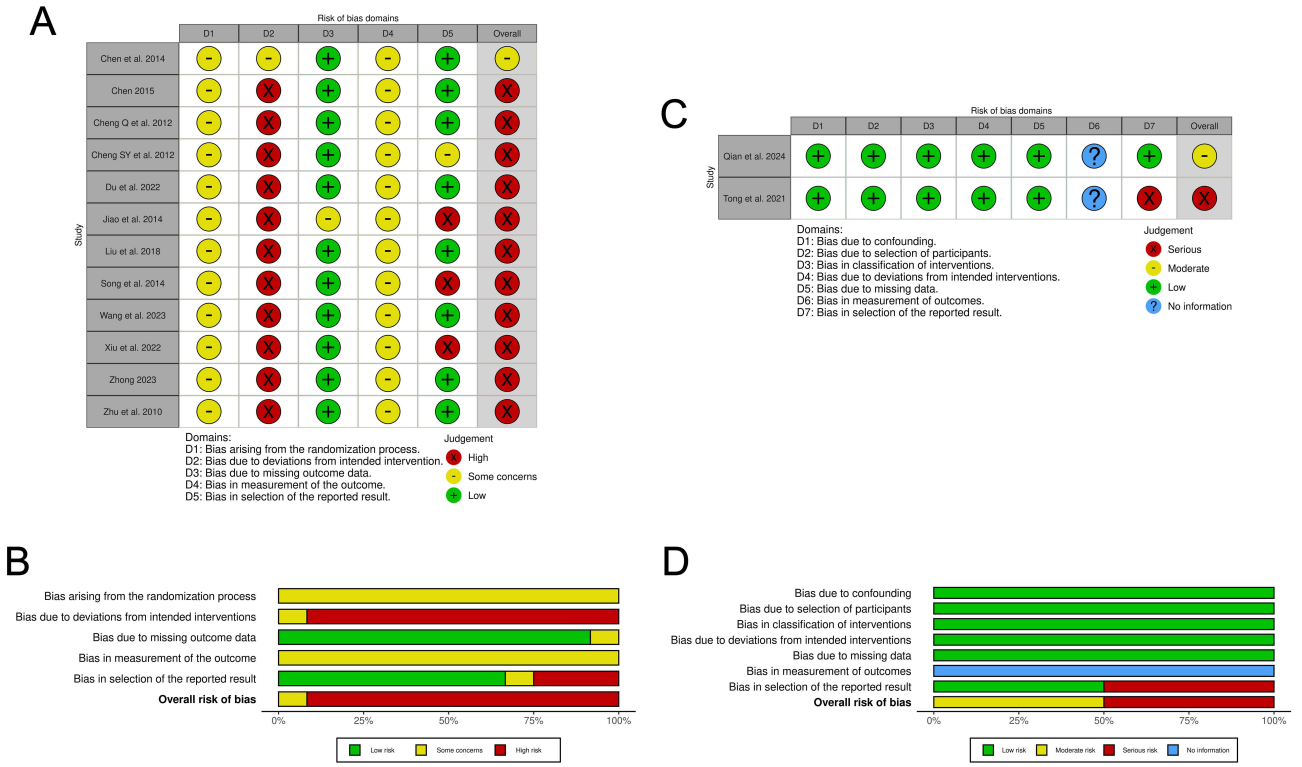

Figure 2 The Risk of Methodological Bias in the Included Studies. (**A**) Risk of Bias Summary for RCTs. (**B**) Risk of Bias Graph for RCTs. (**C**) Risk of Bias Graph for NRCTs. (**D**) Risk of Bias Summary for NRCTs.
Abbreviations: RCTs, Randomized Controlled Clinical Trials; NRCTs, Non-Randomized Controlled Clinical Trials.

Assessing NRCTs Quality: ROBINS-I Shows Moderate to High RoB

Two NRCTs were assessed as having low RoB in the "confounding" and "participants selection" domains due to their use of standard diagnostic guidelines for participant screening. Baseline equivalence tests also indicated no significant differences between groups, ensuring comparability. All participants completed the intervention, the methods were clearly defined, and there were no deviations from the intended interventions. Thus, these two studies also received low RoB ratings in the "intervention classification", "deviations from intended interventions", and "missing data" domains. However, neither study reported measures to control for measurement or observer bias. One trial[46] was deemed to have significant risk in the "selective reporting outcome" domain, as it only provided the clinical efficacy rate of medications for comorbid insomnia, omitting primary depression symptoms.

Overall, one NRCT had moderate RoB, while the other was classified as having serious RoB (Figure 2C and D).

Analyses of Outcome Measures

SMC vs Waitlist Control or Placebo-SMC

No trials qualified for this comparison.

SMC vs Standard Care

Only one RCT addressed this comparison.[43] The study reported that both SMC and Estazolam effectively reduced HAM-D_{17} and PSQI scores in depressed patients with comorbid insomnia, with SMC demonstrating a more pronounced effect. This effect persisted for one week after the cessation of treatment. Additionally, SMC significantly alleviated patients' concomitant anxiety, as evidenced by a decline in the Hamilton Rating Scale for Anxiety scores.

No studies compared the efficacy of SMC with psychotherapy.

https://doi.org/10.2147/NDT.S499574

SMC Combined With Standard Care vs Standard Care

This category included 13 trials (participants = 884), comprising 11 RCTs and two NRCTs, all of which utilized psychiatric drugs as standard care. No trial demonstrated evidence for the combined use of SMC with psychotherapy. Meta-analyses were conducted for HAM-D, PSQI and QoLI global scores, and clinical efficacy rate.

HAM-D Global Scores

All trials (participants = 884) compared HAM-D scores between SMC combined with psychiatric drugs and psychiatric drugs alone. Pooled analysis favored the combination therapy in reducing HAM-D scores [SMD = −0.92, 95% CI (−1.53, −0.31), $p < 0.01$] (Figure 3). The *Z*-curve for HAM-D in TSA exceeded the required information size (RIS = 891), confirming that the sample size was adequate for producing the current results (Appendix 7).

In addition to endpoint data, some trials reported HAM-D scores at various treatment stages (Appendix 8). A meta-synthesis of these scores revealed that combination therapy resulted in greater reductions in HAM-D scores at the first [SMD = −0.75, 95% CI (−1.29, −0.21), $p < 0.01$], second [SMD = −0.83, 95% CI (−1.37, −0.29), $p < 0.01$], fourth [SMD = −1.04, 95% CI (−2.23, 0.16), $p < 0.01$], and eighth [−0.52, 95% CI (−1.08, −0.02), $p = 0.04$] weeks compared to psychiatric drugs alone, with no significant difference observed at the sixth week [SMD = −1.05, 95% CI (−2.15, 0.05), $p = 0.06$].

Subgroup analyses were carried out due to high heterogeneity, revealing significant interaction effects based on study type (Chi^2 statistic 5.88, df = 1, $p = 0.02$), patients' comorbid condition (Chi^2 statistic 10.94, df = 1, $p < 0.01$), and psychiatric drugs used in the controls (Chi^2 statistic 66.76, df = 2, $p < 0.01$). Both RCTs and NRCTs showed combined therapies were more effective than psychiatric drugs alone in reducing HAM-D scores, albeit with high heterogeneity (I^2 from 88 to 94). SMC combined with any psychiatric drug significantly reduced HAM-D scores compared to psychiatric drugs alone, though high heterogeneity persisted ($I^2 = 88$). Among depressed patients without comorbid insomnia, no significant difference was found between treatments in HAM-D scores reduction [SMD = −0.09, 95% CI (−0.32, 0.14), $p = 0.45$], with no observed heterogeneity ($I^2 = 0$). However, in patients with comorbid insomnia, the combined therapy significantly reduced HAM-D scores more than psychiatric drugs alone [SMD = −1.29, 95% CI (−1.96, −0.62), $p < 0.01$], with high heterogeneity ($I^2 = 95$). These findings suggest that heterogeneity may be linked to comorbid conditions, though this remains partially unexplained. No interaction was identified in other subgroups (Appendix 9).

Meta-regression indicated a potential weak association between heterogeneity and publication year ($I^2 = 92.61\%$, $Tau^2 = 0.85$, $p = 0.04$), while factors such as study sample size ($I^2 = 94.45\%$, $Tau^2 = 1.19$, $p = 0.72$), study type ($I^2 = 89.54\%$, $Tau^2 = 0.58$, $p = 0.06$), patients' comorbid condition ($I^2 = 73.57\%$, $Tau^2 = 0.14$, $p = 0.08$), treatment duration (I^2

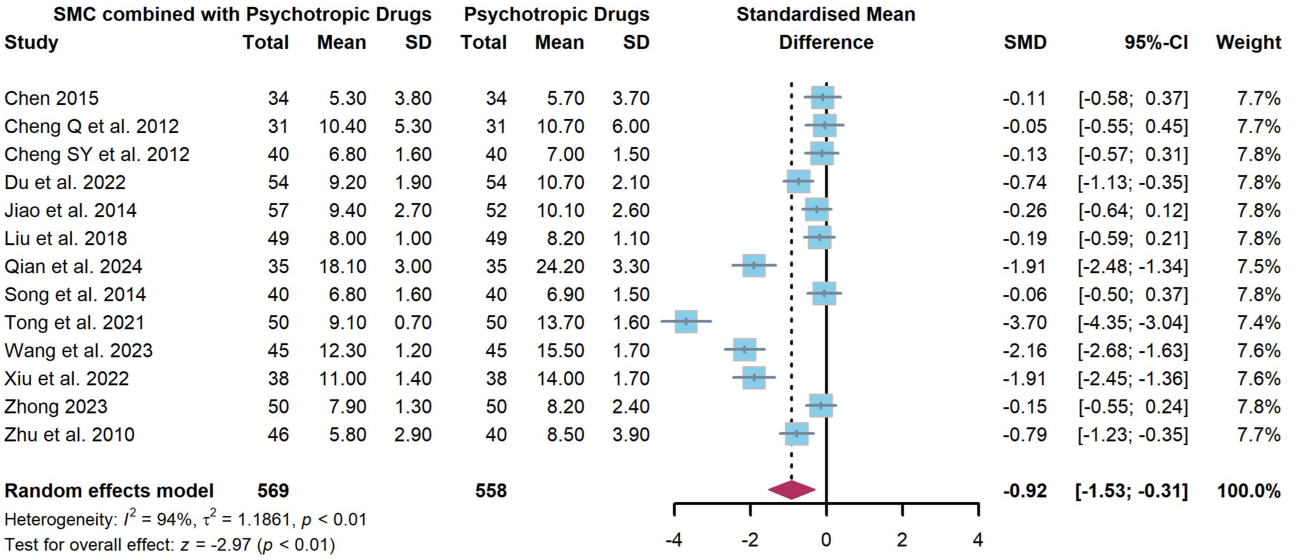

Figure 3 Forest Plots of HAM-D Global Scores Assessed at Endpoints (SMC combined with Standard Care vs Standard Care).

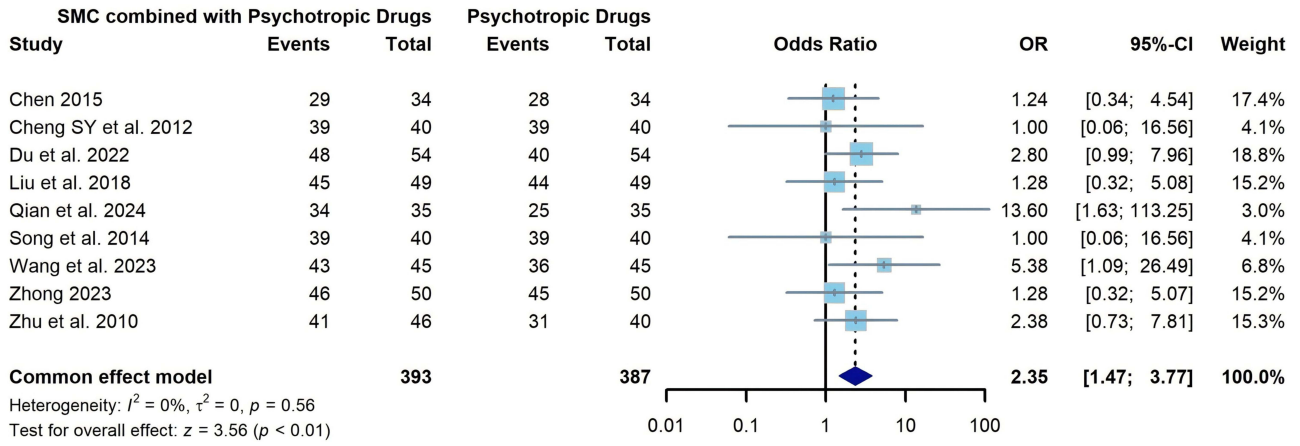

Figure 4 Forest Plots of Clinical Efficacy Rate (SMC combined with Standard Care vs Standard Care).

= 82.13%, Tau^2 = 0.24, p = 0.92), and control medication (I^2 = 0%, Tau^2 = 0, p= 0.34) did not account for heterogeneity (Appendix 10).

Sensitivity analysis further validated the overall robustness of the results (Appendix 11).

Clinical Efficacy Rate

Clinical efficacy rate was assessed in nine trials (participants = 780). All but one study, which employed an antipsychotic as an active control, utilized antidepressants. The results favored SMC combined with psychiatric drug, showing a significantly higher clinical efficacy rate than administering psychiatric drug alone [OR = 2.35, 95% CI (1.47, 3.77), p < 0.01] (Figure 4).

PSQI Global Scores

Seven trials (participants = 667) employed PSQI global scores as an outcome, all employing an RCT design with participants having comorbid insomnia. Each study used antidepressants as the psychiatric intervention. Pooled analysis favored SMC combined with antidepressants in reducing PSQI scores [SMD = −1.53, 95% CI (−1.95, −1.11), p < 0.01] (Figure 5), and the sufficiency of the sample size for this comparison was affirmed by TSA (Appendix 12).

No interaction was identified in the subgroup analysis (Appendix 13).

QoLI Global Scores

Three RCTs (participants = 288) used QoLI as an outcome, with antidepressants as the psychiatric drug in all trials. The

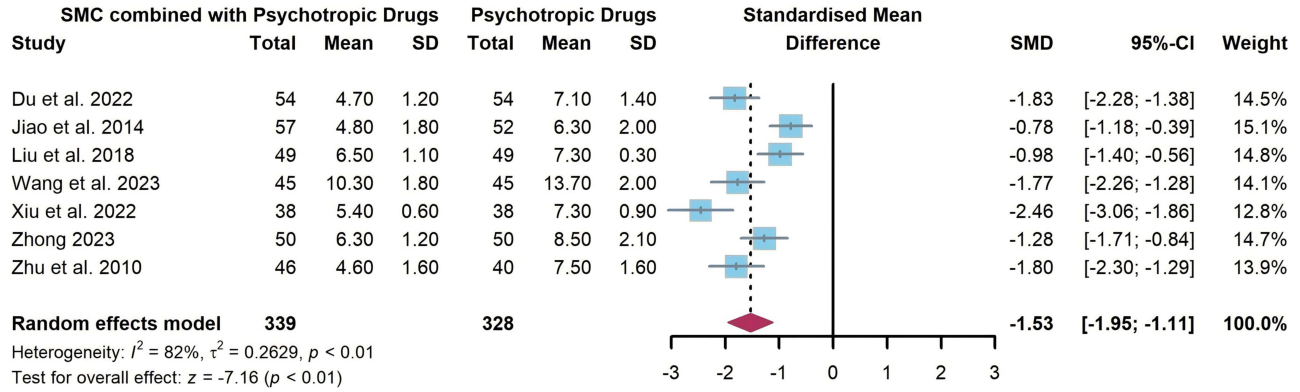

Figure 5 Forest Plots of PSQI Global Scores (SMC combined with Standard Care vs Standard Care).

https://doi.org/10.2147/NDT.S499574

results favored SMC combined with antidepressants, demonstrating a higher QoLI scores than administering antidepressants alone [SMD = 1.88, 95% CI (1.36, 2.40), $p < 0.01$] (Figure 6).

Publication Bias Test

We performed a publication bias test based on HAM-D scores (Appendix 14 and Figure 7). The studies displayed a marked asymmetry around the center line, indicating a significant risk of publication bias ($p < 0.01$). The Trim and Fill method identified no missing studies, with the iterative process concluding at *diff* = 0, indicating robust results despite potential publication bias (Appendix 15).

Certainty and Quality of Evidence

The certainty and quality of evidence from meta-analyses of four outcomes are summarized in Appendix 16. As per the GRADE system, the quality of evidence ranged between very low and low ratings, with three outcomes rated as "Very low" and one rated as "Low". The predominant factor for downgrading the evidence quality included substantial RoB

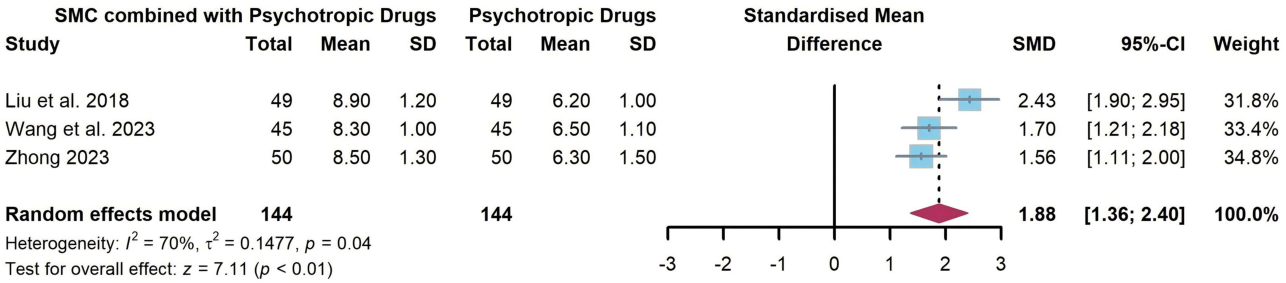

Figure 6 Forest Plots of QoLI Global Scores (SMC combined with Standard Care vs Standard Care).

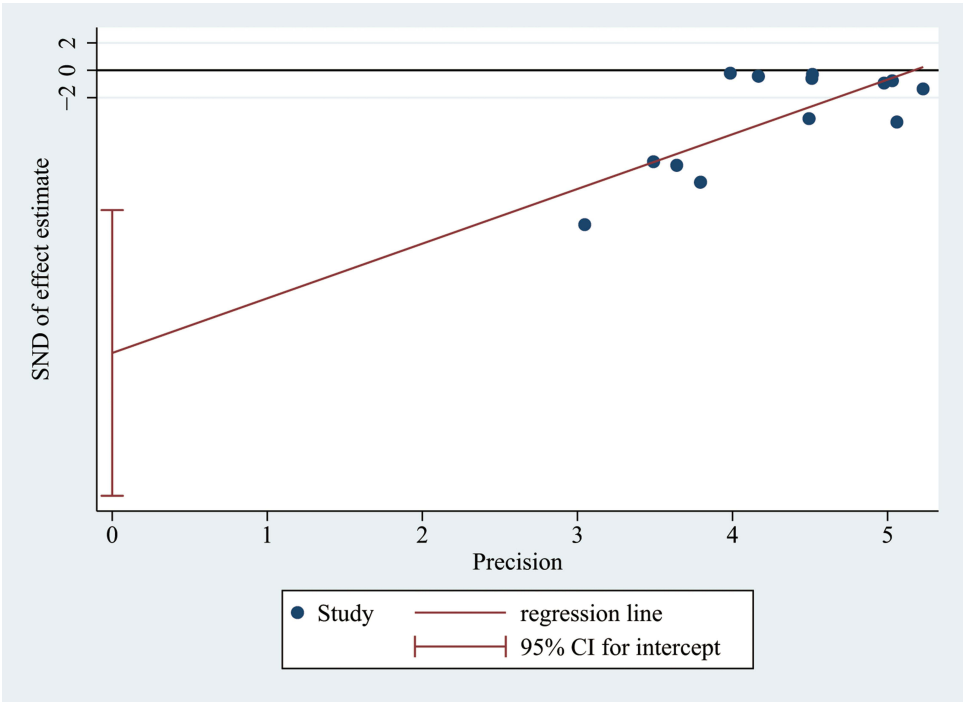

Figure 7 Publication Bias Test Based on HAM-D Global Scores.

within the included trials and the high heterogeneity across the trials. Some of the included trials were NRCT rather than RCT designs, further contributing to initial downgrade.

Discussion

Summary of Findings

This review summarized the current knowledge of SMC use for depression with or without comorbid insomnia. For depressed patients without comorbid insomnia, there was no significant difference in HAM-D score reduction between SMC combined with psychiatric drugs and psychiatric drugs alone. Conversely, for depressed patients with comorbid insomnia, the addition of SMC resulted in a further reduction of HAM-D scores by 0.1 to 6.1 points and PSQI scores by 0.8 to 3.4 points. Previous studies showed that the estimated minimal clinically important difference, representing the smallest amount an outcome must change to be meaningful to patients,[51] for HAM-D ranged from 3 to 5 points,[52] and for PSQI from 2.5 to 2.7 points.[53] Thus, the addition of SMC to standard care might have meaningful effects for improving patients' mood and sleep. Patients responded to SMC as early as one week after administration, with the effect lasting at least eight weeks without diminishing. The addition of SMC also alleviated insomnia symptoms and improved patients' QoL. The cumulative sample size of the meta-analysis was sufficient. The evidence supporting these findings was rated very-low-to-low quality due to inadequate blinding and underuse of RCT design. Insufficient data prevented comparisons of SMC with waitlist control, placebo-SMC, or antidepressants, rendering its effectiveness as an alternative unclear. Similarly, no data were available to evaluate differences between SMC combined with psychotherapy and psychotherapy alone. Although the combination of SMC with antidepressants slightly increased the risk of blurred vision, SMC overall demonstrated good tolerability. Additionally, SMC significantly reduced the incidence of dizziness, gastrointestinal symptoms, and weight gain associated with antipsychotics, as well as fatigue and daytime drowsiness related to hypnotics, and sleep disturbances linked to antidepressants.

Overall, combining SMC with psychiatric drugs appeared safe and reduced the incidence of common AEs associated with these medications. However, due to quality deficiencies in most trials, no definitive conclusions could be drawn regarding its applicability as an adjunctive therapy for depressed patients with comorbid insomnia. The main findings of this study are summarized in bullet points under the "Research & Clinical Insights" box (See Box 1).

Strengths, Limitations, and Comparison With Previous Systematic Reviews

With over 30 years of extensive use in China and growing popularity in Europe and North America,[16] a comprehensive evaluation of CCPP's efficacy and safety, including SMC, is essential. This study was the first systematic review to assess SMC's role in managing depression, offering significant value for guiding psychiatrists' clinical decision-making.

Two Chinese and one English systematic reviews/meta-analyses have evaluated SMC for insomnia.[17,23,54] However, these reviews improperly included trials lacking valid diagnostic criteria, those without internationally recognized sleep questionnaires or objective parameters, and trials where the control group's hypnotic differed from that in the intervention group (hypnotic + SMC). Such inconsistencies introduced extra variability, complicating result interpretation. One

Box 1 Key Research & Clinical Insights Summarized in This Study

Research & Clinical Insights
• **Limited Efficacy for Depression Without Comorbid Insomnia**: SMC shows minimal benefits for depression without comorbid insomnia, with improvements limited to reducing sleep disturbances caused by antidepressants.
• **Potential Benefits for Comorbid Depression and Insomnia**: Adding SMC to antidepressants may significantly improve depressive and sleep symptoms in depressed patients with comorbid insomnia.
• **Good Safety Profile**: SMC appears to be safe when used alongside conventional antidepressants.
• **Poor Evidence Quality**: The current evidence is of low quality, requiring caution in clinical use and further high-quality research.
• **Research Recommendations**: Future studies should include placebo-controlled trials and comparisons with psychotherapy to address existing gaps.

review[23] mistakenly classified an NRCT[46] as an RCT for analysis and RoB evaluation, while the other two[17,54] suffered from incomplete retrieval and inclusion, further undermining their reliability.

Our review not only introduced a novel theme but also employed a more rigorous methodology compared to existing systematic reviews. Key innovations included: (1) expanded inclusion of eligible trials and minimized variability through updated retrieval and stricter selection criteria; (2) assessment of RoB in both RCTs and NRCTs using appropriate tools, which previous reviews overlooked;[17,23,54] (3) incorporation of participants' QoL as a secondary outcome, addressing a critical issue inadequately covered before; and (4) application of TSA to evaluate sample size adequacy, absent in prior SMC-related reviews.

However, some limitations must be acknowledged. First, the poor methodological quality of included trials undermined evidence reliability. Second, despite sensitivity, subgroup, and meta-regression analyses, high heterogeneity remained not fully explained. This does not warrant exclusion of low-quality trials, as a prior methodological study indicates risks in excluding trials due to the unclear distinction between high- and low-quality evidence.[55] TSA analysis confirmed adequate sample size for meta-synthesis, and result robustness was supported by subgroup, meta-regression, and sensitivity analyses, showing that none of the influencing factors significantly altered overall findings. As more studies accumulated, future updates of the systematic review should consider including trials with greater homogeneity (uniform diagnostic criteria, treatment protocols, and outcomes) to improve comparability and reduce heterogeneity in pooled analyses. Finally, all trials were conducted in China, potentially inflating the perceived effectiveness of TCM therapies due to cultural confidence.[15] There may also be a bias towards reporting positive outcomes,[15] evidenced by significant publication bias (Figure 7). The applicability of these findings beyond Chinese communities is limited, although some CCPPs with sedative and mood-regulating effects have been registered and made available in Western countries like Australia[56] and the Netherlands,[57] laying groundwork for further research on their applicability in diverse populations.

Interpretation of Findings

Evidence-based practice extends beyond efficacy, requiring consideration of patient preferences in treatment selection.[58] While antidepressants are commonly prescribed for depression with generally satisfactory outcomes, their prevalent AEs raise concerns and contribute significantly to non-adherence.[59] Consequently, many patients turn to CAM, viewed as "natural" and having fewer AEs than antidepressants.[60] A systematic review also found CAM therapies may be more cost-effective than usual care in many conditions.[61] Thus, assessing whether SMC is a safe and effective alternative to antidepressants is critical. However, no studies have yet compared SMC to waitlist control, placebo, or antidepressants in treating depression.

Over 90% of the reviewed trials examined whether adding SMC to psychotropic drugs augments efficacy or reduces AEs. This co-administration is an established practice in China for managing mental illness,[15] though less so in Western countries. Our findings highlighted this combination as a promising option and offered insights for policymakers of other countries to consider WHO's recommendation of integrating traditional medicine into the national healthcare system.[62] While CCPP, as a CAM product, may cause some adverse drug reactions,[63] current evidence showed that combining SMC with psychotropic drugs reduced common AEs such as fatigue, daytime sleepiness, dizziness, gastrointestinal issues, and weight gain compared to psychotropic drugs alone (Appendix 6). Evidence-based psychotherapies like cognitive-behavioral therapy, interpersonal therapy, acceptance and commitment therapy, problem-solving therapy, and self-management/self-control therapy are also first-line treatments for depression,[64,65] particularly for those seeking non-medication options.[64] Whether SMC can serve as a viable alternative or complement to these therapies remained unresolved. Given that depression is a leading indication for CAM use and a strong predictor of its utilization,[60] high-quality RCTs are warranted to address these gaps.

Subgroup analysis showed that in depressed patients without comorbid insomnia, adding SMC to antidepressants only reduced AEs, particularly sleep disorders, but did not significantly amplify efficacy. In contrast, for those with comorbid insomnia, SMC both reduced AEs and enhanced antidepressive effects, with patients remaining responsive to the medication for up to eight weeks, though slightly diminished after six weeks. Accumulated evidence has established a bidirectional relationship between depression and insomnia, in which comorbid insomnia complicates depression treatment, while addressing insomnia improves depression outcomes.[66] Given that SMC is known to aid insomnia,[17]

we hypothesize that SMC may alleviate depressive symptoms both by its direct mood-regulating effects and through improving insomnia. Together, SMC offers substantial benefits for depression with comorbid insomnia, while in cases without comorbid insomnia, it may primarily serve to reduce antidepressant-related AEs.

Some animal and pharmacological studies have explored the mechanisms by which SMC regulates mood and improves sleep. SMC is rich in tryptophan,[18] an amino acid that metabolizes through serotonin or kynurenine pathways, playing a critical role in depression-related factors like neuroinflammation, chronic stress, gut microbiota dysregulation, and brain-derived neurotrophic factor (BDNF) expression.[67] A deficiency[68] or impaired metabolism[69] of tryptophan disrupts serotonin biosynthesis, increasing susceptibility to depression, while higher tryptophan availability boosts serotonin levels and alleviates depressive symptoms.[68] Sleep disorders are also linked to reduced tryptophan levels,[70] and increased intake improves sleep by shortening sleep onset latency, extending total sleep time, and reducing wakefulness.[71] Some scholars suggest that tryptophan's benefits on sleep may be mediated by not only neuronal serotonin but also melatonin produced by peripheral cells.[72] Li et al confirmed the involvement of melatonin receptors in SMC's antidepressive and sedative effects through network pharmacology and functional enrichment analysis.[73] In open-field and forced swimming tests, SMC reduced depressive-like behavior and improved sleep in sleep-deprived rodents, showing effects similar to Ramelteon.[73] Additionally, SMC contains metabolites like saikosaponin,[74] paeoniflorin,[74] quercetin,[74,75] and jujuboside A,[75] which contribute to its therapeutic effects. Saikosaponin modulates neuroinflammation, the brain-gut axis, and oxidative stress, supporting its antidepressive properties.[76] Paeoniflorin enhances monoaminergic neurotransmitters, neurogenesis, neuroplasticity, and neuroprotection while suppressing neuroinflammation, contributing to its antidepressive effects.[77] Quercetin mitigates corticosterone-induced depression-like behaviors, partially through the repression of neuroinflammation and oxidative damage.[78] Jujuboside A's antidepressive effect is linked to the activation of BDNF and its receptors and regulators.[79] Jujuboside A can also induce increased expression of gamma-aminobutyric acid A receptor (α1, α5, β2) genes, thereby exerting a sedative-hypnotic effect.[80] Collectively, these findings may elucidate the biological effects of SMC.

While SMC holds promise as an adjunctive treatment for depression, caution is required in interpreting current positive findings due to several reliability concerns. First, a previous systematic review indicated a dropout rate of about 10% in herbal medicine RCTs.[81] However, our review found that 13 trials (92.9%) did not report any attrition (Figure 2), which is atypical for depression[82] and insomnia[15] clinical trials. Second, adequate blinding of personnel, participants, and evaluators is crucial to minimize RoBs in intervention and evaluation, particularly since primary outcome measures in depression trials often rely on participants' self-reports or clinicians' subjective assessments.[15] While placebos are feasible for proper blinding in natural product trials, none of the reviewed trials implemented adequate allocation concealment and blinding (Figure 2). Additionally, selective outcome reporting was another significant concern, as none of the studies provided pre-registration information, compromising trial transparency and hindering replication efforts across laboratories.[83] Thus, prospective registration and protocol submission are vital for future research. Finally, depression is a highly relapsing and recurrent disorder; most patients will eventually experience either a relapse (a depressive episode within six months after response or remission) or recurrence (another episode after six months) if not continuously treated.[84] Our prior study on comorbid depression and insomnia in perimenopausal women reported significant rebounds in depressive symptoms after treatment cessation.[85] However, only one reviewed trial had a follow-up period of just one week,[43] severely limiting our ability to judge the medium- to long-term efficacy and safety of SMC in managing depression.

Conclusion

Data are insufficient to determine if SMC can replace standard antidepressive care, although it may serve as an adjunct. Our study indicates that for depressed patients without comorbid insomnia, adding SMC to antidepressants alleviates sleep disorders caused by medication without augmenting efficacy. In contrast, for depressed patients with comorbid insomnia, SMC not only reduces antidepressants-related AEs, such as gastrointestinal symptoms, weight gain, and sleep disturbances, but also enhances efficacy, with patients remaining highly responsive to the medication even after eight weeks of administration. Nonetheless, the credibility of this evidence is significantly undermined by the poor quality of the included studies. Overall, current evidence is insufficient to conclusively support SMC as an alternative or adjunct to standard depression treatments. Well-designed RCTs with adequate follow-up are required to reassess the practical applicability of administering SMC in depression management.

Abbreviations

AE(s), Adverse Effect(s); BDNF, Brain-Derived Neurotrophic Factor; CAM, Complementary and Alternative Medicine; CCPP, Commercial Chinese polyherbal preparation; HAM-$D_{17/24,}$ 17/24-item Hamilton Rating Scale for Depression; MD, Mean Difference; NRCT(s), Non-Randomized Controlled Clinical Trial(s); OR, Odds Ratio; PICOS, Participant, Intervention, Comparator, Outcome, Study; PSQI, Pittsburgh Sleep Quality Index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL, Quality of Life; QoLI, Quality of Life Index; RCT(s), Randomized Controlled Trial(s); RoB, Risk of Bias; ROB 2.0 Tool, Revised Cochrane Risk of Bias Tool for Randomized Trials; ROBINS-I Tool, Cochrane Risk of Bias in Non-Randomized Studies-of Interventions; RR, Relative Risk; SDS, Self-rating Depression Scale; SMC, Shu Mian Capsule; SMD, Standardized Mean Difference; TCM, Traditional Chinese Medicine.

Funding

This work was supported by the Chinese Medicine Development Fund [23B2/030A], Hong Kong SAR to YS-H; Scientific Research Fund Project of Shanghai Sanda University [2024BSZX03] to FY-Z; and Shanghai Jiao Tong University School of Medicine: Nursing Development Program [SJTUHLXK2023] to X-J.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Moreno-Agostino D, Wu YT, Daskalopoulou C, Hasan MT, Huisman M, Prina M. Global trends in the prevalence and incidence of depression: a systematic review and meta-analysis. *J Affect Disord*. 2021;281:235–243. doi:10.1016/j.jad.2020.12.035
2. Shumye S, Belayneh Z, Mengistu N. Health related quality of life and its correlates among people with depression attending outpatient department in Ethiopia: a cross sectional study. *Health Qual Life Outcomes*. 2019;17(1):169. doi:10.1186/s12955-019-1233-7
3. Voinov B, Richie WD, Bailey RK. Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord*. 2013;15(2):PCC.12r01468. doi:10.4088/PCC.12r01468
4. Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. *BMJ*. 2005;330(7488):373–374. doi:10.1136/bmj.330.7488.373
5. Lépine JP, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):3–7. doi:10.2147/ndt.S19617
6. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). *Pharmacoeconomics*. 2021;39(6):653–665. doi:10.1007/s40273-021-01019-4
7. Wu Y, Jin S, Guo J, Zhu Y, Chen L, Huang Y. The economic burden associated with depressive symptoms among middle-aged and elderly people with chronic diseases in China. *Int J Environ Res Public Health*. 2022;19(19):12958. doi:10.3390/ijerph191912958
8. Tomonaga Y, Haettenschwiler J, Hatzinger M, et al. The economic burden of depression in Switzerland. *Pharmacoeconomics*. 2013;31(3):237–250. doi:10.1007/s40273-013-0026-9
9. Chang SM, Hong JP, Cho MJ. Economic burden of depression in South Korea. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(5):683–689. doi:10.1007/s00127-011-0382-8
10. Hammen C, Brennan PA. Interpersonal dysfunction in depressed women: impairments independent of depressive symptoms. *J Affect Disord*. 2002;72(2):145–156. doi:10.1016/s0165-0327(01)00455-4
11. Butler L, Pilkington K. Chinese herbal medicine and depression: the research evidence. *Evid Based Complement Alternat Med*. 2013;2013:739716. doi:10.1155/2013/739716
12. Kessler RC, Soukup J, Davis RB, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am J Psychiatry*. 2001;158(2):289–294. doi:10.1176/appi.ajp.158.2.289
13. Alonso-Castro AJ, Ruiz-Padilla AJ, Ortiz-Cortes M, et al. Self-treatment and adverse reactions with herbal products for treating symptoms associated with anxiety and depression in adults from the central-western region of Mexico during the Covid-19 pandemic. *J Ethnopharmacol*. 2021;272:113952. doi:10.1016/j.jep.2021.113952
14. Tan J, Li X, Zhu Y, et al. Antidepressant Shugan Jieyu capsule alters gut microbiota and intestinal microbiome function in rats with chronic unpredictable mild stress-induced depression. *Front Pharmacol*. 2022;13:828595. doi:10.3389/fphar.2022.828595
15. Zhao FY, Xu P, Kennedy GA, et al. Commercial Chinese polyherbal preparation Zao Ren An Shen prescription for primary insomnia: a systematic review with meta-analysis and trial sequential analysis. *Front Pharmacol*. 2024;15:1376637. doi:10.3389/fphar.2024.1376637
16. Wang JX, Sun R, Si DX, et al. Clinical practice guidelines of Chinese patent medicine in China: a critical review. *Complement Ther Med*. 2024;85:103077. doi:10.1016/j.ctim.2024.103077
17. Wang C, Yang Y, Ding X, et al. Efficacy and safety of Shumian capsules in treating insomnia: a systematic review and meta-analysis. *Medicine*. 2021;100(50):e28194. doi:10.1097/md.0000000000028194
18. Chen S, Xu Z, Li Y, et al. Clinical efficacy of the Chinese herbal medicine Shumian capsule for Insomnia: a randomized, double-blind, placebo-controlled trial. *Neuropsychiatr Dis Treat*. 2022;18:669–679. doi:10.2147/ndt.S349427
19. Du CR, Yan FY, Zhang XH. Clinical study of Shu Mian Capsule Combined with Paroxetine in the treatment of depression with Insomnia. *New Chin Med*. 2022;54(20):44–47.

20. Jiao XY, Yang XL, Zhang YL, Yang GZ, Lv HB. Clinical study on the adjunctive treatment of depression with sleep disorders with Shu Mian capsule. *World J Sleep Med*. 2014;1(6):347–350.
21. Chen ZG. Clinical analysis of Shu Mian capsule combined with Sertraline in the treatment of depression. *Med Inf*. 2015;13:185.
22. Zhu YH, Tao JQ. Efficacy of sertraline combined with Shu Mian capsule in the treatment of depression with sleep disorders. *China Pharm*. 2010;21 (20):1868–1869.
23. Shan XJ, Kang D, Chen Z, Zhang SY, Liu CX. Systematic review and meta-analysis of the efficacy and safety of Shu Mian capsule in the treatment of insomnia. *China J Chin Mater Med*. 2024;49(1):268–278. doi:10.19540/j.cnki.cjcmm.20230825.501
24. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*. 2008;10(3):329–336. doi:10.31887/DCNS.2008.10.3/dnutt
25. Stewart R, Besset A, Bebbington P, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. *Sleep*. 2006;29(11):1391–1397. doi:10.1093/sleep/29.11.1391
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372: n71. doi:10.1136/bmj.n71
27. Qaseem A, Barry MJ, Kansagara D. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;164(5):350–359. doi:10.7326/m15-2570
28. Roberts RJ, Lohano KK, El-Mallakh RS. Antipsychotics as antidepressants. *Asia Pac Psychiatry*. 2016;8(3):179–188. doi:10.1111/appy.12186
29. Lim B, Sproule BA, Zahra Z, Sunderji N, Kennedy SH, Rizvi SJ. Understanding the effects of chronic benzodiazepine use in depression: a focus on neuropharmacology. *Int Clin Psychopharmacol*. 2020;35(5):243–253. doi:10.1097/yic.0000000000000316
30. Benasi G, Guidi J, Offidani E, Balon R, Rickels K, Fava GA. Benzodiazepines as a monotherapy in depressive disorders: a systematic review. *Psychother Psychosom*. 2018;87(2):65–74. doi:10.1159/000486696
31. Duan Y, Wei J, Geng W, et al. The effect of short-term use of benzodiazepines on cognitive function of major depressive disorder patients being treated with antidepressants. *J Affect Disord*. 2019;256:1–7. doi:10.1016/j.jad.2019.05.059
32. Kishi T, Matsunaga S, Iwata N. Efficacy and tolerability of Z-drug adjunction to antidepressant treatment for major depressive disorder: a systematic review and meta-analysis of randomized controlled trials. *Eur Arch Psychiatry Clin Neurosci*. 2017;267(2):149–161. doi:10.1007/s00406-016-0706-5
33. Wang C, Wang X, Wang J, et al. Prevalence and clinical correlates of benzodiazepine use in the patients with major depressive disorder. *J Affect Disord*. 2024;363:619–625. doi:10.1016/j.jad.2024.07.142
34. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
35. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355: i4919. doi:10.1136/bmj.i4919
36. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc*. 2015;13(3):196–207. doi:10.1097/xeb.0000000000000065
37. Takeshima N, Sozu T, Tajika A, Ogawa Y, Hayasaka Y, Furukawa TA. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? *BMC Med Res Methodol*. 2014;14:30. doi:10.1186/1471-2288-14-30
38. Prasad K. What are relative risk, number needed to treat and odds ratio? *Ann Indian Acad Neurol*. 2007;10(4):225–230. doi:10.4103/0972-2327.37814
39. Phillips M. Healthcare recommendations: grades of recommendation, assessment, development, and evaluation (GRADE) approach. *Evidence-Based Orthopedics*. 2021:19–23.
40. Cheng Q, Wang YW, Yang XS. Clinical analysis of Shu Mian capsule combined with paroxetine in the treatment of depression. *China Pract Med*. 2012;7(15):153–154.
41. Cheng SY, Ma HX, Zhao Y, Yuan J. Clinical observation on the combined treatment of 40 cases of adolescent depression with Traditional Chinese Medicine and Western Medicine. *Shandong Med J*. 2012;52(4):58–59.
42. Song YX, Huo J. Comparative study of Sertraline combined with Shu Mian capsule and Sertraline alone in the treatment of adolescent depression. *Chin J Mod Drug App*. 2014;8(9):139–140.
43. Chen JY, Aynuer, Xiao CX. Clinical efficacy of "Suppressing Hyperactive Liver and Subsiding Yang" method in the treatment of depression with sleep disorder. *J Sichuan Tradit Chin Med*. 2014;32(5):125–127.
44. Liu WJ, Chen YX, Zhang RL. Efficacy of Shu Mian capsule combined with escitalopram in the treatment of depression with sleep disorders. *Strait Pharm J*. 2018;30(12):63–65.
45. Qian XL, Wang Y, Guo CH, Fang J. Clinical study of Shu Mian capsule combined with Olanzapine in the treatment of depression with Insomnia. *New Chin Med*. 2024;56(13):83–87.
46. Tong JY. Analysis of the efficacy of Shu Mian capsule as an adjunctive treatment for sleep disorders in depression. *J Aerosp Med*. 2021;32 (3):335–339.
47. Wang J, Yang YR. The effect of Shu Mian capsule combined with mirtazapine on patients with depression and Insomnia. *Med Innovation China*. 2023;20(31):72–75.
48. Xiu YF, Pan XJ. Clinical study of Shu Mian capsule combined with venlafaxine in the treatment of depression with Insomnia. *New Chin Med*. 2022;54(10):92–94.
49. Zhong LL. Effect of Shu Mian capsule combined with escitalopram in the treatment of depression with Insomnia among elderly patients. *Smart Healthc*. 2023;9(4):213–216.
50. Health NIo M. TESS (treatment emergent symptom scale-write-in). *Psychopharmacol Bull*. 1985;21:1069–1072.
51. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. *JAMA*. 2014;312(13):1342–1343. doi:10.1001/jama.2014.13128
52. Winslow M, White E, Rose SJ, Salzer E, Nemec EC. The efficacy of zuranolone versus placebo in postpartum depression and major depressive disorder: a systematic review and meta-analysis. *Int J Clin Pharm*. 2024;46(3):590–601. doi:10.1007/s11096-024-01714-0
53. Qin Z, Zhu Y, Shi DD, Chen R, Li S, Wu J. The gap between statistical and clinical significance: time to pay attention to clinical relevance in patient-reported outcome measures of insomnia. *BMC Med Res Methodol*. 2024;24(1):177. doi:10.1186/s12874-024-02297-0

54. Zhang J, Fan SD, Luo H, Xiang X. Systematic review of Shu Mian Capsule combined with chemical drugs in the treatment of insomnia. *Drug Eval Res*. 2018;41(5):898–903.
55. Harvey LA, Dijkers MP. Should trials that are highly vulnerable to bias be excluded from systematic reviews? *Spinal Cord*. 2019;57(9):715–716. doi:10.1038/s41393-019-0340-y
56. Birling Y, Zhu X, Avard N, et al. Zao Ren An Shen capsule for insomnia: a double-blind, randomized, placebo-controlled trial. *Sleep*. 2022;45(2): zsab266. doi:10.1093/sleep/zsab266
57. Wang Q, Gao S, Zhang W, et al. Traditional use and safety evaluation of combination Traditional Chinese medicine in European registration: with XiaoYao Tablets as an example. *Die Pharmazie*. 2022;77(3–4):125–130.
58. McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry*. 2013;74(6):595–602. doi:10.4088/JCP.12r07757
59. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. *Br J Psychiatry*. 2009;195(3):202–210. doi:10.1192/bjp.bp.108.061960
60. Solomon D, Adams J. The use of complementary and alternative medicine in adults with depressive disorders. A critical integrative review. *J Affect Disord*. 2015;179:101–113. doi:10.1016/j.jad.2015.03.031
61. Herman PM, Craig BM, Caspi O. Is complementary and alternative medicine (CAM) cost-effective? A systematic review. *BMC Complement Altern Med*. 2005;5:11. doi:10.1186/1472-6882-5-11
62. von Schoen-Angerer T, Manchanda RK, Lloyd I, et al. Traditional, complementary and integrative healthcare: global stakeholder perspective on WHO's current and future strategy. *BMJ Glob Health*. 2023;8(12):e013150. doi:10.1136/bmjgh-2023-013150
63. Chan K, Zhang H, Lin ZX. An overview on adverse drug reactions to traditional Chinese medicines. *Br J Clin Pharmacol*. 2015;80(4):834–843. doi:10.1111/bcp.12598
64. Lampe L, Coulston CM, Berk L. Psychological management of unipolar depression. *Acta Psychiatr Scand Suppl*. 2013;127(443):24–37. doi:10.1111/acps.12123
65. Voytenko V, Anderson K, Wyngarden N, et al. Evidence-based practice guideline for the treatment of adult patients with depressive disorders. Part II: psychotherapy. *Psychiatria i Psychologia Kliniczna*. 2018;18(3):242–247. doi:10.15557/PiPK.2018.0030
66. Gebara MA, Siripong N, DiNapoli EA, et al. Effect of insomnia treatments on depression: a systematic review and meta-analysis. *Depress Anxiety*. 2018;35(8):717–731. doi:10.1002/da.22776
67. Correia AS, Vale N. Tryptophan metabolism in depression: a narrative review with a focus on Serotonin and Kynurenine pathways. *Int J mol Sci*. 2022;23(15):8493. doi:10.3390/ijms23158493
68. Kałużna-Czaplińska J, Gątarek P, Chirumbolo S, Chartrand MS, Bjørklund G. How important is tryptophan in human health? *Crit Rev Food Sci Nutr*. 2019;59(1):72–88. doi:10.1080/10408398.2017.1357534
69. Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D. Neopterin production, tryptophan degradation, and mental depression--what is the link? *Brain Behav Immun*. 2002;16(5):590–595. doi:10.1016/s0889-1591(02)00006-5
70. Song C, Lin A, Bonaccorso S, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord*. 1998;49(3):211–219. doi:10.1016/s0165-0327(98)00025-1
71. Yousef P, Rosen J, Shapiro C. Chapter 1-Tryptophan and its role in sleep and mood. In: Atta-Ur R, editor. *Studies in Natural Products Chemistry*. Vol. 80. Elsevier; 2024:1–14.
72. Fernstrom JD. Effects and side effects associated with the non-nutritional use of tryptophan by humans. *J Nutr*. 2012;142(12):2236s–2244s. doi:10.3945/jn.111.157065
73. Li W, Cheng Y, Zhang Y, et al. Shumian capsule improves the sleep disorder and mental symptoms through melatonin receptors in sleep-deprived mice. *Front Pharmacol*. 2022;13:925828. doi:10.3389/fphar.2022.925828
74. Li J, Cheng SY, Fu ZJ. Determination of the content of seven components in Shu Mian Capsule and principal component analysis using HPLC. *China Pharm*. 2020;23(6):1211–1215.
75. Wang HL, Zhang YP, Wang CS, Shi TY. Determination of Jujuboside A and Quercetin in Shu Mian capsule using HPLC. *China Pharm*. 2013;24 (8):739–741.
76. Chen S, Wang K, Wang H, et al. The therapeutic effects of saikosaponins on depression through the modulation of neuroplasticity: from molecular mechanisms to potential clinical applications. *Pharmacol Res*. 2024;201:107090. doi:10.1016/j.phrs.2024.107090
77. Wang XL, Feng ST, Wang YT, Chen NH, Wang ZZ, Zhang Y. Paeoniflorin: a neuroprotective monoterpenoid glycoside with promising anti-depressive properties. *Phytomedicine*. 2021;90:153669. doi:10.1016/j.phymed.2021.153669
78. Ge C, Wang S, Wu X, Lei L. Quercetin mitigates depression-like behavior via the suppression of neuroinflammation and oxidative damage in corticosterone-induced mice. *J Chem Neuroanat*. 2023;132:102313. doi:10.1016/j.jchemneu.2023.102313
79. Li H, Li J, Zhang T, Xie X, Gong J. Antidepressant effect of Jujuboside A on corticosterone-induced depression in mice. *Biochem Biophys Res Commun*. 2022;620:56–62. doi:10.1016/j.bbrc.2022.06.076
80. You ZL, Xia Q, Liang FR, et al. Effects on the expression of GABAA receptor subunits by jujuboside A treatment in rat hippocampal neurons. *J Ethnopharmacol*. 2010;128(2):419–423. doi:10.1016/j.jep.2010.01.034
81. Jeon SR, Nam D, Kim TH. Dropouts in randomized clinical trials of Korean medicine interventions: a systematic review and meta-analysis. *Trials*. 2021;22(1):176. doi:10.1186/s13063-021-05114-x
82. Zhao F-Y, Li L, Xu P, et al. Inadequate evidence for acupuncture as an alternative or adjunct to antidepressants/psychotherapy for postpartum depression: a bayesian systematic review and network meta-analysis. *Neuropsychiatr Dis Treat*. 2024;20:1741–1755. doi:10.2147/ndt.S484387
83. van 't Veer AE, Giner-Sorolla R. Pre-registration in social psychology—A discussion and suggested template. *J Exp Soc Psychol*. 2016;67:2–12. doi:10.1016/j.jesp.2016.03.004
84. Nierenberg AA, Petersen TJ, Alpert JE. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J Clin Psychiatry*. 2003;64(Suppl 15):13–17.
85. Zhao FY, Zheng Z, Fu QQ, et al. Acupuncture for comorbid depression and insomnia in perimenopause: a feasibility patient-assessor-blinded, randomized, and sham-controlled clinical trial. *Front Public Health*. 2023;11:1120567. doi:10.3389/fpubh.2023.1120567