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Herbal medicine for post-stroke anxiety: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The study was conducted to investigate the efficacy and safety of herbal medicine (HM) for post-stroke anxiety (PSA). Through comprehensive searches, twenty randomized controlled trials were included. Meta-analysis showed that compared to the HM group, the conventional pharmacotherapy group showed significantly lower Hamilton anxiety rating scale (HAMA) score after 1 week of treatment, but not after 2, 4, and 6 weeks of treatment, and higher HAMA score after 8 weeks and 3 months of treatment. Meanwhile, compared to the conventional pharmacotherapy alone group, the HM plus conventional pharmacotherapy group showed significantly better results in HAMA score after 2, 4, 6, and 8 weeks of treatment. HM group was associated with lower incidence of adverse events. Current evidence suggests that HM or HM plus conventional pharmacotherapy may be safe and effective in PSA patients within a certain time period. However, due to limited strength of evidence, definite conclusions are not possible.

1. Introduction

Stroke is the leading cardiovascular disease causing morbidity and mortality worldwide [1–3], and approximately 75–120 per 100,000 people are known to be affected by this disorder annually [4]. Stroke is not only associated with short-term outcomes (such as severe headache, seizure, eye movement disorder, and agitation [5]) and long-term outcomes (such as hemiplegia, motor and sensory dysfunction, and cognitive impairment [6]), it is also associated with increased risk of several secondary diseases. For example, stroke patients are at a high risk for dementia [7], mood disturbance [8], insomnia [9], fracture [10], myocardial infarction, cardiac arrhythmias, and even cardiac arrest [11,12]. In addition, stroke-related mental health risks such as depression and anxiety are attracting increasing attention. Studies have shown that these conditions can affect not only the quality of life (QoL) of patients and the caregivers [13], but also negatively affect stroke outcomes such as adherence to treatment [14], re-hospitalization, or even death [15].

Several studies have reported a two-way relationship between stroke and anxiety [16–18]. The Rotterdam Study (2016), a population-based cohort study, concluded that anxiety disorders are not associated with the risks of stroke [19]. However, a subsequent meta-analysis found that the presence of anxiety disorders increased the risk of stroke by approximately 24% [16]. More importantly, anxiety is a common psychiatric complication observed after a stroke. Several systematic reviews have revealed that post-stroke anxiety (PSA) occurs in about 20–30% of stroke survivors [17,18], and the presence of lifetime anxiety was indicated as a significant PSA predictor [20]. A recent brain imaging study indicated brain network dysfunction as the underlying mechanism for psychiatric complications, including depression and anxiety after a stroke, in addition to regional structural damage after ischemic events [21]. Moreover, involvement of inflammatory response after brain ischemia has been proposed as an underlying mechanism for the abovementioned complications [22].

Antidepressant/anxiolytic-based pharmacotherapies are used to treat PSA [23]; however, PSA treatment lacks strong evidence [24], and some patients may experience side effects associated with pharmacotherapy strategies such as increased risks of falls [25], cognitive impairment [26], and even recurrence of stroke [27]. In addition, benzodiazepines and other sedative-hypnotic drugs are associated with an increased risk of falls and hip fractures [28], which should be particularly avoided in elderly patients [29]. Therefore, effective and safe alternatives for the treatment of PSA are needed.

Herbal medicine (HM), a complementary and integrative medicine modality, has played a primary role in healthcare for thousands of

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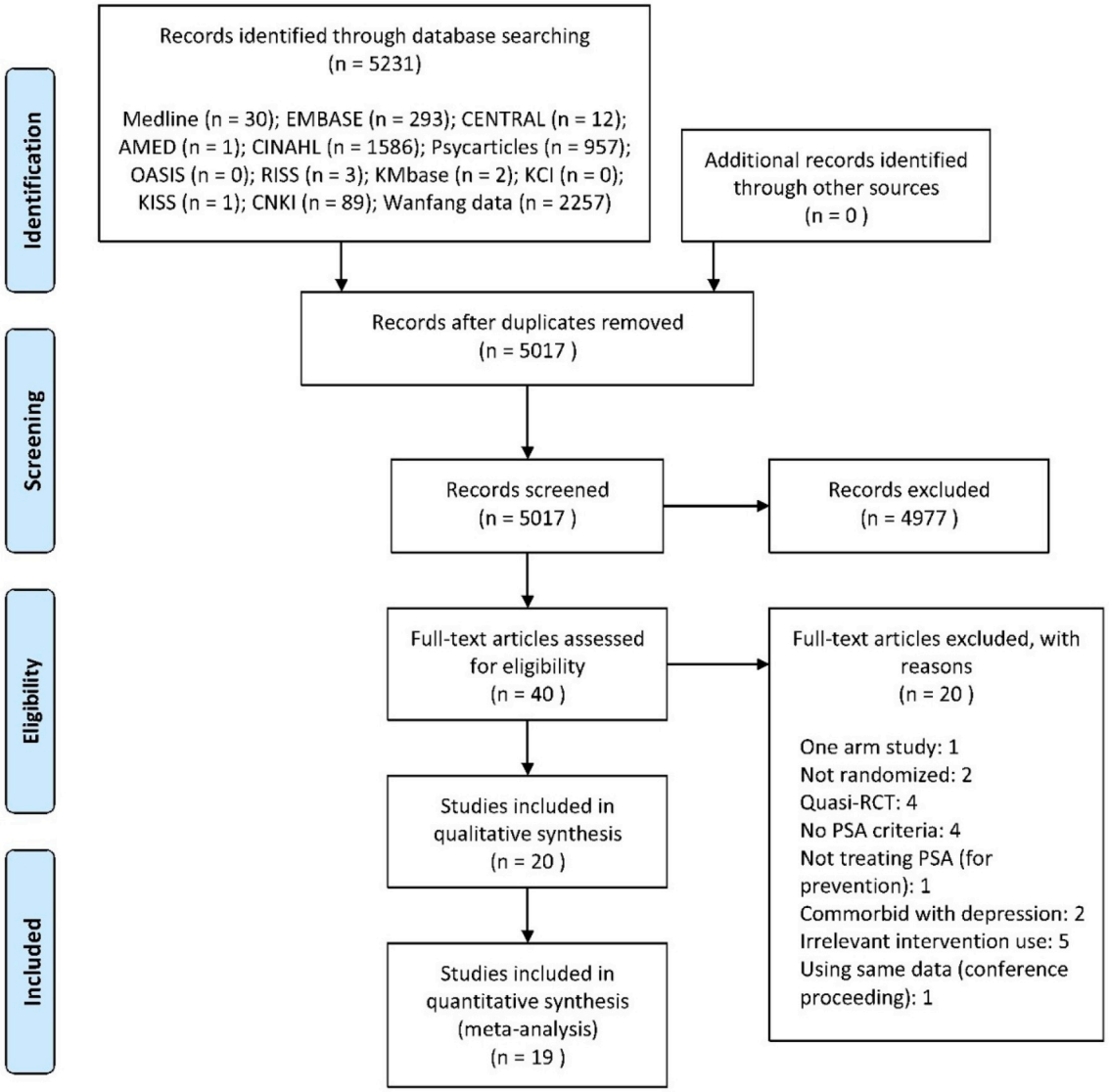

Fig. 1. PRISMA flow chart for the study selection.
AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure; KCI, Korea Citation Index; KISS, Koreanstudies Information Service System; KMbase, Korean Medical Database; OASIS, Oriental Medicine Advanced Searching Integrated System; PSA, post-stroke anxiety; RCT, randomized controlled trial; RISS, Research Information Service System.

years, especially in East Asia. Recently, HM has been attracting attention as an alternative to the limits of conventional synthetic drugs due to characteristics of complex compound-complex targets [30]. Moreover, the efficacy and safety of HM in various neuropsychological conditions have been investigated through several clinical studies [31,32], and recent systematic reviews have shown that HM can improve anxiety and anxiety-related pathologies [33–36].

The major feature of HM in the clinical aspect is that it can simultaneously work on several pathological pathways associated with disease, and has a high safety profile [37,38]. Therefore, in complex pathologies such as post-stroke depression and PSA, HM may not only improve depression and anxiety symptoms, but also improve neuroplasticity, reduce oxidative stress, improve cerebral blood flow, and reduce inflammation, resulting in further improvements in survivors' neurological function and better rehabilitation outcomes [39]. Furthermore, based on these properties, HM with multiple active components that can act on multiple targets [38] may reduce the risk of polypharmacy, generally defined as taking five or more medicines per day [40].

However, as there have been no systematic reviews critically evaluating the clinical implications, a comprehensive synthesis is urgently needed to make optimal recommendations with respect to efficacy and safety of HM for PSA treatment. Therefore, we aimed to elucidate the efficacy and safety of HM in the treatment of PSA and to derive the clinical implications by comprehensively collecting and synthesizing published research so far.

2. Materials and methods

We reported this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [41]. The protocol for this review is registered in PROSPERO (registration number: CRD42018114428).

2.1. Data sources and search strategy

The following databases were comprehensively searched from their inception to October 12, 2018: 6 English-language databases (Medline

Table 1
General characteristics of included studies.

Study ID	Sample size (included →analyzed)	Mean age (range) (yr)	Diagnostic criteria	Pattern identification	(A) Experimental intervention (duration)	(B) Control intervention	Outcome and results	Adverse events
HM vs. conventional pharmacotherapy								
Huang 2007 [44]	71(36:35)→ 71(36:35)	(A) 66.4 ± 8.62 (NR) (B) 65.9 ± 6.62 (NR)	CCMD-3 (generalized anxiety disorder) HAMA > 14	yin deficiency with effulgent fire and non-interaction between the heart and kidney	(1) Routine care for stroke (2) HM (1 mo)	(1) Routine care for stroke§ (2) Benzodiazepines (Alprazolam from 0.4 mg qd to tid-qid)	(1) TER (HAMA): N.S (2) HAMA: N.S	(A) dizziness, dry mouth, and GI symptoms (B) drowsiness, fatigue, dizziness, dry mouth, GI symptoms, and drug dependence Incidence: (A) < (B)+
Jiang 2007 [45]	60(30:30)→ 60(30:30)	(A) 60.1 (42–70) (B) 59.8 (43–69)	HAMA ≥ 14	NA	(1) Routine care for stroke (2) HM (6 wks)	(1) Routine care for stroke (2) SSRI (Sertraline hydrochloride 50 mg qd)	(1) TER (HAMA): N.S (2) HAMA: N.S	TESS: (A) < (B)*
Yu 2009 [46]	68(34:34)→ 68(34:34)	(A) 55.35 ± 8.52 (NR) (B) 52.76 ± 7.86 (NR)	ICD-10 (organic anxiety disorder) HAMA ≥ 14	NA	(1) Routine care for stroke (2) HM (8 wks)	(1) Routine care for stroke (2) Benzodiazepines (Alprazolam 0.4 mg qd)	(1) TER (HAMA): (A) > (B)* (2) HAMA: (A) < (B)* (3) NFIA: (A) < (B)*	(A) none (B) nausea and loss of appetite (2 cases), dry mouth (1 case), drowsiness (3 cases), dizziness and headache (2 cases). The symptoms were mild and the patient was tolerated without affecting treatment.
Zhang 2009 [47]	99(49:50)→ 99(49:50)	(A) 56.2 (45–75) (B) 58.6 (49–78)	HAMA > 14	NA	(1) Routine care for stroke (2) HM (2 wks)	(1) Routine care for stroke (2) Benzodiazepines (Alprazolam 0.4 mg tid)	(1) TER (HAMA): (A) > (B)*	(A) none (B) sleepiness and drowsiness (18 cases), drug dependence (15 cases)
Zhang 2010 [48]	65(32:33)→ 65(32:33)	(A) 60.50 ± 5.32 (NR) (B) 65.90 ± 6.62 (NR)	CCMD-3 (NR) HAMA > 14	yin deficiency with effulgent fire and non-interaction between the heart and kidney	(1) Routine care for stroke (2) HM (1 mo)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) TER (HAMA): N.S	(A) sleep disorders (2 cases), dry mouth (1 case), GI symptoms (1 case); total 12.50% (B) sleep disorders (6 cases), fatigue (1 case), dry mouth (2 cases), GI symptoms (2 cases); total 33.33%
Wang 2012 [49]	100(50:50)→100(50:50)	64 ± 9.2 (48–79)	HAMA > 14	NA	(1) Routine care for stroke (2) HM (8 wks)	(1) Routine care for stroke (2) SSRI (Paroxetine hydrochloride 20 mg qd)	(1) TER (HAMA): (A) > (B)* (at 2 wks), NR (at 4, 8 wks) (2) HAMA: (A) < (B)* (at 2 wks), N.S (at 4, 8 wks)	(A) none (B) nausea and stomach discomfort (12 cases)
Yu 2012 [50]	66(36:30)→66(36:30)	NR (over 40)	HAMA ≥ 14	NA	(1) Routine care for stroke (2) HM (4 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) HAMA: N.S	NR
Zhang 2012 [51]	60(30:30)→60(30:30)	(A) 50.41 ± 8.15 (NR) (B) 48.36 ± 7.55 (NR)	HAMA ≥ 14	NA	(1) Routine care for stroke (2) HM (4 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) TER (HAMA): (A) > (B)* (2) HAMA: (A) < (B)+	NR
Chang 2013 [52]	68(33:35)→65(32:33)	NR (over 50)	CCMD-3 (generalized anxiety disorder) HAMA ≥ 14	NA	(1) Routine care for stroke (2) HM (8 wks)	(1) Routine care for stroke (2) Benzodiazepines (Estazolam 2 mg tid)	(1) TER (HAMA): NR (2) HAMA: N.S (3) TER (TCM syndrome): NR (87.2% vs. 63.6%) (4) TCM syndrome: (A) < (B)+	(A) none (B) none
Guo 2014 [53]	100(50:50)→100(50:50)	61.5 (45–83)	HAMA ≥ 18	NA	(1) Routine care for stroke (2) HM (3 mo)	(1) Routine care for stroke (2) Azapirone (Tandospirone citrate 5 mg tid)	(1) TER (HAMA, BI): (A) > (B)* (2) HAMA: (A) < (B)+ (3) BI: (A) > (B)+	NR
Li 2015 [54]	120(60:60)→120(60:60)	(A) 62.5 ± 9.1 (NR)	HAMA ≥ 14	deficiency of the heart-spleen	(1) HM (6 wks)	(1) SSRI (Citalopram hydrobromide 20 mg qd)	(1) TER (HAMA): N.S (2) HAMA: N.S	(A) dry mouth (3 cases), dizziness (1 case), nausea and vomiting (4 cases)

(*continued on next page*)

Table 1 (*continued*)

Study ID	Sample size (included →analyzed)	Mean age (range) (yr)	Diagnostic criteria	Pattern identification	(A) Experimental intervention (duration)	(B) Control intervention	Outcome and results	Adverse events
		(B) 60.6 ± 5.4 (NR)					(3) CSS: N.S (4) CGI: N.S	(B) dry mouth (4 cases), dizziness (4 cases), nausea and vomiting (5 cases), constipation (2 cases), diarrhea (3 cases), drowsiness (2 cases)
Ma 2016 [55]	70(35:35)→70(35:35)	(A) 61.35 ± 7.23 (23–75) (B) 59.87 ± 7.87 (14–28)	ICD-10 (organic anxiety disorder) HAMA > 21	NA	(1) Routine care for stroke (2) HM (4 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg qd)	(1) TER (HAMA): N.S (2) TCM syndrome: (A) < (B)+ (3) SS-QOL: N.S (4) BI: N.S	NR
Tang 2017 [56]	52(26:26)→52(26:26)	65 ± 10 (NR)	HAMA ≥ 7	NA	(1) Routine care for stroke (2) HM (8 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg qd)	(1) TER (subjective symptom): NR (2) TER (HAMA): NR (3) HAMA: (A) < (B)*	(A) none (B) dry mouth (2 cases), constipation (1 case)
HM + conventional pharmacotherapy vs. conventional pharmacotherapy								
Qian 2010 [57]	100(50:50)→100(50:50)	(A) NR (43–75) (B) NR (45–75)	ICD-10 (organic anxiety disorder)	NA	(B) + HM (4 wks)	(1) Routine care for stroke (2) Benzodiazepines (Alprazolam 0.4 mg bid) (4 wk)	(1) TER (SAS): (A) > (B)+ (2) SAS: (A) < (B)+	NR
Chen 2014 [58]	120(60:60)→120(60:60)	(A) 69.10 ± 5.50 (NR) (B) 70.14 ± 5.56 (NR)	CCMD-3 (anxiety disorder) HAMA ≥ 14 HAMD < 7	NA	(B) + HM (8 wks)	(1) Azapirone (Tandospirone citrate from 5 mg 1T tid to 2T tid)	(1) TER (HAMA): (A) > (B)* (2) HAMA: (A) < (B)+	TESS: N.S (A) dry mouth (5 cases), drowsiness (2 cases), constipation (4 cases); 18.33% (B) dry mouth (4 cases), drowsiness (3 cases), constipation (3 cases); 16.67%
Lian 2014 [59]	86(44:42)→86(44:42)	NR	CCMD-3 (NR)	NA	(B) + HM (4 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) TER (HAMA): (A) > (B)* (2) HAMA: (A) < (B)*	NR
Fang 2016 [60]	75(37:38)→75(37:38)	(A) 59.28 ± 7.64 (NR) (B) 58.76 ± 8.42 (NR)	CCMD-2-R (organic anxiety disorder) HAMA > 14	NA	(B) + HM (4 wks)	(1) Deanxit (Flupentixol/melitracen 10.5 mg qd-bid)	(1) TER (HAMA): (A) > (B)* (2) HAMA: (A) < (B)*	(A) dizziness, drowsiness, dry mouth, nausea, constipation; total 31.48% (B) dizziness, drowsiness, dry mouth, nausea, constipation; total 27.56% Incidence: N.S
Jia 2017 [61]	120(60:60)→120(60:60)	(A) 61.8 ± 7.9 (NR) (B) 60.9 ± 8.1 (NR)	HAMA ≥ 21	non-interaction between the heart and kidney	(B) + HM (6 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) TER (HAMA): N.S (2) HAMA: (A) < (B)* (3) SAS: N.S (4) SS-QOL: (A) > (B)*	(A) dry mouth (2 cases), dizziness (1 case), nausea and vomiting (2 cases) (B) dry mouth (3 cases), dizziness (2 cases), nausea and vomiting (2 cases), drowsiness (1 case)
Wang 2017 [62]	84(42:42)→84(42:42)	(A) 57.2 ± 2.9 (NR) (B) 56.1 ± 3.4 (NR)	CCMD-3 (anxiety disorder)	NA	(B) + HM (4 wks)	(1) Routine care for stroke (2) Deanxit (Flupentixol/melitracen 10.5 mg bid)	(1) HAMA: (A) < (B)+ (2) ADL: (A) > (B)+	(A) none (B) none
Xu 2017 [53]	108(54:54)→108(54:54)	(A) 52 ± 5.7 (41–70) (B) 57 ± 6.2 (43–72)	DSM-IV-TR (anxiety disorder)	dual deficiency of qi and yin	(B) + HM (2 wks)	(1) SSRI (Paroxetine hydrochloride 10 mg qd)	(1) HAMA: (A) < (B)*	NR

'*' and '+' indicated significant differences between groups, $p < 0.05$ and $p < 0.01$, respectively. 'N.S' means no significant difference between groups, $p > 0.05$.

Routine care for stroke: improving cerebral blood circulation, nurturing brain cells, regulating blood pressure, preventing and treating various system complications, and symptomatic treatment. **Abbreviations**. ADL, activities of daily living; BI, Barthel index; CCMD, Chinese classification of mental disorders; CGI, clinical global impression; CSS, China stroke scale; DSM-IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revision; GI, gastrointestinal; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression scale; HM, herbal medicine; ICD, international classification of diseases; NFIA, nervous functional impairment assessment; NA, not applicable; NR, not recorded; SAS, Zung self-rating anxiety scale; SS-QOL, stroke specific quality of life; SSRI, selective Serotonin reuptake inhibitor; TCM, traditional Chinese medicine; TER, total effective rate; TESS, treatment emergent symptom scale.

via PubMed, EMBASE via Elsevier, the Cochrane Central Register of Controlled Trials [CENTRAL], Allied and Complementary Medicine Database [AMED] via EBSCO, Cumulative Index to Nursing and Allied Health Literature [CINAHL] via EBSCO, and PsycARTICLES via ProQuest), 5 Korean-language databases (Oriental Medicine Advanced Searching Integrated System [OASIS], Koreanstudies Information Service System [KISS], Research Information Service System [RISS], Korean Medical Database [KMbase], and Korea Citation Index [KCI]), and 2 Chinese databases (China National Knowledge Infrastructure [CNKI] and Wanfang Data). We also checked the reference lists of relevant articles and manually searched on Google Scholar to identify any additional gray literature. There was no restriction on language or publication status. The following search terms were used in Medline: ("anxiety disorders"[MH] OR "anxiety"[MH] OR anxiety) AND ("stroke"[MH] OR stroke) AND ("Plants, Medicinal"[MH] OR "Drugs, Chinese Herbal"[MH] OR "Medicine, Chinese Traditional"[MH] OR "Medicine, Kampo"[MH] OR "Medicine, Korean Traditional"[MH] OR "Herbal Medicine"[MH] OR "Prescription Drugs"[MH] OR "traditional Korean medicine" OR "traditional Chinese medicine" OR "traditional Oriental medicine" OR "Kampo medicine" OR "alternative medicine" OR "complementary medicine" OR herb* OR decoction* OR botanic*) (Appendix 1).

2.2. Inclusion criteria

2.2.1. Types of studies

We only included randomized controlled trials (RCTs) that aimed to assess the efficacy of HM for PSA. We excluded quasi-RCTs using inappropriate random sequence generation methods such as alternate allocation. If only the expression "randomization" (隨机) was mentioned without a detailed randomization method, it was included in this review. We included both parallel and crossover studies. In crossover designs, only first-phase data was used in calculating the effect size and conducting the meta-analysis.

2.2.2. Types of participants

We included studies on patients with a diagnosis of anxiety following stroke, using standardized diagnostic criteria such as the diagnostic and statistical manual of mental disorders (DSM) and Chinese classification of mental disorder (CCMD), or validated assessment tools such as the Hamilton anxiety rating scale (HAMA) and Zung self-rating anxiety scale (SAS), regardless of gender, age, or race of participants. We excluded studies that did not refer to diagnostic criteria or validated tools for inclusion. We excluded studies on patients with drug allergies, other psychiatric problems such as depression, or other serious illnesses such as cancer, liver disease, or kidney disease.

2.2.3. Types of interventions

We included studies involving oral HM as a monotherapy or as an adjunctive therapy to conventional pharmacotherapies such as anxiolytics and antidepressants as experimental interventions, and that used conventional pharmacotherapies as control interventions. We allowed any formulation (e.g., decoction, tablets, capsules, pills, powders, and extracts) of HM prescribed based on traditional East Asian medicine theories. Studies involving routine care for stroke such as anti-hypertensives and rehabilitation were included if it was used equally in both the experimental and the control groups. We excluded studies involving psychotherapy as experimental or control interventions. Except for patented drugs, we excluded studies that did not list the composition of the HM used. We excluded studies comparing different types of HM.

2.2.4. Types of outcome measures

The primary outcome measure was the degree of post-intervention anxiety measured using validated assessment tools, such as HAMA and SAS. A secondary outcome measure was total effective rate (TER), a non-validated outcome measure that is processed secondarily according to certain evaluation criteria such as the improvement rates of quantified outcomes or clinical symptom. For the calculation of TER, participants are generally classified as "cured" (痊愈), "markedly improved" (顯效), "improved" (有效), or "non-responder" (無效) after treatment. TER was calculated consistently using the following formula: $TER = N1 + N2 + N3/N$, where $N1$, $N2$, $N3$, and N were the number of patients who were cured, markedly improved, improved, and the total sample size, respectively. We also analyzed neurological function, activities of daily living (ADL), QoL, and adverse events (AEs) as secondary outcome measures.

2.3. Study selection

After excluding duplicates, two researchers (XX and XX) independently screened the titles and abstracts of the searched studies for first inclusion. We then evaluated the full-texts of the selected articles that potentially met the eligibility criteria for final inclusion. Any disagreement on study selection was resolved through discussion with other researchers in order to reach consensus.

2.4. Data extraction

Using a standardized data collection form in Excel 2010 (Microsoft, Redmond, WA, USA), one author (XX) conducted data extraction and another author (XX) reviewed the data. Discrepancies were resolved through discussion with other researchers. Items extracted from each study included the first author's name; year of publication; country; sample size and number of dropouts; diagnostic criteria; pattern identification; research ethics-related information such as approval of the institutional review board; details about the participants, experimental intervention, and comparisons; duration of the intervention; outcome measures; results; AEs associated with interventions; and information for the assessment of the risk of bias. We contacted the corresponding authors of the included studies via e-mail if additional information was needed.

2.5. Risk of bias

Two researchers (XX and XX) independently assessed the methodological quality using the risk of bias tool developed by Cochrane group [42]. Discrepancies were resolved via discussion with other researchers. We assessed selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (completeness of outcome data), reporting bias (selective reporting), and other biases. We assessed the study to be at high risk of bias in the random sequence generation domain, when only the expression "randomization" (隨机) was mentioned without specific randomization methods. We assessed other potential bias categories with particular emphasis on baseline imbalances between experimental and control group such as participant characteristics, which include mean age and baseline anxiety level. Each item was rated as "low risk," "unclear," or "high risk."

2.6. Data synthesis and analysis

Descriptive analyses of the details of the participants, interventions, outcomes, and results were conducted for all included studies. We performed meta-analysis using Review Manager software version 5.3 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012) if there were studies using the same type of experimental intervention, comparison, and outcome measure. We pooled the data with mean difference (MD) for continuous outcomes and risk ratio (RR) for binary outcomes, with 95% confidence intervals (CIs). Heterogeneity between the studies was assessed using both the chi-

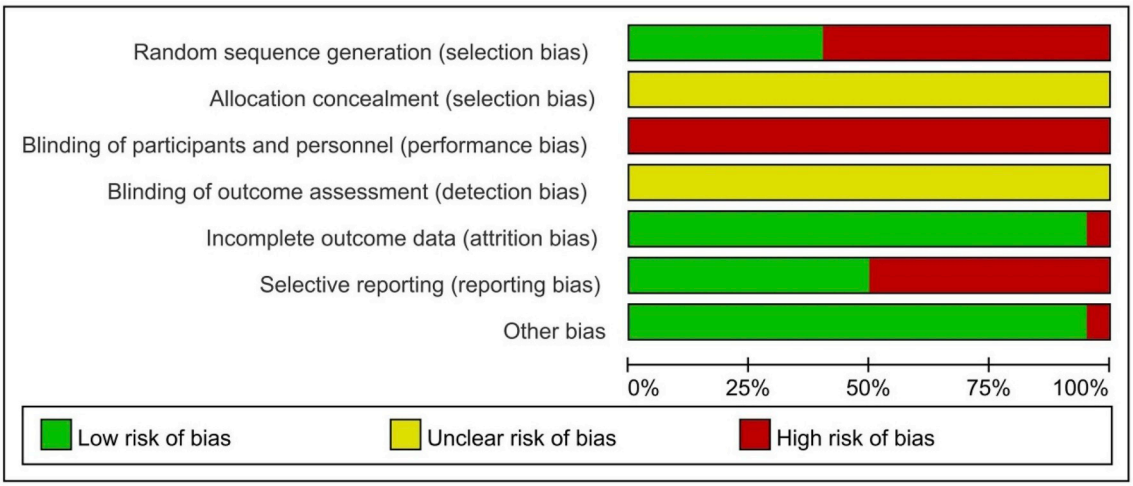

Fig. 2. Risk of bias graph for all included studies.

squared test and the I-squared statistic. We considered I-squared values ≥ 50% and ≥75% indicative of substantial and serious heterogeneity, respectively. The data were pooled using a random effects model when the heterogeneity was significant (I-squared value ≥ 50%), while a fixed effects model was used when the heterogeneity was non-significant. We also used the fixed-effects model when the number of studies included in a meta-analysis was very small, where the estimates of between-study variance had poor accuracy [43]. If the necessary data were available, we conducted a subgroup analysis according to the severity of anxiety and types of conventional pharmacotherapy used such as antidepressants and anxiolytics. If there were more than 10 trials included in the meta-analysis, we assessed evidence of publication bias using funnel plots.

3. Results

3.1. Study selection and description

We identified 5231 studies through the database search and no additional studies from the reference lists of relevant articles. After removing 214 duplications, 40 articles were considered to be relevant following screening of the titles and abstracts. After assessing the full-texts of 40 articles, we finally included 20 RCTs [44–63] in the systematic review and 19 RCTs [44–56,58–63] in the meta-analysis (Fig. 1).

The general characteristics of the included studies are summarized in Table 1. All included studies were conducted in China. There were 2 theses [52,55], while the remaining were journal articles. Thirteen studies [44–56] compared HM to conventional pharmacotherapy, while the remaining seven studies [57–63] compared HM combined with conventional pharmacotherapy to conventional pharmacotherapy alone. For diagnostic criteria, HAMA was used the most in 16 studies [44–56,58,60,61], CCMD was used in seven [44,48,52,58–60,62], the International Classification of Diseases in three [46,55,57], DSM in one [63], and Hamilton depression scale in one [58]. Five studies recruited participants with specific traditional Chinese medicine (TCM) patterns: non-interaction between the heart and kidney in 3 studies [44,48,61], deficiency of the heart-spleen in one [54], and dual deficiency of qi and yin in one [63]. Treatment duration ranged from 2 weeks to 3 months; 4 weeks (or 1 month) was the most commonly used in 9 studies [44,48,50,51,55,57,59,60,62]. In 16 studies [44–53,55–57,59,61,62], routine care for stroke including improving cerebral blood circulation, nurturing brain cells, regulating blood pressure, preventing and treating various system complications, and symptomatic treatment was performed in both experimental and control groups. As a control, antidepressants were used in 13 studies [45,48–51,54–56,59–63]: 9 of which [48,50,51,55,56,59–62] used Deanxit and 4 of which [45,49,54,63] used selective serotonin reuptake inhibitors (SSRIs). Anxiolytics were used in 7 studies [44,46,47,52,53,57,58] as a control: 5 of which [44,46,47,52,57] were benzodiazepines and 2 [53,58] were azapirone. As outcome measures, anxiety level was evaluated in all studies, 16 of which [44–46,49–54,56,58–63] used HAMA, 2 [57,61] used SAS, and 16 [44–49,51–56,58–61] used TER calculated based on HAMA. Neurological function, ADL, and QoL were evaluated in 2 [46,54], 3 [53,55,62], and 2 studies [55,61], respectively. One study [58] reported the approval of the institutional review board, and 8 [46,49,53,55,56,58,61,62] reported that they had received consent from the participants.

3.2. Risk of bias

Eight studies [49,52,54,55,58,59,61,62] using an appropriate method of random sequence generation (such as a random number table), were assessed to have low risk of bias on the random sequence generation domain. The remaining 12 studies [44–48,50,51,53,56,57,60,63] with no description of the randomization method were considered to be at high risk of bias. No studies reported the allocation concealment and blinding of participants, personnel, or outcome assessors. Since no studies used a placebo treatment, the risk of performance bias was evaluated as high in all studies. There was no dropout in 18 studies [44–51,53,55–63]. One study [52] that processed missing data with a per-protocol analysis method was evaluated as having high risk of attrition bias, and another study [54] using an intention-to-treat analysis method was evaluated as having low risk. Ten studies [47–51,53,55,57,59,63] were rated as high risk of reporting bias because they reported only TER without reporting raw data, or they did not report anxiety or AEs-related outcome measures. Nineteen studies [44–55,57–63] reported that there was no statistical heterogeneity of demographic data between groups and were assessed to have low risk of bias (Figs. 2 and 3).

3.3. Details of HM used

Details of the HM used for PSA are summarized in Table 2. Nine studies [47,49,50,53,55–58,60] used Chinese patented HMs, of which “Jiuwei Zhenxin Granule” [54,58] and “Shensong Yangxin Granule” [47,53] were used in two studies, respectively. In the case of dosage form, decoction was most frequently used in 10 studies [44–46,48,51,52,59,61–63] followed by granule in 6 [49,50,54,55,57,58], capsule in 3 [47,53,56], and pian in 1 [60].

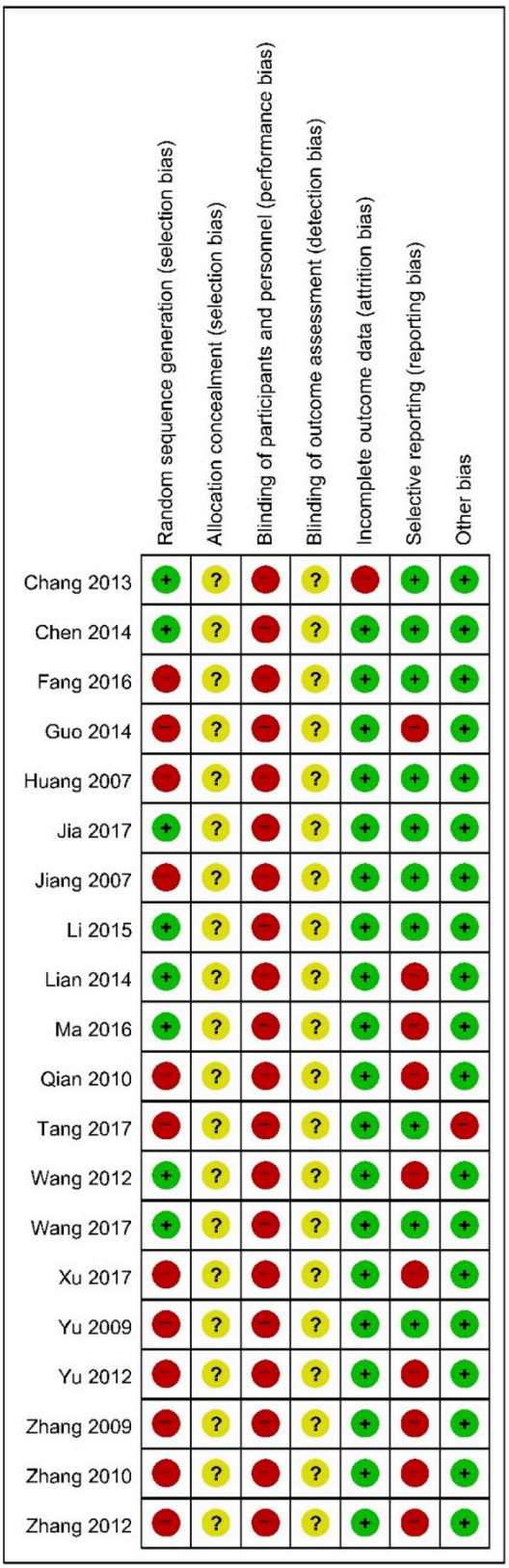

Fig. 3. Risk of bias summary for all included studies.
Low, unclear, and high risk are represented with the following symbols: "+", "?", and "-"

Based on basic components, 80 different herbs were used. The most frequently used herbs were *Zizyphi Semen* in 9 studies (45%), followed by *Coptidis Rhizoma* in eight (40%), and *Glycyrrhizae Radix et Rhizoma*, *Salviae Miltiorrhizae Radix*, *Paeoniae Radix Alba*, *Schisandrae Fructus*, and *Polygalae Radix* in six (Table 3). In three studies [45,46,62], some herbs were added according to the participants' symptoms or specific TCM patterns, in addition to the basic components of the HM.

3.4. Efficacy of HM for PSA

3.4.1. HM vs. conventional pharmacotherapy (13 RCTs)

Meta-analysis revealed that after 1 week of treatment, conventional pharmacotherapy significantly lowered HAMA scores compared to HM (2 RCTs; MD 2.46, 95% CI 0.80 to 4.12, $I^2 = 81\%$) (Fig. 4). After 2, 4, and 6 weeks of treatment, there was no significant difference in HAMA scores between HM and conventional pharmacotherapy (2 weeks: 5 RCTs; MD -2.13, 95% CI -5.39 to 1.12, $I^2 = 90\%$; 4 weeks: 7 RCTs; MD -0.91, 95% CI -2.51 to 0.70, $I^2 = 77\%$; 6 weeks: 2 RCTs; MD 0.39, 95% CI -1.09 to 1.88, $I^2 = 0\%$) (Figs. 5–7). However, after 8 weeks and 3 months of treatment, the HM group showed significantly lower HAMA scores than the conventional pharmacotherapy group (8 weeks: 4 RCTs; MD -0.94, 95% CI -1.41 to −0.48, $I^2 = 97\%$; 3 months: 1 RCT; MD -6.50, 95% CI -8.16 to −4.84) (Figs. 8 and 9). In subgroup analysis according to the types of conventional pharmacotherapy used, after 8 weeks of treatment in studies using antidepressants as controls, HAMA scores were significantly lower in the HM group (2 RCTs; MD -6.79, 95% CI -8.21 to −5.38, $I^2 = 72\%$). However, there was no difference between the groups when anxiolytics were used as controls (2 RCTs; MD -0.23, 95% CI -0.72 to 0.26, $I^2 = 90\%$) (Table 4). Despite excluding the study by Tang (2017) [56] which included participants exhibiting mild anxiety (HAMA ≥ 7) from the sensitivity analysis, the statistical significance of the meta-analysis after 8 weeks of treatment was not significantly affected (8 weeks: 3 RCTs; MD -0.77, 95% CI -1.25 to −0.30, $I^2 = 97\%$).

Meta-analysis revealed that the HM group had significantly higher TER values, based on improvement in HAMA scores after 2 and 8 weeks of treatment compared to the conventional pharmacotherapy group (2 weeks: 2 RCTs; RR 1.16, 95% CI 1.05 to 1.27, $I^2 = 0\%$; 8 weeks: 2 RCTs; RR 1.21, 95% CI 1.00 to 1.46, $I^2 = 0\%$). However, there was no difference between the groups after 4 and 6 weeks of treatment (4 weeks: 4 RCTs; RR 1.06, 95% CI 0.95 to 1.18, $I^2 = 0\%$; 6 weeks: 3 RCTs; RR 1.05, 95% CI 0.95 to 1.16, $I^2 = 70\%$) (Table 4).

Two studies evaluated neurological function. In one study [46], neurological function as measured by the nervous functional impairment assessment was significantly improved in the HM group ($p < 0.05$). There was no difference between the groups in the other study measuring the China stroke scale ($p > 0.05$) [54]. Of the 2 studies evaluating ADL using the Barthel index, 1 [53] showed significant results in favor of HM ($p < 0.01$) and the other [55] showed no difference between the groups ($p > 0.05$). Ma (2016) [55] assessed QoL using the stroke specific QoL after 4 weeks of treatment, and there was no difference between the two groups ($p > 0.05$).

3.4.2. HM plus conventional pharmacotherapy vs. conventional pharmacotherapy alone (7 RCTs)

Meta-analysis showed that HAMA scores were significantly lower in the combined treatment group after 2, 4, 6, and 8 weeks of treatment compared to the conventional pharmacotherapy group (2 weeks: 4 RCTs; MD -3.42, 95% CI -4.03 to −2.82, $I^2 = 83\%$; 4 weeks: 5 RCTs; MD -3.00, 95% CI -3.60 to −2.40, $I^2 = 20\%$; 6 weeks: 1 RCT; MD -3.92, 95% CI -5.82 to −2.02; 8 weeks: 1 RCT; MD -2.78, 95% CI -4.16 to −1.40) (Figs. 10–13). When added to conventional pharmacotherapy, HM showed significantly lower SAS scores after 2 and 4 weeks of treatment compared with conventional pharmacotherapy alone (2 weeks: 1 RCT; MD -2.47, 95% CI -4.77 to −0.17; 4 weeks: 2 RCTs; MD -4.95, 95% CI -6.71 to −3.19, $I^2 = 77\%$). However, there was no difference after 6 weeks of treatment (1 RCT; MD -1.04, 95% CI -3.05 to

Table 2
Details of herbal medicine used.

Study ID	Dosage form	Administration duration and frequency	HM name	Basic components (one day)	Modifying components
HM vs. conventional pharmacotherapy					
Huang 2007 [44]	decoction	1 mo, qid	Modified Huanglianajiao Decoction	*Coptidis Rhizoma* 30 g, *Thujae Semen* 30 g, *Zizyphi Semen* 30 g, *Scutellariae Radix* 24 g, *Paeoniae Radix Alba* 24 g, *Asini Corii Colla* 30 g, *Testudinis Chinemis Plastrum et Carapax* 30 g, *Rehmanniae Radix Recens* 40 g, *Fossilia Ossis Mastodi* 60 g, *Ostreae Testa* 60 g	NA
Jiang 2007 [45]	decoction	6 wks, NR	Baihejielu Decoction	*Lilii Bulbus* 15 g, *Poria Sclerotium* 15 g, *Nardostachyos Radix et Rhizoma* 15 g, *Saxifragae Herba* 3 g, *Zizyphi Semen* 12 g, *Polygalae Radix* 10 g, *Curcumae Radix* 10 g, *Glycyrrhizae Radix et Rhizoma* 10 g	1) liver depression with effulgent fire: *Gastrodiae Rhizoma*, *Uncariae Ramulus cum Uncus*, *Gardeniae Fructus* 2) wind-phlegm obstructing the collaterals: *Arisaematis Rhizoma, Scorpio, Acori Graminei Rhizoma* 3) liver-kidney yin deficiency: *Rehmanniae Radix Preparata, Corni Fructus, Angelicae Gigantis Radix* 4) dual deficiency of the heart and spleen: *Codonopsis Pilosulae Radix, Atractylodis Rhizoma Alba, Dioscoreae Rhizoma*
Yu 2009 [46]	decoction	8 wks, NR	Qileng Decoction	*Astragali Radix* 30 g, *Sparganii Rhizoma* 9 g, *Mori Fructus* 9 g, *Trichosanthis Radix* 9 g, *Hirudo* 9 g, *Lumbricus* 9 g, *Curcumae Rhizoma* 9 g, *Aurantii Fructus Immaturus* 9 g, *Coptidis Rhizoma* 6–12 g, *Asini Corii Colla* 9 g, *Scutellariae Radix* 9 g, *Paeoniae Radix Alba* 9 g	1) phlegm exuberance: *Phyllostachyos Caulis in Taeniam, Arisaematis Rhizoma* 2) qi deficiency with blood stasis: increase the amount of tonify qi and activate blood medicine
Zhang 2009 [47]	capsule	2 wks, 4 caps tid	Shensong Yangxin Granule*	*Ginseng Radix, Liriopis seu Ophiopogonis Tuber, Corni Fructus, Salviae Miltiorrhizae Radix, Zizyphi Semen, Loranthi Ramulus Et Folium, Paeoniae Radix Rubra, Eupolyphaga Sinensis, Nardostachyos Radix et Rhizoma, Coptidis Rhizoma, Schisandrae Fructus, Fossilia Ossis Mastodi*	NA
Zhang 2010 [48]	decoction	1 mo, bid	self-made Ziyin Rougan Qianyang Decoction	*Adenophorae Radix* 15 g, *Liriopis seu Ophiopogonis Tuber* 15 g, *Angelicae Gigantis Radix* 15 g, *Rehmanniae Radix Recens* 30 g, *Lycii Fructus* 18 g, *Paeoniae Radix Alba* 18 g, *Uncariae Ramulus cum Uncus* 12 g, *Gardeniae Fructus* 12 g, *Fossilia Ossis Mastodi* 15 g, *Ostreae Testa* 15 g, *Salviae Miltiorrhizae Radix* 12 g, *Paeoniae Radix Rubra* 12 g, *Glycyrrhizae Radix et Rhizoma* 6 g	NA
Wang 2012 [49]	granule	8 wks, tid	Wenxin Granule*	*Codonopsis Pilosulae Radix, Polygonati Rhizoma, Notoginseng Radix Et Rhizoma, Saxifragae Herba, Nardostachyos Radix et Rhizoma*	NA
Yu 2012 [50]	granule	4 wks, bid	Zaobaining Granule*	*Thujae Semen, Zizyphi Semen, Schisandrae Fructus, Salviae Miltiorrhizae Radix, Polygoni Multiflori Caulis,* etc	NA
Zhang 2012 [51]	decoction	4 wks, bid	NR	*Poria Sclerotium* 10 g, *Arisaematis Rhizoma* 10 g, *Pinelliae Tuber* 10 g, *Phyllostachyos Caulis in Taeniam* 10 g, *Acori Graminei Rhizoma* 10 g, *Curcumae Radix* 10 g, *Citri Unshius Pericarpium* 10 g, *Gardeniae Fructus* 10 g, *Paeoniae Radix Alba* 10 g, *Polygalae Radix* 10 g, *Albizziae Flos* 10 g, *Coptidis Rhizoma* 6 g, *Ponciri Fructus Immaturus* 6 g, *Glycyrrhizae Radix et Rhizoma* 6 g	NA
Chang 2013 [52]	decoction	8 wks, bid	Wenyang Sini Decoction	*Aconiti Lateralis Radix Preparata, Magenetitum, Pinelliae Tuber, Arecae Pericarpium, Poria Sclertum Cum Pini Radix, Zizyphi Semen, Atractylodis Rhizoma Alba, Zingiberis Rhizoma, Epimedii Herba, Coptidis Rhizoma, Curcumae Radix, Ostreae Testa, Psoraleae Semen, Zingiberis Rhizoma Recens, Glycyrrhizae Radix et Rhizoma*, etc	NA
Guo 2014 [53]	capsule	3 mo, tid	Shensong Yangxin Granule*	*Ginseng Radix, Liriopis seu Ophiopogonis Tuber, Corni Fructus, Salviae Miltiorrhizae Radix, Zizyphi Semen, Loranthi Ramulus Et Folium, Paeoniae Radix Rubra, Eupolyphaga Sinensis, Nardostachyos Radix et Rhizoma, Coptidis Rhizoma, Schisandrae Fructus, Fossilia Ossis Mastodi*	NA
Li 2015 [54]	granule	6 wks, tid	Jiuwei Zhenxin Granule*	*Ginseng Radix, Zizyphi Semen, Schisandrae Fructus, Poria Sclerotium, Polygalae Radix, Corydalis Tuber, Asparagi Tuber, Rehmanniae Radix Preparata, Cinnamomi Cortex*	NA
Ma 2016 [55]	granule	4 wks, bid	Modified Danzhi Xiaoyao granule	*Moutan Radicis Cortex* 10 g, *Gardeniae Fructus* 10 g, *Bupleuri Radix* 12 g, *Angelicae Gigantis Radix* 10 g, *Paeoniae Radix Alba* 10 g, *Atractylodis Rhizoma Alba* 10 g, *Poria Sclerotium* 10 g, *Zingiberis Rhizoma Recens* 6 g, *Menthae Herba* 3 g, *Glycyrrhizae Radix et Rhizoma* 6 g, *Albizziae Cortex* 30 g, *Fossilia Ossis Mastodi* 20 g, *Ostreae Testa* 20 g, *Acori Graminei Rhizoma* 6 g	NA

(*continued on next page*)

Table 2 (*continued*)

Study ID	Dosage form	Administration duration and frequency	HM name	Basic components (one day)	Modifying components
Tang 2017 [56]	capsule	8 wks, tid	Wuling Capsule*	*Xylaria Nigripes*	NA
HM + conventional pharmacotherapy vs. conventional pharmacotherapy alone					
Qian 2010 [57]	granule	4 wks, tid	Tianzhi Granule*	*Gastrodiae Rhizoma, Uncariae Ramulus cum Uncus, Nardotidis seu Sulculii Concha, Eucommiae Cortex, Loranthi Ramulus Et Folium, Poria Sclertum Cum Pini Radix, Polygoni Multiflori Caulis, Sophorae Flos, Gardeniae Fructus, Scutellariae Radix, Achyranthis Radix, Leonuri Herba*	NA
Chen 2014 [58]	granule	8 wks, tid	Jiuwei Zhenxin Granule*	*Ginseng Radix, Zizyphi Semen, Schisandrae Fructus, Poria Sclerotium, Polygalae Radix, Corydalis Tuber, Asparagi Tuber, Rehmanniae Radix Preparata, Cinnamomi Cortex*	NA
Lian 2014 [59]	decoction	4 wks, bid	Shugan Huoxue Decoction	*Bupleuri Radix* 12 g, *Cyperi Rhizoma* 12 g, *Cnidii Rhizoma* 15 g, *Angelicae Gigantis Radix* 20 g, *Scorpio* 10 g, *Acori Graminei Rhizoma* 10 g, *Poria Sclertum Cum Pini Radix* 30 g, *Salviae Miltiorrhizae Radix* 30 g, *Curcumae Radix* 20 g, *Gardeniae Fructus* 12 g	NA
Fang 2016 [60]	pian	4 wks, tid	Shenqi Wuweizi Pian*	*Schisandrae Fructus, Codonopsis Pilosulae Radix, Astragali Radix, Zizyphi Semen*	NA
Jia 2017 [61]	decoction	6 wks, bid	Yishen Anshen Decoction	*Rehmanniae Radix Preparata* 20 g, *Acanthopanacis Cortex* 20 g, *Achyranthis Radix* 10 g, *Gastrodiae Rhizoma* 10 g, *Coptidis Rhizoma* 9 g, *Cinnamomi Cortex* 3 g, *Poria Sclertum Cum Pini Radix* 15 g, *Polygalae Radix* 15 g	NA
Wang 2017 [62]	decoction	4 wks, bid	Shugan Tongluo Decoction	*Rehmanniae Radix Recens* 15 g, *Paeoniae Radix Alba* 15 g, *Spatholobi Caulis* 12 g, *Salviae Miltiorrhizae Radix* 12 g, *Cnidii Rhizoma* 10 g, *Lilii Bulbus* 12 g, *Albizziae Cortex* 12 g, *Curcumae Radix* 12 g, *Poria Sclertum Cum Pini Radix* 12 g, *Polygalae Radix* 12 g, Jiaosanxian 10 g	1) wind exuberance: *Uncariae Ramulus cum Uncus, Gastrodiae Rhizoma* 2) constipation: *Rhei Radix et Rhizoma, Ponciri Fructus Immaturus* 3) insomnia: *Zizyphi Semen, Thujae Semen* 4) vexing heat in the chest: *Gardeniae Fructus, Gardeniae Fructus* 5) obvious phlegm-heat: *Phyllostachyos Caulis in Taeniam, Arisaematis Rhizoma*
Xu 2017 [63]	decoction	2 wks, bid	Modified Ganmaidazao Decoction	*Glycyrrhizae Radix et Rhizoma* 15 g, *Tritici Fructus Levis* 30 g, *Zizyphi Fructus* 10 pieces, *Astragali Radix* 30 g, *Codonopsis Pilosulae Radix* 15 g, *Angelicae Gigantis Radix* 30 g, *Dendrobii Caulis* 15 g, *Liriopis seu Ophiopogonis Tuber* 10 g, *Loranthi Ramulus Et Folium* 15 g, *Cnidii Rhizoma* 15 g, *Achyranthis Radix* 15 g	NA

*Chinese herbal patented medicines.

Abbreviations. HM, herbal medicine; NA, not applicable; NR, not recorded.

Table 3
Frequency of Herb used.

Frequency (%)	Herbs
9 (45%)	*Zizyphi Semen*
8 (40%)	*Coptidis Rhizoma*
6 (30%)	*Glycyrrhizae Radix et Rhizoma, Salviae Miltiorrhizae Radix, Paeoniae Radix Alba, Schisandrae Fructus, Polygalae Radix*
5 (25%)	*Poria Sclerotium, Poria Sclertum Cum Pini Radix, Fossilia Ossis Mastodi, Curcumae Radix, Gardeniae Fructus*
4 (20%)	*Nardostachyos Radix et Rhizoma, Angelicae Gigantis Radix, Liriopis seu Ophiopogonis Tuber, Ostreae Testa, Loranthi Ramulus Et Folium, Ginseng Radix*
3 (15%)	*Codonopsis Pilosulae Radix, Pinelliae Tuber, Rehmanniae Radix Recens, Acori Graminei Rhizoma, Rehmanniae Radix Preparata, Achyranthis Radix, Cinnamomi Cortex, Paeoniae Radix Rubra, Cnidii Rhizoma, Scutellariae Radix, Astragali Radix*
2 (10%)	*Thujae Semen, Atractylodis Rhizoma Alba, Lilii Bulbus, Corni Fructus, Zingiberis Rhizoma Recens, Bupleuri Radix, Asini Corii Colla, Uncariae Ramulus cum Uncus, Asparagi Tuber, Gastrodiae Rhizoma, Eupolyphaga Sinensis, Albizziae Cortex, Corydalis Tuber, Saxifragae Herba, Polygoni Multiflori Caulis*
1 (5%)	*Zingiberis Rhizoma, Spatholobi Caulis, Sophorae Flos, Lycii Fructus, Testudinis Chinemis Plastrum et Carapax, Arisaematis Rhizoma, Arecae Pericarpium, Zizyphi Fructus, Eucommiae Cortex, Moutan Radicis Cortex, Psoraleae Semen, Adenophorae Radix, Sparganii Rhizoma, Notoginseng Radix Et Rhizoma, Mori Fructus, Nardotidis seu Sulculii Concha, Dendrobii Caulis, Tritici Fructus Levis, Hirudo, Curcumae Rhizoma, Acanthopanacis Cortex, Xylaria Nigripes, Aconiti Lateralis Radix Preparata, Epimedii Herba, Leonuri Herba, Magenetitum, Scorpio, Phyllostachyos Caulis in Taeniam, Aurantii Fructus Immaturus, Lumbricus, Ponciri Fructus Immaturus, Citri Unshius Pericarpium, Trichosanthis Radix,* Jiaosanxian, *Albizziae Flos, Cyperi Rhizoma*

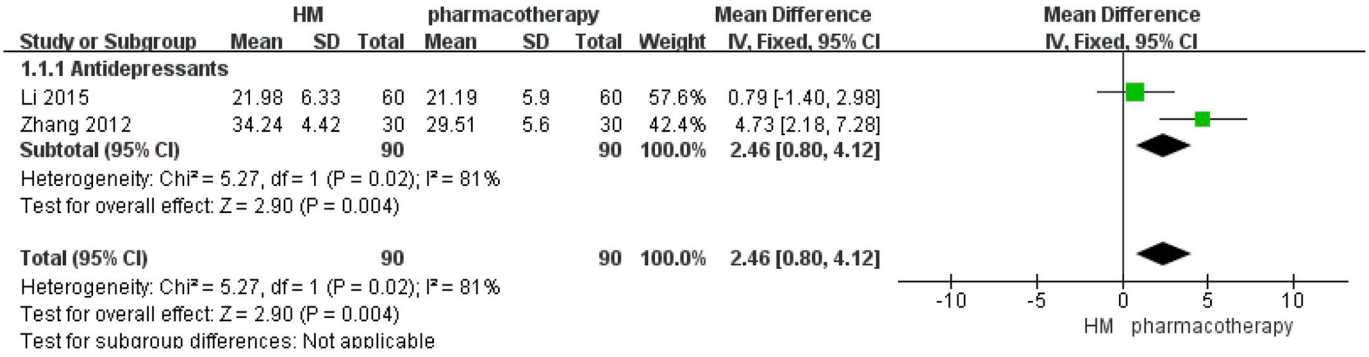

Fig. 4. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 1 week of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

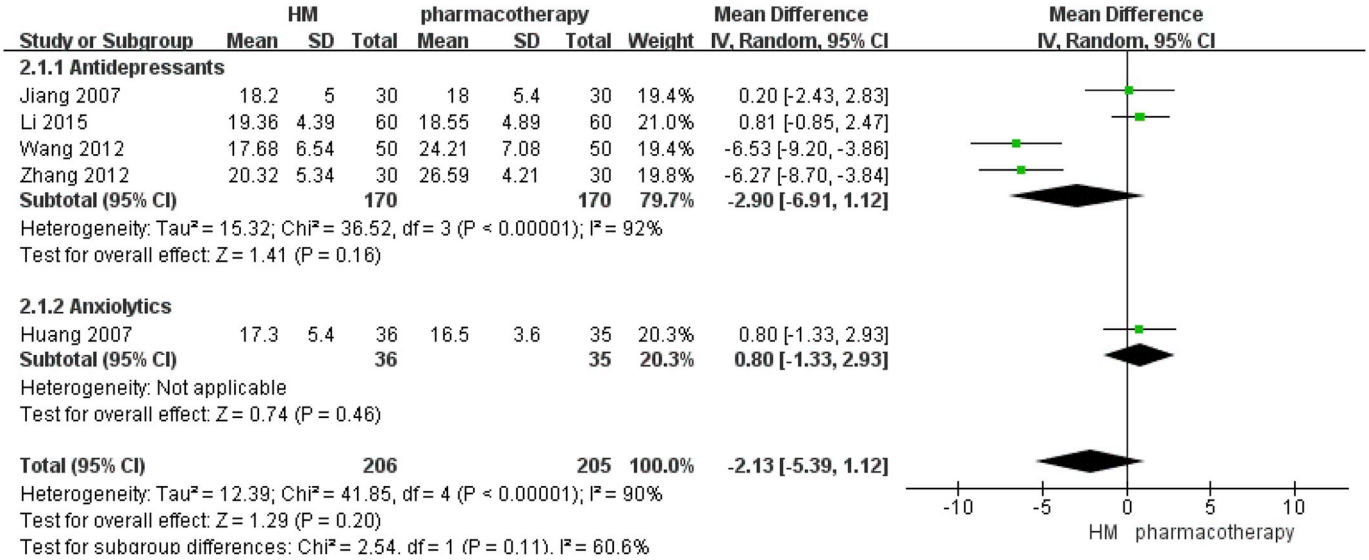

Fig. 5. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 2 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

0.97). No significant changes in effect size were observed in the subgroup analysis performed according to the type of antipsychotic drugs used (Table 4).

The meta-analysis showed that HM plus conventional pharmacotherapy group had significantly higher TER values based on improvement in HAMA scores after 4 weeks of treatment compared with the conventional pharmacotherapy group (2 RCTs; RR 1.23, 95% CI 1.02 to 1.47, I^2 = 0%). However, there was no difference between the groups after 6 and 8 weeks of treatment (6 weeks: 1 RCT; RR 0.95, 95% CI 0.83 to 1.07; 8 weeks: 1 RCT; RR 1.18, 95% CI 0.99 to 1.42). After 4 weeks of treatment, TER calculated based on improvement in SAS scores was significantly higher in the combination group (1 RCT; RR 1.32, 95% CI 1.07 to 1.64) (Table 4).

Wang (2017) [62] evaluated ADL, and the combination group significantly improved after 4 weeks of treatment compared to the conventional pharmacotherapy alone group ($p < 0.01$). Jia et al. (2017) [61] reported that the combination group had significantly higher stroke-specific QoL scores after 6 weeks of treatment ($p < 0.05$).

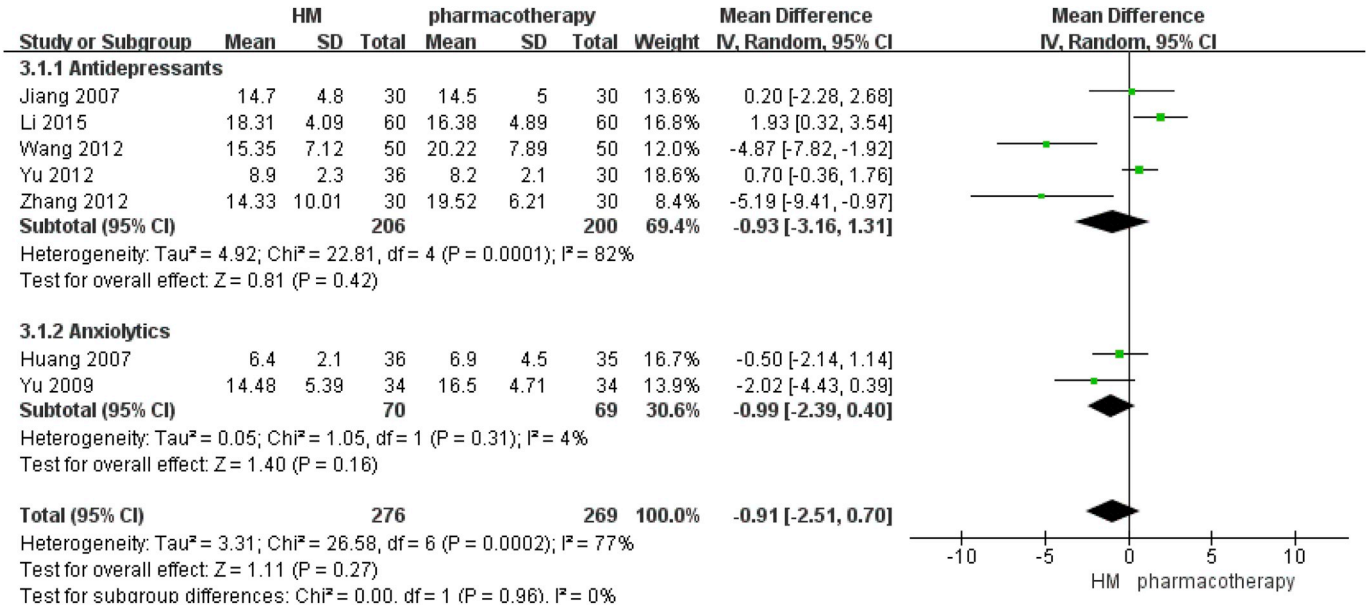

Fig. 6. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 4 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

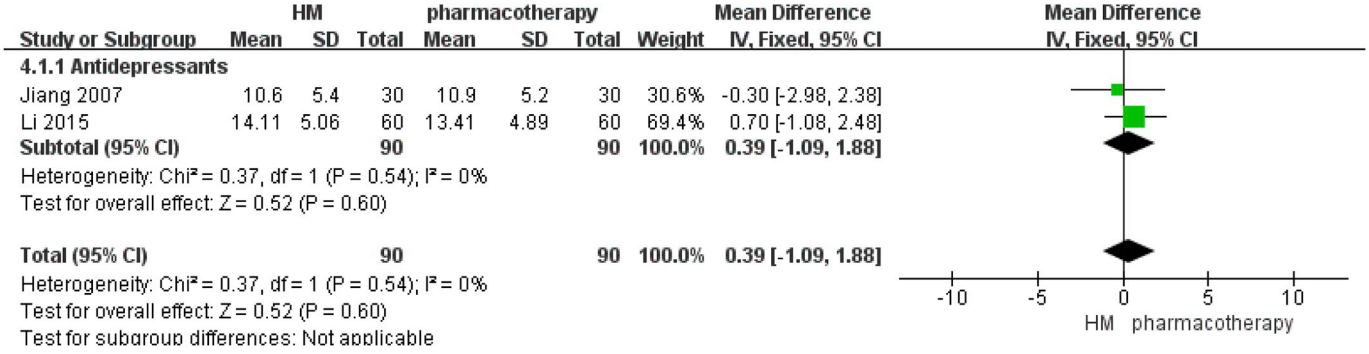

Fig. 7. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 6 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

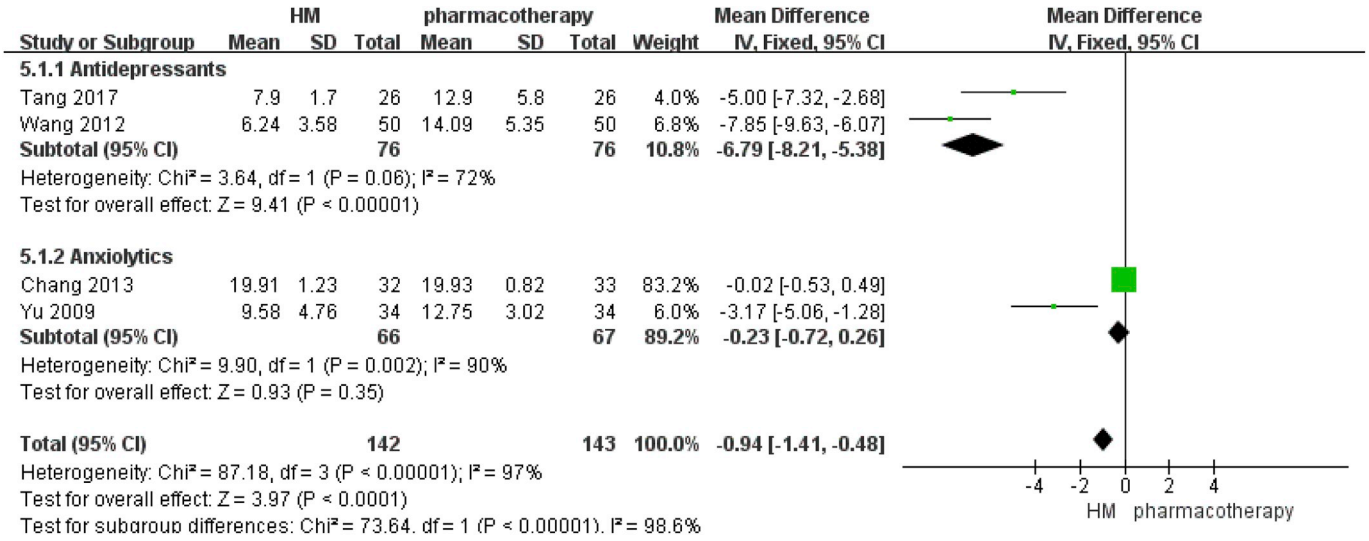

Fig. 8. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 8 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

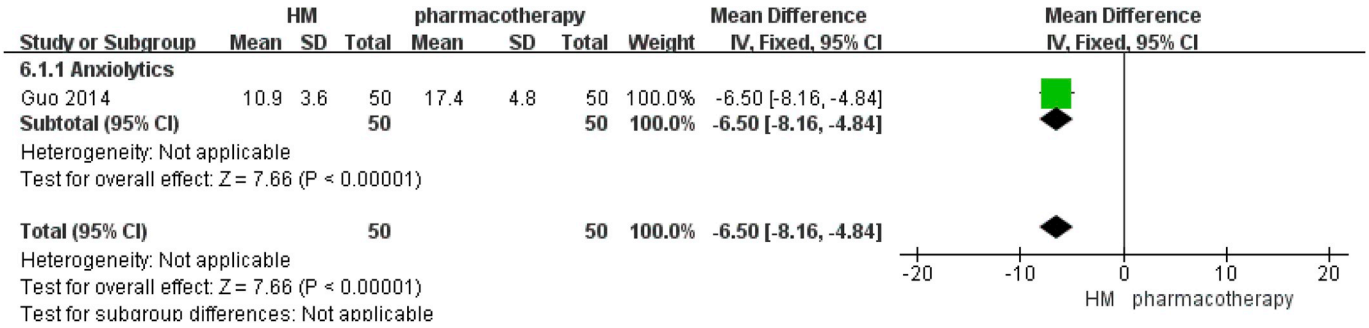

Fig. 9. Forest plot for the comparison of HM with conventional pharmacotherapy. Outcome: HAMA score after 3 months of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

Table 4
Summary of results of meta-analysis.

Duration	Outcomes		Studies	Sample size	RR or MD	Effects model	95% CI	I^2 value	Z value	P value
HM vs. conventional pharmacotherapy										
1 wk after treatment	HAMA	Total (vs. AD)	2	180	MD 2.46	Fixed	0.80, 4.12	81	2.90	0.004
2 wks after treatment	HAMA	Total	5	411	MD -2.13	Random	−5.39, 1.12	90	1.29	0.20
		vs. AD	4	340	MD -2.90		−6.91, 1.12	92	1.41	0.16
		vs. AX	1	71	MD 0.80		−1.33, 2.93	NA	0.74	0.46
	TER (HAMA)	Total	2	199	RR 1.16	Fixed	1.05, 1.27	0	2.95	0.004
		vs. AD	1	100	RR 1.17		1.02, 1.35	NA	2.18	0.03
		vs. AX	1	99	RR 1.14		1.00, 1.31	NA	1.94	0.05
4 wks or 1 mo after treatment	HAMA	Total	7	545	MD -0.91	Random	−2.51, 0.70	77	1.11	0.27
		vs. AD	5	406	MD -0.93		−3.16, 1.31	82	0.81	0.42
		vs. AX	2	139	MD -0.99		−2.39, 0.40	4	1.40	0.16
	TER (HAMA)	Total	4	274	RR 1.06	Fixed	0.95, 1.18	0	0.96	0.34
		vs. AD	2	135	RR 1.02		0.88, 1.17	0	0.22	0.83
		vs. AX	2	139	RR 1.10		0.93, 1.30	0	1.09	0.28
6 wks after treatment	HAMA	Total (vs. AD)	2	180	MD 0.39	Fixed	−1.09, 1.88	0	0.52	0.60
	TER (HAMA)	Total (vs. AD)	3	240	RR 1.05	Fixed	0.95, 1.16	70	0.93	0.35
8 wks after treatment	HAMA	Total	4	285	MD -0.94	Fixed	−1.41, −0.48	97	3.97	< 0.0001
		vs. AD	2	152	MD -6.79		−8.21, −5.38	72	9.41	< 0.00001
		vs. AX	2	133	MD -0.23		−0.72, 0.26	90	0.93	0.35
	TER (HAMA)	Total (vs. AX)	2	133	RR 1.21	Fixed	1.00, 1.46	0	2.00	0.05
3 mo after treatment	HAMA	Total (vs. AX)	1	100	MD -6.50	Fixed	−8.16, −4.84	NA	7.66	< 0.00001
NA	Adverse events	Total	7	569	RR 0.15	Random	0.05, 0.48	61	3.21	0.001
		vs. AD	4	337	RR 0.33		0.17, 0.63	9	3.37	0.0007
		vs. AX	3	232	RR 0.03		0.00, 0.21	0	3.50	0.0005
HM + conventional pharmacotherapy vs. conventional pharmacotherapy										
2 wks after treatment	HAMA	Total	4	423	MD -3.42	Fixed	−4.03, −2.82	83	11.09	< 0.00001
		vs. AD	3	303	MD -3.36		−4.03, −2.69	89	9.82	< 0.00001
		vs. AX	1	120	MD -3.68		−5.07, −2.29	NA	5.17	< 0.00001
	SAS	Total (vs. AD)	1	20	MD -2.47	Fixed	−4.77, −0.17	NA	2.10	0.04
4 wks or 1 mo after treatment	HAMA	Total	5	447	MD -3.00	Fixed	−3.60, −2.40	20	9.78	< 0.00001
		vs. AD	4	327	MD -3.03		−3.70, −2.37	46	8.93	< 0.00001
		vs. AX	1	120	MD -2.86		−4.26, −1.46	NA	3.99	< 0.0001
	SAS	Total	2	220	MD -4.95	Fixed	−6.71, −3.19	77	5.52	< 0.00001
		vs. AD	1	120	MD -3.65		−5.80, −1.50	NA	3.33	0.0009
		vs. AX	1	100	MD -7.61		−10.68, −4.54	NA	4.86	< 0.00001
	TER (HAMA)	Total (vs. AD)	2	161	RR 1.23	Fixed	1.02, 1.47	0	2.21	0.03
	TER (SAS)	Total (vs. AX)	1	100	RR 1.32	Fixed	1.07, 1.64	NA	2.60	0.009
6 wks after treatment	HAMA	Total (vs. AD)	1	120	MD -3.92	Fixed	−5.82, −2.02	NA	4.04	< 0.0001
	SAS	Total (vs. AD)	1	120	MD -1.04	Fixed	−3.05, 0.97	NA	1.01	0.31
	TER (HAMA)	Total (vs. AD)	1	120	RR 0.95	Fixed	0.83, 1.07	NA	0.88	0.38
8 wks after treatment	HAMA	Total (vs. AX)	1	120	MD -2.78	Fixed	−4.16, −1.40	NA	3.95	< 0.0001
	TER (HAMA)	Total (vs. AX)	1	120	RR 1.18	Fixed	0.99, 1.42	NA	1.80	0.07
NA	Adverse events	Total	3	360	RR 0.89	Fixed	0.48, 1.66	0	0.37	0.71
		vs. AD	2	240	RR 0.63		0.22, 1.80	NA	0.87	0.37
		vs. AX	1	120	RR 1.10		0.51, 2.39	NA	0.24	0.81

Abbreviations. AD, antidepressants; AX, anxiolytics; HAMA, Hamilton anxiety rating scale; HM, herbal medicine; MD, mean difference; NA, not applicable; RR, risk ratio; SAS, Zung self-rating anxiety scale; TER, total effective rate.

3.5. Safety profile

There were 13 studies [44–49,52,54,56,58,60–62] that reported safety data. When comparing HM and conventional pharmacotherapy, the HM group was associated with significantly lower incidence of AEs (7 RCTs; RR 0.15, 95% CI 0.05 to 0.48, I^2 = 61%). One study [45] reported treatment emergent symptom scale (TESS) scores, which were significantly lower in the HM group after 2, 4, and 6 weeks of treatment (all p < 0.05). When comparing HM combined with conventional pharmacotherapy to conventional pharmacotherapy alone, there was no significant difference between the groups in the incidence of AEs (3 RCTs; RR 0.89, 95% CI 0.48 to 1.66, I^2 = 0%). In addition, there was no

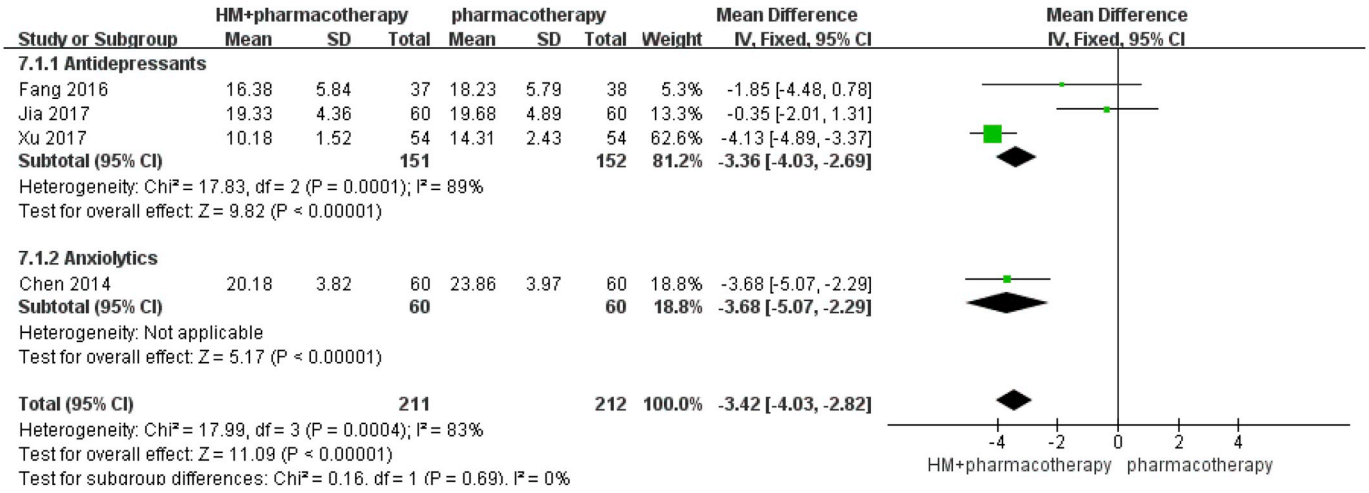

Fig. 10. Forest plot for the comparison of HM plus conventional pharmacotherapy with conventional pharmacotherapy alone. Outcome: HAMA score after 2 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

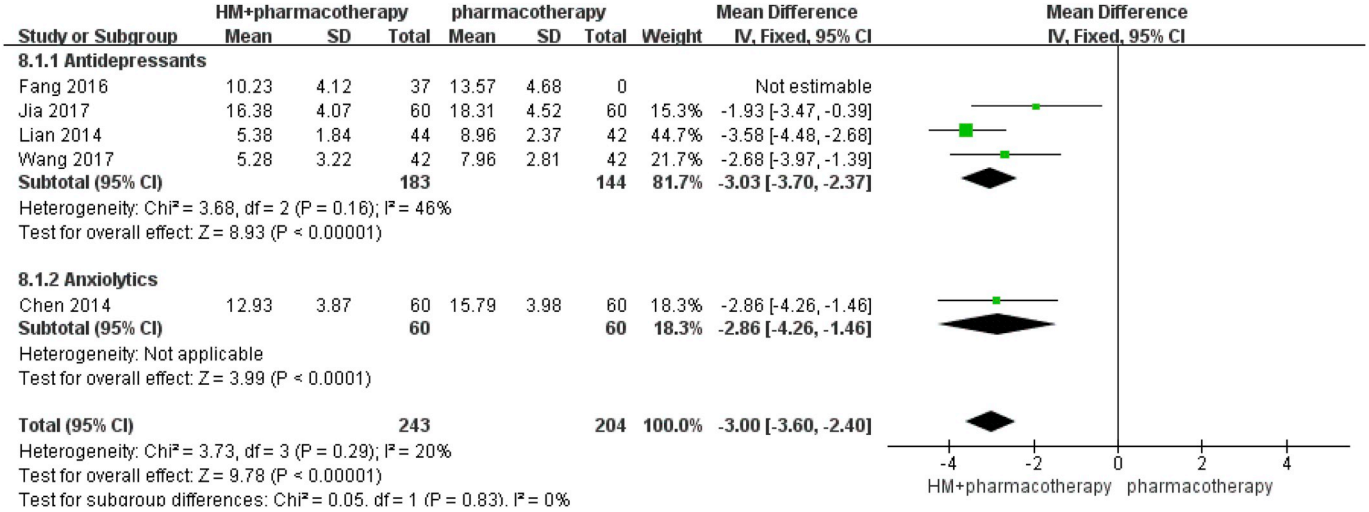

Fig. 11. Forest plot for the comparison of HM plus conventional pharmacotherapy with conventional pharmacotherapy alone. Outcome: HAMA score after 4 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

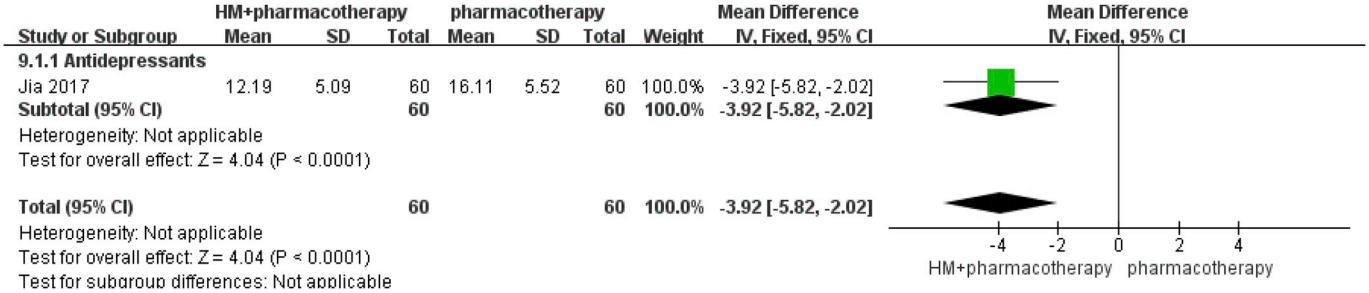

Fig. 12. Forest plot for the comparison of HM plus conventional pharmacotherapy with conventional pharmacotherapy alone. Outcome: HAMA score after 6 weeks of treatment
HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

difference in TESS score between the groups ($p > 0.05$) [58]. There were 5 studies [52,56,60–62] that analyzed blood, urine, stool, liver and kidney function, and electrocardiogram after treatment, and there were no significant abnormalities reported (Table 4).

3.6. Publication bias

Because the meta-analysis did not involve more than 10 studies, evaluation of publication bias using funnel plots was impossible.

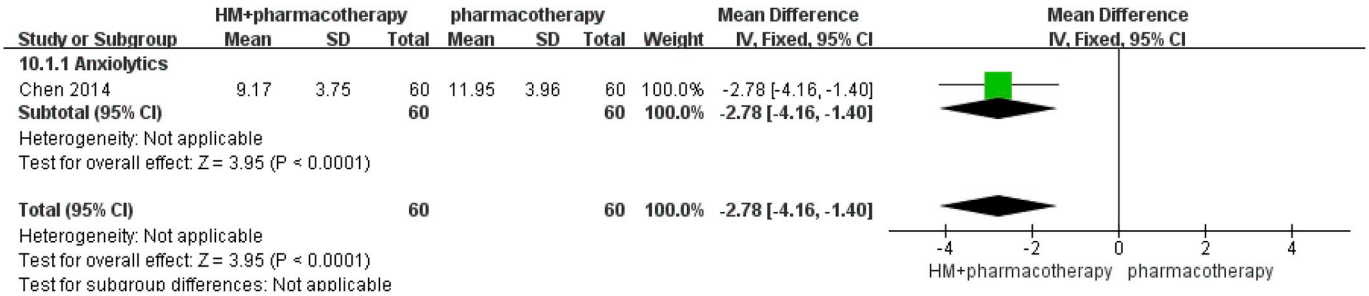

Fig. 13. Forest plot for the comparison of HM plus conventional pharmacotherapy with conventional pharmacotherapy alone. Outcome: HAMA score after 8 weeks of treatment

HAMA, Hamilton anxiety rating scale; HM, herbal medicine; PSA, post-stroke anxiety.

4. Discussion

This aim of this review was to evaluate the efficacy and safety of HM for PSA. Through comprehensive searches, 20 RCTs were included in this review.

The comparison of HM and conventional pharmacotherapy using meta-analyses revealed that the conventional pharmacotherapy group showed significantly better results in HAMA score than the HM group after 1 week of treatment. There was no significant difference between the groups after 2, 4, and 6 weeks of treatment. However, the HM group showed significantly lower HAMA scores than the conventional pharmacotherapy group after 8 weeks and 3 months of treatment. According to the subgroup analysis, when the type of conventional pharmacotherapy used was antidepressants, significantly favorable results were observed in the HM group after 8 weeks of treatment. When the type of drug used was anxiolytic, significantly favorable results were observed only after 3 months of treatment. Similarly, in the case of TER calculated from HAMA scores, the HM group showed significantly better results than the control group after 8 weeks of treatment. These results suggest that HM may have a significant advantage in reducing anxiety following long-term use, while being less advantageous than conventional pharmacotherapy in the short-term. However, contrary to expectation, mixed results were reported for neurological function, ADL, and QoL.

In the comparison between HM plus conventional pharmacotherapy and conventional pharmacotherapy alone, the combined group showed significantly better results in HAMA score after 2, 4, 6, and 8 weeks of treatment. However, in the case of SAS and TER calculated from HAMA scores, there was no significant difference between the groups after 6 and 8 weeks of treatment. Nonetheless, there was significant difference in favor of the combination treatment group after 2 and 4 weeks of treatment. These results suggest that the addition of HM to conventional pharmacotherapy may provide additional benefits in a relatively short time. In addition, combination therapy had a positive impact on improving ADL and QoL of PSA patients compared with conventional pharmacotherapy alone.

Thirteen studies [44–49,52,54,56,58,60–62] reported safety data. According to the meta-analysis of the incidence of AEs, the HM group was associated with significantly lower incidence, regardless of the type of conventional pharmacotherapy used for treatment. However, there was no significant difference in the incidence of AEs between the HM plus conventional pharmacotherapy and the conventional pharmacotherapy alone groups. These results suggest that the use of conventional pharmacotherapy may be a major cause of AEs, and that the use of HM may be relative safe. These results are consistent with the results of existing systematic reviews showing that HM is relatively safer than the conventional pharmacotherapy for treatment of anxiety [34,36]. Severe adverse reactions such as abnormalities of blood, urine, stool, liver and kidney function, and electrocardiogram were not reported in the included studies.

Of the studies included in this review, 45% used *Zizyphi Semen* and 40% used *Coptidis Rhizoma* as components of HM for PSA treatment, thereby making them the most commonly used herbs in HM. In particular, *Zizyphi Semen* with its major component, jujuboside, has been recognized for its anxiolytic effects in preclinical studies and its modulatory effects on circadian rhythm, serotonergic system [63], noradrenergic system [64], and GABAergic system [65]. Additionally, *Coptidis Rhizoma* serves as a herbal source of berberine, which is known to be a promising natural isoquinoline alkaloid for the treatment of various central nervous system disorders, including anxiety [66]. Regulatory effects on serotonergic system [67] and dopamine expression [68] have been suggested to constitute the anxiolytic mechanisms of berberine. More importantly, this alkaloid has a potent anti-inflammatory effect that is protective against stroke [69,70]. However, further studies are needed to evaluate the effects of these herbs and their active ingredients for treatment of PSA and the stroke itself.

Despite these promising results, given the low methodological quality of the studies included, some heterogeneity not resolved by subgroup analysis, and some results based on 1–2 RCTs, the strength of evidence from our results is weak. Therefore, no definite conclusions could be drawn. Nevertheless, this review is the first to systematically evaluate the efficacy and safety of HM in the treatment of PSA, and has strength in suggesting the potential clinical efficacy of HM within a specific time frame.

We hypothesized that HM could overcome the limitations of conventional synthetic drugs through the characterization of complex compound-complex targets [30] and improve stroke-related pathology as well as anxiety. However, only a small number of studies included in this review have reported neurological function, ADL, and QoL as outcome measures, and HM did not show a distinct head-to-head advantage over conventional pharmacotherapies. To explain this, we hypothesized that a longer period of treatment may be needed to be significantly improved as in HAMA. The treatment period of 1 study [53] reporting that HM significantly improved Barthel index was 3 months, while that of another study [55] that reported that HM did not improve outcome was 4 weeks. Similarly, treatment period of 1 study [46] that reported HM-induced improvement in neurological function was 8 weeks, while that of another study [54] that reported that HM did not improve function was 6 weeks. Lastly, the treatment period of the study [55] that reported that HM did not improve patient's QoL was 4 weeks. Therefore, further studies are needed to determine optimal treatment duration.

This study has the following limitations. First, the overall quality of the studies included in this review was low, which does not allow us to draw robust conclusions. In particular, these studies did not use placebo control and were not double-blinded; therefore, the results from these participants are likely to have been exposed to placebo effects. Secondly, all included studies were conducted in China, and Chinese people are generally accustomed to HM originating from TCM, so it is possible that they had positive experiences with other HM in addition to existing treatments, further contributing to placebo effects. Third, although the publication bias could not be evaluated through funnel plots, all of the included studies were conducted in China, suggesting the potential of publication bias. Fourth, since the diagnostic criteria of PSA have not yet been standardized, the studies included in our review used various diagnostic criteria and/or symptom assessment tools for participant inclusion. However, PSA is a psychiatric complication that

is often seen in stroke patients; standardized diagnosis is necessary. Finally, there were several heterogeneities between each study in the components of HM and/or treatment period, precluding the establishment of optimal HM intervention strategies.

Therefore, we suggest the following for future studies: (1) methodologically rigorous large-scale RCTs on this topic. In particular, research design using a placebo control group that can examine exact efficacy of HM is needed. In addition, a reporting system such as the Consolidated Standards of Reporting Trials (CONSORT) may be a way to improve the quality of HM clinical trials [71]. (2) Currently, HM has been used in various Asian countries such as Korea, China, Japan, and Taiwan. In particular, stroke patients are a major indication of HM. Of the studies included in current review, however, there were no published RCTs in other Asian countries except China. Therefore, relevant clinical studies in countries outside of China are needed, which will reduce potential reporting bias. (3) There is an urgent need for discussion on the standardization of PSA diagnosis. Standardizing diagnosis will help to further characterize these populations, reduce heterogeneity, and establish optimal management strategies. (4) It is necessary to discuss the optimization of HM therapeutic strategy for PSA, such as the components of HM and the treatment duration.

5. Conclusion

Currently available evidence suggests that HM or HM plus conventional pharmacotherapy may be safer and significantly improve anxiety symptoms of PSA patients in a certain time-period, compared to conventional pharmacotherapy. However, due to the limited strength of evidence, conclusions remain indefinite. Standardization of diagnostic criteria and HM treatment strategies for PSA, and relevant methodologically rigorous large-scale RCTs are needed on this topic.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

The study was conceptualized by XX. XX and XX searched and selected the trials, and extracted, analyzed, and interpreted the data. XX and XX drafted the manuscript. XX and XX helped with the study design and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.02.015.

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