Journal of Psychiatric Research 117 (2019) 74–91

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Efficacy and safety of Chinese herbal medicine for depression: A systematic review and meta-analysis of randomized controlled trials

Yong Wang, Yi-hua Shi, Zhen Xu, Huan Fu, Hua Zeng, Guo-qing Zheng*

Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, 325000, China

ARTICLE INFO

Keywords:
Chinese herbal medicine
Traditional Chinese medicine
Depression
Systematic review
Meta-analysis

ABSTRACT

Objective: To conduct a systematic review to assess the current evidence available for the effectiveness and safety of Chinese herbal medicine (CHM) for depression.

Methods: An electronic search was conducted in eight databases from inception until April 2018. Randomized controlled trials with risk of bias (RoB) score ≥ 4 according to the Cochrane RoB tool were included for analyses. The primary outcome was the severity of depression. The secondary outcomes were total effective rate (TER) and adverse events. The minimally important difference (MID) of the severity of depression was a reduction in the Hamilton Rating Scale for Depression 17 items (HAMD-17) scores by 4. RevMan 5.3 Software was used for data analyses. GRADE system was used to assess the certainty of evidence.

Results: A total of 40 eligible studies with 3549 subjects were identified. Meta-analyses showed that CHM monotherapy had better clinically effects than placebo according to HAMD-17 score (Mean Difference (MD) = −4.53, 95% CI (−5.69, −3.37), P < 0.00001; Certainty of evidence: Moderate) and TER (Risk Ratio (RR) = 2.15, 95% CI (1.61, 2.88), P < 0.00001, Certainty of evidence: Low). Meta-analyses showed that CHM was as effective as western conventional medications (WCM) in TER (RR = 0.99, 95% CI (0.95, 1.02), P = 0.41, Certainty of evidence: High) and in reducing HAMD-17 score (MD = 0.44, 95% CI (−0.11, 0.99), P = 0.12, Certainty of evidence: Moderate). Meta-analyses showed that CHM in combination with WCM was better than WCM in TER (RR = 1.16, 95% CI (1.07, 1.27), P = 0.0004, Certainty of evidence: High), while had comparable clinically effects with WCM according to HAMD-17 score (MD = −2.51, 95% CI (−3.24, −1.77), P < 0.00001, Certainty of evidence: Moderate). In additional, CHM were associated with less adverse events than WCM, and adding CHM to WCM reduced adverse events.

Conclusion: The findings of present systematic review, at least to a certain extent, provided supporting evidence for the routine use of CHM for depression.

1. Introduction

Depression, as a major public healthy challenge, substantially degrades the quality of life of patients and their families. According to reports published by the World Health Organization (WHO), an estimated 350 million people of all ages suffer from depression (WHO Global Report, 2016), and depression will be the second most prevalent cause of illness-induced disability worldwide by 2020 (Murray and Lopez, 1996).

Nowadays, the conventional antidepressants used in treating depression including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), agomelatine, bupropion, mirtazapine and vortioxetine. However, the limitations of these pharmacotherapies are still remarkable. A significant portion of patients who receive the treatment often experience high relapse rates or nonresponse to the conventional antidepressants (Trivedi et al., 2006). Additionally, side effects of the conventional antidepressants are various (Kennedy et al., 2016; Keltner et al., 2002). Dissatisfied with the conventional pharmacotherapies, depressed patients also resort to psychological treatments which include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation (BA) (Kennedy et al., 2016). However, the application of psychological treatments is limited because of high cost, requirement of participation and motivation of patients, and inadequate access to skilled providers.

Traditional Chinese medicine (TCM), a main form of complementary and alternative medicine, is an ancient and holistic approach to health and healing (Xu et al., 2013). TCM including Chinese herbal medicine (CHM), acupuncture, and other nonpharmacological

* Corresponding author.
E-mail address: gq_zheng@sohu.com (G.-q. Zheng).

https://doi.org/10.1016/j.jpsychires.2019.07.003
Received 9 January 2019; Received in revised form 8 July 2019; Accepted 12 July 2019

therapies, is still used widely in China and elsewhere in the world (Tang et al., 2008). CHM prescriptions have a better safety profile and have been used to treat depression-like symptoms for a long history (Chen and Guo, 2017). There are a number of CHM prescriptions that continue to be used contemporarily for depression and have been reported to have significant effect on this disease. Danzhi Xiaoyao san (DZXYS) showed clinical antidepressant efficacy following rigorous procedure and was published in international journal (Zhang et al., 2007a,b). Its antidepressant effects were also supported by a meta-analysis (Qin et al., 2011).

Numerous studies have indicated that CHM can generate the therapeutic effects for depression through multi-components, multi-pathways and multi-targets which are interacted with each other (Wang et al., 2017). CHM exerted variety of antidepressant effects as follows: (1) CHM could enhance monoamine transmission systems (Viana et al., 2005; Ren et al., 2006; Zhu et al., 2006). The antidepressant effect of Xiaochaihu decoction was related with the promotion of 5-hydroxytryptamine (5-HT) release or inhibition of reuptake (Su et al., 2014); Jiaotai pill can efficaciously elevated the content of 5-HT and suppressed the consumption of norepinephrine (NE) level in the prefrontal cortex in lipopolysaccharide (LPS)-treated mice (Qian et al., 2016); (2) CHM could down-regulate hypothalamic-pituitary-adrenal (HPA) axis activity (Xu et al., 2008; Ye et al., 2012). Kaixin-San can normalize the HPA axis by countering the increase in the concentrations of serumal ACTH induced by chronic mild stress (Dang et al., 2009); (3) CHM have the effect of neuroprotection. Kaixin-San could normalize neurotransmitter regulation enzymes and enhance the effect of nerve growth factor (NGF) in inducing neurite outgrowth (Zhu et al., 2016); Kaixin-san could improve serum Brain Derived Neurotrophic Factor (BDNF) expression and exert the neuroprotective and antidepressant-like effects (Hu et al., 2012); (4) CHM exert the effect of anti-inflammation and immunity regulation. Jiaotai pill could exert the effect of anti-inflammation via normalizing the levels of serum tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) elevated by the pretreatment with lipopolysaccharide (Qian et al., 2016). (5) CHM have the effect of antioxidant. 20 (S)-protopanaxadiol could reduce brain oxidative stress via elevating the superoxide dismutase (SOD) level and reducing Malondialdehyde (MDA) level in the brain of rats (Xu et al., 2010) (Figure S1).

Evidence-based medicine (EBM) is a strategy for the critical evaluation and uniform comparison of clinical trial data with conclusions according to predetermined efficacy criteria. Owing to the significant health risk of depression and the side-effects of conventional antidepressants, there have been a number of controlled studies over the past decade to evaluate the efficacy and safety of CHM for depression. Two previous systematic reviews addressing the efficacy and safety of CHM for depression has been published in 2014 by Yeung et al. (2014) and in 2015 by Yi et al. (2015), respectively. However, the review conducted by Yeung et al. (2014) included not only randomized trials but also quasi-randomized clinical trials. The quality of studies included in the review conducted by Yi R et al. (2015) was low, and most of the included studies had high risk of bias during conducting and reporting. Additionally, a number of high-quality controlled studies on CHM for depression were published after these two systematic reviews. Thus, it is worth conducting an updated systematic review of randomized controlled trials (RCTs) assessing the efficacy and safety of CHM for depression after the strict exclusion of “not-so-good” studies as indicated by the Cochrane group guidelines for clinical reviews (Chan et al., 2012).

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Moher et al., 2010).

2.1. Database and search strategies

We electronically searched four international databases (PubMed, EMBASE, Cochrane library and Web of Science) and four Chinese databases (VIP information database, Chinese National Knowledge Infrastructure (CNKI), WanFang Data Information Site and Chinese Biomedical Literature Database) from inception to April 2018. Conference proceedings, dissertations, and references of previously published systematic reviews were also searched manually for additional relevant studies. The search strategies of all databases were included in Table S1.

2.2. Eligibility criteria

2.2.1. Types of studies

Only RCTs for assessing the efficacy and safety of CHM for depression were included, regardless of language, blinding or publication type. Quasi-RCTs studies, in which participants were allocated according to the date of birth, hospital record number, date of admission or identity (ID) number, were excluded.

2.2.2. Types of participants

All participants with a diagnosis of primary depression met one of the following criteria: (i) The Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV) (Do, 1994); (ii) The International Classification of Disease 10th revision (ICD-10) (Saxena and Saraceno, 1993); (iii) Chinese Classification of Mental Disorders (CCMD-3) (Psychological Branch of Chinese Medical Association, 2001). Other diagnostic criteria with comparable definitions were also used.

2.2.3. Types of interventions

CHM monotherapy or in combination with western conventional medications (WCM) or plus placebo of WCM was used in the treatment groups. Both Chinese patent medicines and decoction of herbal medicines were included in CHM. There is no limitation on form, dose, administration methods of CHM. The comparator was one of the followings: WCM, placebo of CHM, or WCM plus placebo of CHM. The included studies should include one of the following comparisons: (1) CHM vs. placebo; (2) CHM vs. WCM; (3) CHM plus WCM vs. WCM; (4) CHM plus placebo WCM vs. placebo CHM plus WCM; (5) CHM plus WCM vs. placebo CHM plus WCM.

2.2.4. Types of outcome measures

The primary outcome was the severity of depression, which was assessed by different instruments including the Hamilton Rating Scale for Depression (17-items) (HAMD-17) (Hamilton, 1960), the Hamilton Rating Scale for Depression (24-items) (HAMD-24) (Bech et al., 2015), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery, 1979), Self-rating Depression Scale (SDS) (Zung and Gianturco, 1971) and Clinical Global Impression (CGI) rating scales (Guy, 1976). The HAMD-17 scale scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression (Zimmerman et al., 2013). The HAMD-24 scale consisted of 24 items with each one scores 0 to 4 or 0 to 2. The maximum score of HAMD-24 is 76 (Bech et al., 2015). The MADRS consists of ten rating items; each item is scored on a 0–6 scale, with 6 indicating maximum symptom severity; the total score is calculated by summing the ten item scores (Davidson et al., 1986); it was built on a large database of depressed patients and was designed to evaluate change (Khan et al., 2002). SDS consists of 20 questions which were scored as 1–4 points individually, resulting in 20–80 raw score, subsequently standard score was calculated by int (1.25*raw score) (Zung and Gianturco, 1971).The CGI rating scales are measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders; it consisted of three parts including the Clinical Global Impression-Severity scale (CGI-S),

the Clinical Global Impression-Improvement scale (CGI-I) and the Clinical Global Impression-Efficacy Index (CGI-E) (Guy, 1976).

The second outcomes were the total effective rate (TER) and adverse events. The clinical response was assessed based on reduction in HAMD score for depression as follows: (i) recovery: a ≥75% reduction; (ii) markedly effective: a ≥50% reduction; (iii) improvement: a ≥25% reduction; (iv) ineffective: a < 25% reduction; TER was defined as the proportion of subjects with a baseline-to-endpoint reduction in HAMD score of ≥25%. All of the outcome measurements were conducted at the endpoint of treatment by the researchers in each trial.

2.2.5. Study selection and data collection

Two investigators individually selected potential references by screening their title and abstract. For potentially useful studies, full articles were obtained. The two investigators read the whole articles independently and made final decision on including the articles or not. For each study, we extracted the following information: name of the first author and year of publication, types of depressive disorder, diagnosis criteria, study design, sample size, gender composition, mean age, duration of disease, interventions, doses of medications, duration of treatment, follow-up, main outcome measures and its corresponding p value, and adverse events. If the necessary information or data were expressed graphically or not reported in articles, we tried to contact the original author for further information by phone or email or calculated by ourselves if available. Any disagreement between the two investigators was resolved though discussion with the third author (G-Q Z).

2.2.6. Risk of bias

The methodological quality of RCTs was assessed using the 7 criteria recommended by the Cochrane Collaboration (Higgins et al., 2018). The 7 components were as follows: A. adequate sequence generation; B. concealment of allocation; C. blinding (participants and personnel); D. blinding (outcome assessor); E. incomplete outcome data addressed (ITT analysis); F. selective reporting; G. other biases. Each of these indicators was categorized as high risk of bias, low risk of bias and unclear. For each item, a score of 1 or 0 was given depending upon whether the study provided adequate information in the relevant domain. Only RCTs with a cumulative score of at least 4 out of 7 for the Cochrane RoB tool domains were included in our systematic review (Li et al., 2015). Adequate sequence generation was the certain key criteria which must achieve status as low risk of bias. Disagreements were settled by discussion with the corresponding author (G-Q Z).

2.2.7. Grading the certainty of evidence

Using the updated GRADE system (Guyatt et al., 2013), we graded the certainty of evidence as follows: high, moderate, low and very low. The low and very low of certainty of evidence means that we have little or very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Any discrepancy about grading the certainty of evidence was resolved though discussion with the corresponding author (G-Q Z).

2.2.8. Categories of the CHM and WCM

We recorded the specific herbs used in the CHM formulae, and categorized the CHM by the main components or the combinations of main components. The frequency of use of specific herbs was calculated, and those with highly frequent usage were described in detail. We also categorized the WCM by different antidepressant effectiveness.

2.2.9. Data synthesis and analysis

Across outcomes were combined through converting other units into the unit of the most commonly used instrument (Thorlund et al., 2011). Units of HAMD-24, MADRS, SDS and CGI were converted into that of HAMD-17. The minimally important difference (MID) of HAMD-17 was a reduction in its total scores by 4. The software Cochrane Collaboration Review Manage (RevMan 5.3) was used to summary the data of eligible studies and performed meta-analysis. Weighted mean difference (WMD) was adopted to analyze the continuous data whereas risk ratio (RR) was adopted to analyze the dichotomous data. Heterogeneity among trials was assessed using the standard chi-square test and I^2 statistic. Fixed effect models or random effect models were used to analyze pooled effects depending on heterogeneity. A fixed effect model was applied only when no obvious heterogeneity exists ($P > 0.1$, $I^2 < 50\%$), otherwise the random effect model was a more plausible match. Possible sources of heterogeneity were explored by subsequent sensitivity analyses. Probability value $P < 0.05$ indicated that the differences between trial groups and control groups were statistically significant. WMD ≥ MID indicated that the differences between trial and control groups achieved an important difference for many patients.

3. Results

3.1. Description of studies

A total of 24766 studies were retrieved, of which 14933 studies were excluded because of duplicates. After screening the title and abstract of remaining studies, 9203 records were excluded; among which 3324 studies were case reports or reviews, 4074 were not clinical trials and 1805 were irrelevant with the efficacy of CHM for depression. By reading the full text, 587 studies were excluded, including 236 studies that were not RCTs or not real RCTs, 92 that were master or doctoral thesis, 106 that were high risk of bias studies with Cochrane score < 4, 67 that only reported other types of depression and 89 that contained other CAM therapy such as acupuncture. Eventually, 40 studies (Xiu et al., 2010; Bao et al., 2011; Chen et al., 2009; Huang et al., 2016; Li et al., 2013, 2014; Liu et al., 2010, 2013a, 2013b; Luo et al., 2006; Guo et al., 2009; Shen et al., 2004; Shu and Zhang, 2012; Song et al., 2011; Shi et al., 2013; Wu et al., 2010, 2015; Xian et al., 2008; Ye et al., 2014; Zhu et al., 2014, 2016; Zhang et al., 2007a, 2007b, 2012, 2015; Gao and Lei, 2012; Gao et al., 2013; Huo and Fu, 2015; Huo et al., 2008; Jiang et al., 2015; Mao et al., 2013; Tong et al., 2016; Wei and Wei, 2011; Wang et al., 2010, 2016; Yang et al., 2012; Yu and Wu, 2013; Yi et al., 2010; Zhang and Meng, 2017; Zhang and Zhu, 2010) with Cochrane RoB score ≥4 were included in the present study. The process of screening is presented in a PRISMA flow chart (Fig. 1).

3.2. Study characteristics

The characteristics of the included 40 studies with 43 comparisons were summarized in Table S2. All eligible studies were conducted in China and 3 of them published in English. There were 3 trials with three arms, 37 trials with two arms. CCMD-3, DSM-IV and ICD-10 were the three main diagnostic criteria for depression. The types of depression in the present study included mild to moderate depression, major depression, unipolar depression, bipolar depression, treatment-resistant depression, first-episode depression, and depression in elderly. The sample size of the included studies ranged from 18 to 448, enrolling a total of 3549 participants, including 1772 patients in treatment groups and 1777 patients serving as controls. The age of the participants ranged from 30 to 72 years old. Three studies (Xiu et al., 2010; Liu et al., 2013a; Zhang et al., 2007b) with 4 comparisons compared CHM therapies alone with placebo, and 20 studies (Gao and Lei, 2012; Gao et al., 2013; Huo and Fu, 2015; Huo et al., 2008; Jiang et al., 2015; Liu et al., 2013b; Mao et al., 2013; Wu et al., 2015; Tong et al., 2016; Wei and Wei, 2011; Wang et al., 2010, 2016; Yang et al., 2012; Yu and Wu, 2013; Yi et al., 2010; Zhu et al., 2016; Zhang et al., 2007a, 2015; Zhang and Meng, 2017; Zhang and Zhu, 2010) with 21 comparisons compared CHM plus WCM with WCM alone. Comparisons of CHM therapies versus WCM therapies were conducted in 18 studies (Bao et al., 2011; Chen et al., 2009; Huang et al., 2016; Li et al., 2013, 2014; Liu et al.,

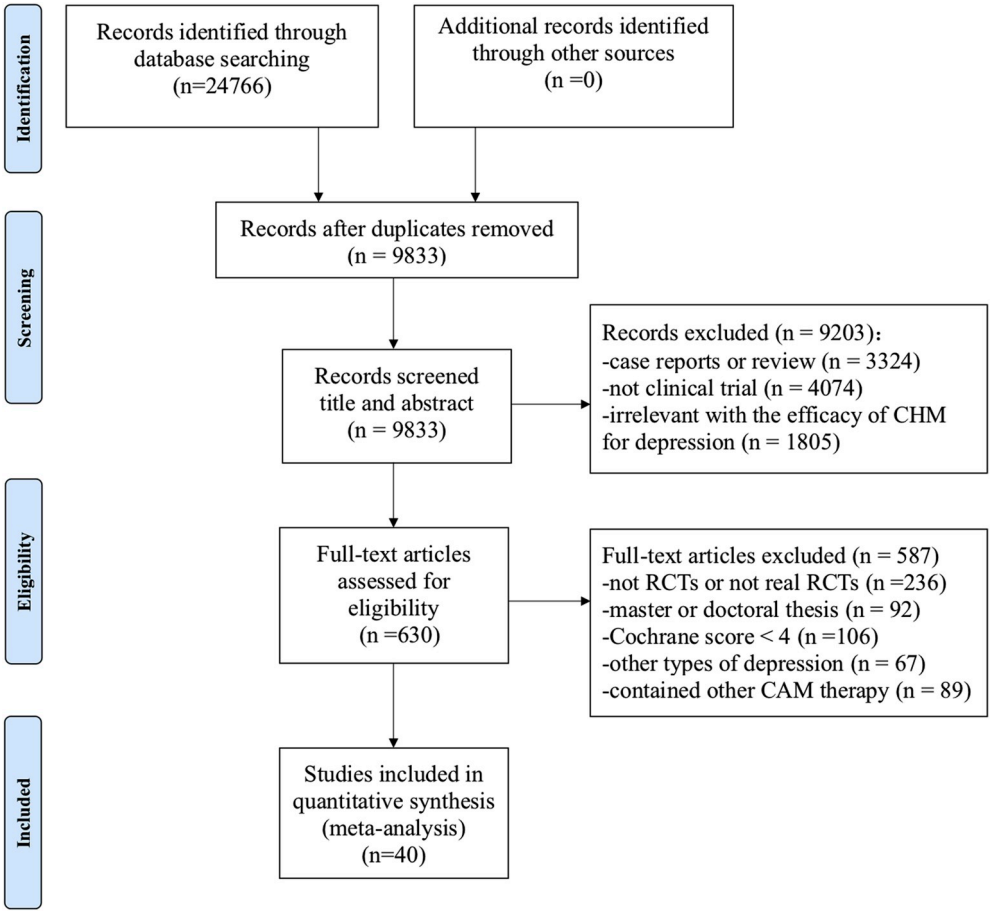

Fig. 1. Prisma 2009 flow diagram.

2010, 2013a; Luo et al., 2006; Guo et al., 2009; Shen et al., 2004; Shu and Zhang, 2012; Song et al., 2011; Shi et al., 2013; Wu et al., 2010; Xian et al., 2008; Ye et al., 2014; Zhu et al., 2014; Zhang et al., 2012). The CHM were administered orally in tablets, capsules, granules, oral liquid, or decoction. The treatment duration ranged from 1 week to 8 weeks, and the duration with 6 weeks was used most widely. Three studies mentioned the length of follow-up, which lasted from 12 weeks to 6 months.

3.3. Risk of bias

RoB assessment information is presented in Table 1. Of the 40 included studies, 1met seven Cochrane criteria (Wu et al., 2015), 4 met six (Luo et al., 2006; Zhu et al., 2016; Zhang et al., 2007a, 2007b), 5 met five (Xian et al., 2008; Zhang et al., 2012; Mao et al., 2013; Yi et al., 2010; Zhang and Zhu, 2010), and 31 met four (Xiu et al., 2010; Bao et al., 2011; Chen et al., 2009; Huang et al., 2016; Li et al., 2013, 2014; Liu et al., 2010, 2013a, 2013b; Guo et al., 2009; Shen et al., 2004; Shu and Zhang, 2012; Song et al., 2011; Shi et al., 2013; Wu et al., 2010; Ye et al., 2014; Zhu et al., 2014; Gao and Lei, 2012; Gao et al., 2013; Huo and Fu, 2015; Huo et al., 2008; Jiang et al., 2015; Tong et al., 2016; Wei and Wei, 2011; Wang et al., 2010, 2016; Yang et al., 2012; Yu and Wu, 2013; Zhang et al., 2015; Zhang and Meng, 2017). All 40 included studies had random allocation using a random number table. Only two studies (Xian et al., 2008; Wu et al., 2015) mentioned allocation concealment with sealed envelopes. Eight studies (Luo et al., 2006; Zhang et al., 2007a, 2007b, 2012; Wu et al., 2015; Yi et al., 2010; Zhu et al., 2016; Zhang and Zhu, 2010) mentioned the blinding of participants and investigator, and five study (Luo et al., 2006; Ye et al., 2014; Mao et al., 2013; Wu et al., 2015; Zhang et al., 2007a; Zhang et al., 2007b) mentioned the blinding of outcome assessment. All studies either had complete data or had dropouts with adequate explanation and appropriate methods to treat missing data. Only one study (Ye et al., 2014) was at unclear RoB of selective reporting. All studies had low risk of other bias, which included funding bias, conflict of interest, and incomparable baseline characteristics between the groups. Funding bias means that the research was funded by relevant stakeholders, such as drug companies. In general, most of the 40 trials were deemed to have a relatively moderate risk.

3.4. Categories of the CHM and WCM

According to the evidence of effectiveness from the mechanism studies, we categorized the CHM by the main components or the combinations of main components (Table 2). The CHM fall into 10 categories as follows: (1) CHM_1 with Chaihu (*Radix Bupleuri*) as the main component (studies 1, 8, 16, 23–24, 28–29, 33–34, 36, 38–40) (Kwon et al., 2010; Wang et al., 2015); (2) CHM_2 with Guanyejinsitao (*Hypericum perfoliatum*) as the main component (studies 4, 5, 12–13, 15, 17, 22) (Do Rego et al., 2007); (3) CHM_3 with Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*) as the main components (9, 11, 20–21, 30–32) (Zhang et al., 2018; Wang et al., 2016); (4) CHM_4 with Renshen (*Radix Ginseng*) & Fuling (*Poria*) as the main components (studies 2, 19, 37) (Chen, 2013); (5) CHM_5 with Zhimu (*Rhizoma Anemarrhenae*) & Baihe (*Bulbus Lilii*) as the main components (studies 7, 10, 25) (Li et al., 2015); (6) CHM_6 with Huangqi (*Radix Astragali seu Hedysari*) & Longyanrou (*Arillus Longan)* as the main components (studies 6, 18) (Ji et al., 2009); (7) CHM_7 with Xiangfu (*Rhizoma Cyperi*) as the main component (studies 27, 35) (Ren and Chen, 2017); (8) CHM_8 with Hehuanhua (*Flos Albiziae*) as the main component (study 14) (Kim et al., 2007); (9)

Table 1
Risk of bias.

No.	First author, year	7-item criteria							
		A	B	C	D	E	F	G	T
1	Xiu lijuan (2010)	+	?	?	?	+	+	+	4
2	Bao zuxiao (2011)	+	?	?	?	+	+	+	4
3	Chen shaomei (2009)	+	?	?	?	+	+	+	4
4	Huang jingliang (2016)	+	?	?	?	+	+	+	4
5	Li yongqiang (2013)	+	?	?	?	+	+	+	4
6	Li haicong (2014)	+	?	?	?	+	+	+	4
7	Liu hongmin (2010)	+	?	?	?	+	+	+	4
8	Luo hechun (2006)	+	?	+	+	+	+	+	6
9	Liu erjun 2013	+	?	?	?	+	+	+	4
10	Guo zhouke (2009)	+	?	?	?	+	+	+	4
11	Shen zhenming (2004)	+	?	?	?	+	+	+	4
12	Shu min (2012)	+	?	?	?	+	+	+	4
13	Song baohua (2011)	+	?	?	?	+	+	+	4
14	Shi xueli (2013)	+	?	?	?	+	+	+	4
15	Wu liming (2010)	+	?	?	?	+	+	+	4
16	Xian hui (2008)	+	+	?	?	+	+	+	5
17	Ye jianfei (2014)	+	?	?	+	+	?	+	4
18	Zhu chenjun (2014)	+	?	?	?	+	+	+	4
19	Zhang ye (2012)	+	?	+	?	+	+	+	5
20	Gao xueqing (2012)	+	?	?	?	+	+	+	4
21	Gao xinli (2013)	+	?	?	?	+	+	+	4
22	Huo jun (2015)	+	?	?	?	+	+	+	4
23	Huo jun (2008)	+	?	?	?	+	+	+	4
24	Jiang jianxin (2015)	+	?	?	?	+	+	+	4
25	Liu jie 2013	+	?	?	?	+	+	+	4
26	Mao zhixia (2013)	+	?	?	+	+	+	+	5
27	Wu ruyan (2015)	+	+	+	+	+	+	+	7
28	Tong zishun (2016)	+	?	?	?	+	+	+	4
29	Wei qing (2011)	+	?	?	?	+	+	+	4
30	Wang yazhen 2016	+	?	?	?	+	+	+	4
31	Wang xinfa (2010)	+	?	?	?	+	+	+	4
32	Yang qiuxia (2012)	+	?	?	?	+	+	+	4
33	Yu yongqing (2013)	+	?	?	?	+	+	+	4
34	Yi zhenghui (2010)	+	?	+	?	+	+	+	5
35	Zhu dandan (2016)	+	?	+	+	+	+	+	6
36	Zhang xinping (2015)	+	?	?	?	+	+	+	4
37	Zhang qingqing (2017)	+	?	?	?	+	+	+	4
38	Zhang jianming (2010)	+	?	+	?	+	+	+	5
39	Zhang Zhang-Jin (2007a)	+	?	+	+	+	+	+	6
40	Zhang Zhang-Jin (2007b)	+	?	+	+	+	+	+	6

A to G, the 7-item criteria. A, adequate sequence generation; B, concealment of allocation; C, Blinding of participants and personnel; D, Blinding of out-come assessment; E, Incomplete out-come data; F, Selective reporting; G, Other bias; +: low risk of bias, −: high risk of bias, ? unclear risk of bias.

CHM_9 with Shengdihuang (*Radix Rehmanniae Recens*) as the main component (study 26) (Wang et al., 2014); (10) CHM_{10} with Yuanbaocao (*Hypericum sampsonii Hance*) as the main component (study 3) (Guo et al., 2005). We categorized the WCM by different antidepressant effectiveness (Bouchard et al., 1987; Li et al., 2008; Kroenke et al., 2001; Szegedi et al., 1997; François et al., 2003; Sørensen et al., 2007; Demyttenaere et al., 2005). The WCM fall into 3 categories as follows: (1) WCM_1 including fluoxetine, paroxetine, sertraline, maprotiline, citalopram and deanxit. (2) WCM_2 including escitalopram and venlafaxine (3) WCM_3 including carbamazepine.

3.5. Effectiveness

3.5.1. CHM vs. placebo

Pooled analysis of 3 studies (Xiu et al., 2010; Liu et al., 2013a; Zhang et al., 2007b) indicated that CHM had significant greater clinically effects than placebo according to HAMD-17 (MID = 4, MD = −4.53, 95% CI (−5.69, −3.37), P < 0.00001, I^2 = 0%, Fig. 2A; Certainty of evidence: Moderate, Table 3) and TER (RR = 2.15, 95% CI (1.61, 2.88), P < 0.00001, I^2 = 0%, Certainty of evidence: Low, Fig. 3A).

3.5.2. CHM_1 vs. placebo

Pooled analysis of 2 studies (Xiu et al., 2010; Zhang et al., 2007b) indicated that CHM_1 had significant greater clinically effects than placebo according to HAMD-17 (MID = 4; MD = −4.43, 95% CI (−5.87, −2.99), P < 0.00001, I^2 = 0%, Certainty of evidence: Moderate, Fig. 4A). One study (Xiu et al., 2010) indicated a significant effect of CHM_1 for improving TER compared with placebo (RR = 1.91, 95% CI (1.19, 3.05), P = 0.007, Certainty of evidence: Low).

3.5.3. CHM_3 vs. placebo

One study (Liu et al., 2013a) showed a significant effect of CHM_3 for improving HAMD-17 (MID = 4, MD = −4.71, 95% CI (−6.65, −2.77), P < 0.00001, Certainty of evidence: Moderate, Table 3) and TER (RR = 2.32, 95% CI (1.60, 3.38), P < 0.0001 Certainty of evidence: Low, Table 3) compared with placebo.

3.5.4. CHM + placebo WCM vs. placebo CHM + WCM

Luo et al. (2006) compared the effect of Danzhi Xiaoyao powder with Maprotiline in improving the severity of depression and anxiety. Chaihu (*Radix Bupleuri*) is the main component of Danzhi Xiaoyao powder. The data indicated that there was no significant group difference between CHM_1 plus placebo WCM_1 and placebo CHM_1 plus WCM_1 in HAMD-17 (MID = 4, MD = 2.33, 95% CI (−1.93, 6.59), P = 0.28, Certainty of evidence: High).

3.5.5. CHM vs. WCM

A total of 17 studies (Bao et al., 2011; Chen et al., 2009; Huang et al., 2016; Li et al., 2013, 2014; Liu et al., 2010, 2013a; Guo et al., 2009; Shen et al., 2004; Shu and Zhang, 2012; Song et al., 2011; Shi et al., 2013; Wu et al., 2010; Xian et al., 2008; Ye et al., 2014; Zhu et al., 2014; Zhang et al., 2012) compared the antidepressant effects of CHM with that of WCM. Pooled analysis of 14 studies (Chen et al., 2009; Huang et al., 2016; Li et al., 2013, 2014; Liu et al., 2010, 2013a; Guo et al., 2009; Shen et al., 2004; Shu and Zhang, 2012; Song et al., 2011; Wu et al., 2010; Ye et al., 2014; Zhu et al., 2014; Zhang et al., 2012) indicated that there was no significant group difference between CHM and WCM in terms of HAMD-17 (MID = 4, MD = 0.44, 95% CI (−0.11, 0.99), P = 0.12, I^2 = 56%, Fig. 2B; Certainty of evidence: Moderate, Table 3). Pooled analysis of 17 studies indicated that there was no significant group difference between CHM and WCM in terms of TER (RR = 0.99, 95% CI (0.95, 1.02), P = 0.41, I^2 = 0%, Fig. 3B; Certainty of evidence: High, Table 3).

3.5.6. CHM_4 vs. WCM_1

Two studies (Bao et al., 2011; Zhang et al., 2012) indicated that there was no difference in the HAMD-17 between CHM_4 and WCM_1 treatment groups (P > 0.05). Pooled analysis indicated that there was no significant group difference between CHM_4 and WCM_1 in terms of TER (RR = 1.06, 95% CI (0.92, 1.21), P = 0.43, I^2 = 0%, Fig. 5A; Certainty of evidence: Moderate, Table 3).

3.5.7. CHM_{10} vs. WCM_1

One study (Chen et al., 2009) showed there was no significant difference between CHM_{10} and WCM_1 in terms of HAMD-17 (MID = 4, MD = 0.79, 95% CI (−2.06, 3.64), P = 0.59, Certainty of evidence: High, Table 3) and TER (RR = 0.98, 95% CI (0.90–1.06), P = 0.58, Certainty of evidence: Moderate, Table 3).

3.5.8. CHM_2 vs. WCM_1

Pooled analysis of 6 studies (Huang et al., 2016; Li et al., 2013; Shu and Zhang, 2012; Song et al., 2011; Wu et al., 2010; Ye et al., 2014) indicated no group difference between CHM_2 and WCM_1 in terms of HAMD-17 (MID = 4, MD = 0.09, 95% CI (−0.33, 0.52), P = 0.66, I^2 = 0%, Fig. 4B; Certainty of evidence: High, Table 3) and TER (RR = 0.98, 95% CI (0.94, 1.03), P = 0.42, I^2 = 0%, Fig. 5B; Certainty of evidence: High, Table 3).

Table 2
Categories of the CHM in included studies.

Chinese herbal formula	Content	Main components	Study (NO.)	Categories	N/40	Evidence of effectiveness
Xiaoyao powder or its modification	Chaihu (*Radix Bupleuri*), Huangqin (*Radix Scutellariae*), Shengjiang (*Rhizoma Zingiberis Recens*), Danggui (*Radix Angelicae Sinensis*), Zhizi (*Fructus Gardeniae*), Mudan (*Cortex Moutan Radici*), Shaoyao (*Paeonia lactiflora Pall*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Fulin (*Poria*), Bohe (*Herba Menthae*), Gancao (*Radix Glycyrrhizae*).	Chaihu (*Radix Bupleuri*)	8, 16, 23, 24, 28, 33, 34, 36, 38, 39, 40	CHM_1	11	Kwon et al. (2010); Wang et al. (2015)
Shugan Jieyu capsule	Guanyejinsitao (*Hypericum perforatum*), Ciwujia (*Radix et Caulis Acanthopanacis Senticosi*).	Guanyejinsitao (*Hypericum perforatum*)	4, 5, 12, 13, 15, 17, 22	CHM_2	7	Do Rego et al. (2007)
Jieyu pill	Chaihu (*Radix Bupleuri*), Baishao (*Radix Paeoniae Alba*), Danggui (*Radix Angelicae Sinensis*), Yujin (*Radix Curcumae*), Fulin (*Poria*), Baihe (*Bulbus Lilii*), Hehuanpi (*Cortex Albiziae*), Gancao (*Radix Glycyrrhizae*), Xiaomai (*Triticum aestivum L*), Dazao (*Fructus Jujubae*).	Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*)	11, 31, 32	CHM_3	3	Hong-Cai et al., 2018; Wang et al. (2016)
Yu-Le decoction	Zhimu (*Rhizoma Anemarrhenae*), Baihe (*Bulbus Lilii*), Maidong (*Radix Ophiopogonis*), Yujin (*Radix Curcumae*), Xiangfu (*Rhizoma Cyperi*), Baishao (*Radix Paeoniae Alba*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Suanzaoren (*Semen Ziziphi Spinosae*), Baiziren (*Semen Platycladi*), Yejiaoteng (*Caulis Polygoni multiflori*), Zhenzhumu (*Concha Margaritifera*), Yuanzhi (*Radix Polygalae*).	Zhimu (*Rhizoma Anemarrhenae*) & Baihe (*Bulbus Lilii*)	7, 10, 25	CHM_5	3	Li et al. (2015)
Yueju pill	Xiangfu (*Rhizoma Cyperi*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Zhizi (*Fructus Gardeniae*), Cangzhu (*Rhizoma Atractylodis*), Shenqu (*Massa Medicata Fermentata*).	Xiangfu (*Rhizoma Cyperi*)	27, 35	CHM_7	2	Ren & Chen (2017)
Modified Guipi decoction	Baizhu (*Rhizoma Atractylodis Macrocephalae*), Fulin (*Poria*), Dangshen (*Radix Codonopsis*), Huangqi (*Radix Astragali seu Hedysari*), Longyanrou (*Arillus Longan*), Suanzaoren (*Semen Ziziphi Spinosae*), Muxiang (*Radix Aucklandiae*), Danggui (*Radix Angelicae Sinensis*), Yuanzhi (*Radix Polygalae*), Dazao (*Fructus Jujubae*), Gancao (*Radix Glycyrrhizae*).	Huangqi (*Radix Astragali seu Hedysari*) & Longyanrou (*Arillus Longan*)	6, 18	CHM_6	2	Ying et al., 2009
Bailongjieyu granule	Chaihu (*Radix Bupleuri*), Fabanxia (*Rhizoma Pinelliae Preparatum*), Baishao (*Radix Paeoniae Alba*), Shichangpu (*Rhizoma Acori Tatarinowi*), Chenpi (*Pericarpium Citri Reticulatae*), Danggui (*Radix Angelicae Sinensis*).	Chaihu (*Radix Bupleuri*)	1	CHM_1	1	Kwon et al. (2010); Wang et al. (2015)
Kaixin powder	Shichangpu (*Rhizoma Acori Tatarinowi*), Yuanzhi (*Radix Polygalae*), Renshen (*Radix Ginseng*), Fulin (*Poria*).	Renshen (*Radix Ginseng*) & Fulin (*Poria*)	2	CHM_4	1	Chen (2013)
Wangyou prescription	Yuanbaocao (*Hypericum sampsonii Hance*), Shichangpu (*Rhizoma Acori Tatarinowi*), Bingpian (*Borneolum Syntheticum*).	Yuanbaocao (*Hypericum sampsonii Hance*)	3	CHM_{10}	1	Guo et al. (2005)
Shugan Jianwei Anshen decotion	Chaihu (*Radix Bupleuri*), Baishao (*Radix Paeoniae Alba*), Shichangpu (*Rhizoma Acori Tatarinowi*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Chenpi (*Pericarpium Citri Reticulatae*), Qingbanxia (*Rhizoma Pinelliae Preparata*), Xiangfu (*Rhizoma Cyperi*), Suanzaoren (*Semen Ziziphi Spinosae*), Shouwuteng (*Caulis Polygoni Multiflori*), Hehuanpi (*Cortex Albiziae*), Cishi (*Magnetitum*), Jineijin (*Endothelium Corneum Gigeriae Galli*), Sharen (*Fructus Amomi Villosi*).	Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*)	9	CHM_3	1	Hong-Cai et al., 2018; Wang et al. (2016)
Hehuanhua decoction	Hehuanhua (*Flos Albiziae*)	Hehuanhua (*Flos Albiziae*)	14	CHM_8	1	Kim et al. (2007)
Qishen Fukang capsule	Huangqi (*Radix Astragali seu Hedysari*), Renshen (*Radix Ginseng*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Tianma (Rhizoma Gastrodiae), Gouqizi (*Fructus Lycii*), Shudihuang (*Radix Rehmanniae Preparata*), Baishao (*Radix Paeoniae Alba*), Ejiao (*Colla Corii Asini*), Yinyanghuo (*Herba Epimedii*), Suanzaoren (*Semen Ziziphi Spinosae*), Yuanzhi (*Radix Polygalae*), Fulin (*Poria*).	Renshen (*Radix Ginseng*) & Fulin (*Poria*)	19	CHM_4	1	Chen (2013)
Jieyu Ningxin decoction	Chaihu (*Radix Bupleuri*), Yujin (*Radix Curcumae*), Baishao (*Radix Paeoniae Alba*), Hehuanpi (*Cortex Albiziae*), Baihe (*Bulbus Lilii*), Shengdihuang (*Radix Rehmanniae Recens*), Danshen (*Radix Salviae Miltiorrhizae*), Zhenzhumu (*Concha Margaritifera*), Gancao (*Radix Glycyrrhizae*).	Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*)	20	CHM_3	1	Hong-Cai et al., 2018; Wang et al. (2016)
Shugan Jieyu decoction	Chaihu (*Radix Bupleuri*), Chenpi (*Pericarpium Citri Reticulatae*), Zhike (*Fructus Aurantii*), Xiangfu (*Rhizoma Cyperi*), Danggui (*Radix Angelicae Sinensis*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Baishao (*Radix Paeoniae Alba*), Chishao (*Radix Paeoniae Rubra*), Fabanxia (*Rhizoma Pinelliae Preparatum*), Fulin (*Poria*), Shichangpu (*Rhizoma Acori Tatarinowi*), Yujin (*Radix Curcumae*), Suanzaoren (*Semen Ziziphi Spinosae*), Zhizi (*Fructus Gardeniae*), Yuanzhi (*Radix Polygalae*), Gancao (*Radix Glycyrrhizae*).	Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*)	21	CHM_3	1	Hong-Cai et al., 2018; Wang et al. (2016)
Yangyin-Qinggan decoction	Shengdihuang (*Radix Rehmanniae Recens*), Maidong (*Radix Ophiopogonis*), Xuanshen (Radix Scrophulariae), Mudanpi (*Cortex Moutan Radicis*), Yujin (*Radix Curcumae*),	Shengdihuang (*Radix Rehmanniae Recens*)	26	CHM_9	1	Wang et al. (2014)

(*continued on next page*)

Table 2 (*continued*)

Chinese herbal formula	Content	Main components	Study (NO.)	Categories	N/40	Evidence of effectiveness
Shugan Bushen Jieyu Decoction	Foshou (*Fructus Citri Sarcodactylis*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Xiangfu (*Rhizoma Cyperi*), Baishao (*Radix Paeoniae Alba*), Danggui (*Radix Angelicae Sinensis*), Chaihu (*Radix Bupleuri*), Chenpi (*Pericarpium Citri Reticulatae*), Yejiaoteng (*Caulis Polygoni multiflori*), Hehuanhua (*Flos Albiziae*), Gancao (*Radix Glycyrrhizae*).	Chaihu (*Radix Bupleuri*)	29	CHM_1	1	
Chinese medicinal formulae	Baishao (*Radix Paeoniae Alba*), Chaihu (*Radix Bupleuri*), Shichangpu (*Rhizoma Acori Tatarinowi*), Yujin (*Radix Curcumae*), Chenpi (*Pericarpium Citri Reticulatae*), Xiangfu (*Rhizoma Cyperi*), Zhike (*Fructus Aurantii*), Fabanxia (*Rhizoma Pinelliae Preparatum*), Suanzaoren (*Semen Ziziphi Spinosae*), Chishao (*Radix Paeoniae Rubra*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Zhizi (*Fructus Gardeniae*), Gancao (*Radix Glycyrrhizae*), Danggui (*Radix Angelicae Sinensis*), Yuanzhi (*Radix Polygalae*)	Chaihu (*Radix Bupleuri*) & Baishao (*Radix Paeoniae Alba*)	30	CHM_3	1	Hong-Cai et al., 2018; Wang et al. (2016)
Modified Yangxin decotion	Dazao (*Fructus Jujubae*), Shengjiang (*Rhizoma Zingiberis Recens*), Banxia (*Rhizoma Pinelliae*), Yuanzhi (*Radix Polygalae*), Gancao (*Radix Glycyrrhizae*), Chuangxiong (*Rhizoma Ligustici Chuanxiong*), Rougui (*Cortex Cinnamomi*), Baiziren (*Semen Platycladi*), Wuweizi (*Fructus Schisandrae Chinensis*), Danggui (*Radix Angelicae Sinensis*), Renshen (*Radix Ginseng*), Suanzaoren (*Semen Ziziphi Spinosae*), Huangqi (*Radix Astragali seu Hedysari*), Fulin (*Poria*).	Renshen (*Radix Ginseng*) & Fulin (*Poria*)	37	CHM_4	1	Chen (2013)

Note: CHM: Chinese herbal medicine.

3.5.9. CHM_6 vs. WCM_1

One study (Li et al., 2014) indicated that CHM_6 had comparable clinically effect with WCM_1 according to HAMD-17 (MID = 4, MD = −2.20, 95% CI (−4.32, −0.08), P = 0.04, Certainty of evidence: High, Table 3), while CHM_6 was better than WCM_1 in TER (RR = 1.18, 95% CI (1.02, 1.37), P = 0.03, Certainty of evidence: Moderate, Table 3). One study (Zhu et al., 2014) showed no group difference in terms of HAMD-17 (MID = 4, MD = −0.12, 95% CI (−4.32, −0.08), P = 0.88, Certainty of evidence: High, Table 3) and TER (RR = 1.09, 95% CI (0.82, 1.44), P = 0.54, Certainty of evidence: Moderate, Table 3).

3.5.10. CHM_5 vs. WCM_1

One study (Liu et al., 2010) showed no group difference between CHM_5 and WCM_1 in terms of HAMD-17 (MID = 4, MD = 0.75, 95%CI (−1.65, 1.41), P = 0.26, Certainty of evidence: High, Table 3) and TER (RR = 0.92, 95%CI(0.71, 1.19), P = 0.52, Certainty of evidence: Moderate, Table 3).

3.5.11. CHM_5 vs. WCM_2

One study (Guo et al., 2009) indicated that there was no group difference between CHM_5 and WCM_2 in terms of HAMD-17 (MID = 4, MD = 0.75, 95%CI (−0.59, 2.09), P = 0.27, Certainty of evidence: High, Table 3) and TER (RR = 0.90, 95%CI (0.74, 1.08), P = 0.25, Certainty of evidence: Moderate, Table 3).

3.5.12. CHM_3 vs. WCM_1

Pooled analysis of 2 studies (Liu et al., 2013a; Shen et al., 2004) indicated that CHM_3 had comparable clinically effect with WCM_1 according to HAMD-17 (MID = 4, MD = 1.72, 95% CI (0.22, 3.23), P = 0.02, I^2 = 47%, Fig. 4C, Certainty of evidence: High, Table 3) and TER (RR = 0.93, 95% CI (0.81, 1.06), P = 0.29, I^2 = 48%, Fig. 5C, Certainty of evidence: Moderate, Table 3).

3.5.13. CHM_1 vs. WCM_1

One study (Xian et al., 2008) indicated there was no group difference between CHM_1 and WCM_1 in TER (RR = 1.14, 95% CI (0.87, 1.49), P = 0.35, Certainty of evidence: Moderate, Table 3).

3.5.14. CHM_8 vs. WCM_2

One study (Shi et al., 2013) indicated there was no group difference between CHM_8 and WCM_2 in TER (RR = 0.95, 95% CI (0.77, 1.17), P = 0.63, Certainty of evidence: Moderate, Table 3).

3.5.15. CHM + WCM vs. WCM

Thirteen studies (Gao and Lei, 2012; Gao et al., 2013; Huo and Fu, 2015; Huo et al., 2008; Jiang et al., 2015; Mao et al., 2013; Wei and Wei, 2011; Wang et al., 2010, 2016; Yang et al., 2012; Yu and Wu, 2013; Zhang et al., 2015; Zhang and Meng, 2017) compared the antidepressant effects of CHM plus WCM with that of WCM. Pooled analysis of 11 studies indicated that CHM plus WCM had comparable clinically effects with WCM alone according to HAMD-17 (MID = 4, MD = −2.51, 95% CI (−3.24, −1.77), P < 0.00001, I^2 = 75%, Fig. 2C, Certainty of evidence: Moderate, Table 3). Pooled analysis of 12 studies indicated that CHM plus WCM was superior than WCM alone in terms of TER (RR = 1.16, 95% CI (1.07, 1.27), P = 0.0004, I^2 = 68%, Fig. 3C, Certainty of evidence: High, Table 3).

3.5.16. CHM_1 + WCM_1 vs. WCM_1

Five studies (Huo et al., 2008; Jiang et al., 2015; Wei and Wei, 2011; Yu and Wu, 2013; Zhang et al., 2015) indicated that CHM_1 plus WCM_1 had comparable clinically effects with WCM_1 alone according to HAMD-17 (MID = 4, MD = −2.16, 95% CI (−2.86, −1.46), P < 0.00001, I^2 = 47%, Fig. 4D, Certainty of evidence: High, Table 3), while CHM_1 plus WCM_1 was superior to WCM_1 alone in terms of TER (RR = 1.18, 95% CI (1.07, 1.31), P = 0.002, I^2 = 28%, Fig. 5D,

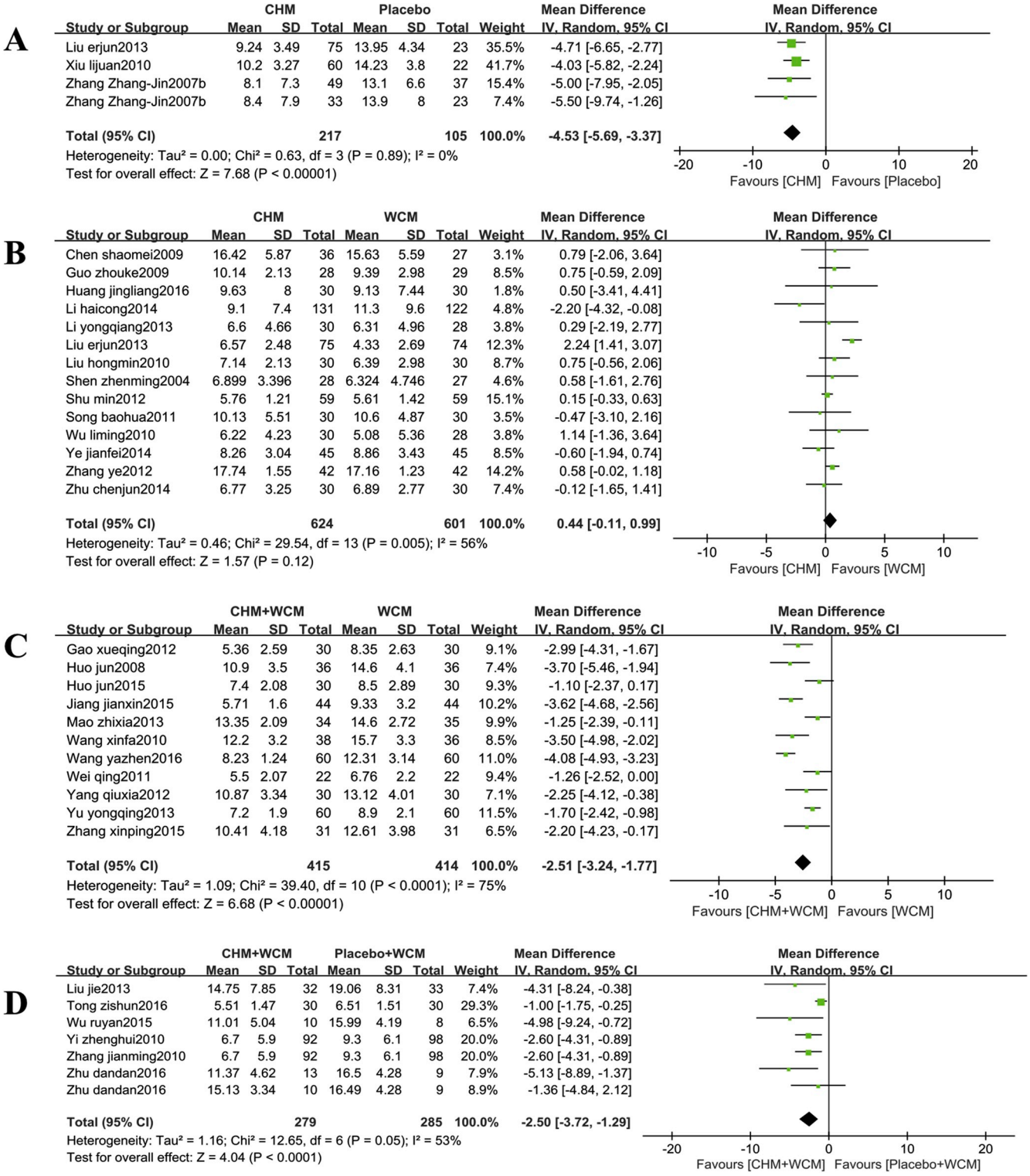

Fig. 2. Forest plot of HAMD-17: (A) CHM *vs.* placebo; (B) CHM *vs.* WCM; (C) CHM + WCM *vs.* WCM; (D) CHM + WCM *vs.* placebo CHM + WCM. (CHM, Chinese herbal medicine; WCM, western conventional medications; HAMD-17, the Hamilton Rating Scale for Depression 17 items).

Certainty of evidence: High, Table 3).

3.5.17. CHM_2 + WCM_1 vs. WCM_1

One study (Huo and Fu, 2015) indicated that there was no significant group difference between CHM_2 plus WCM_1 and WCM_1 in terms of HAMD-17 (MID = 4, MD = −1.10, 95% CI (−2.37, 0.17), P = 0.09, Certainty of evidence: High, Table 3) and TER (RR = 1.04, 95% CI (0.92, 1.16), P = 0.55, Certainty of evidence: Moderate, Table 3).

3.5.18. CHM_3 + WCM_1 vs. WCM_1

Three studies (Gao and Lei, 2012; Wang et al., 2010; Yang et al., 2012) indicated that CHM_3 plus WCM_1 had comparable clinically effects with WCM_1 alone according to HAMD-17 (MID = 4, MD = −3.01, 95% CI (−3.88, −2.13), P < 0.00001, I^2 = 0%, Fig. 4E, Certainty of evidence: High, Table 3). Three studies (Gao and

Table 3
Summary of GRADE on evidences of outcomes of CHM for depression.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trial	Control	**Relative (95% CI)**	**Absolute (95% CI)**		
The Hamilton Rating Scale for Depression (CHM *vs.* Placebo)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	217	105	–	MD **4.53 lower** (5.69 lower to 3.37 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM_1 *vs.* Placebo)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	142	82	–	MD **4.43 lower** (5.87 lower to 2.99 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM_3 *vs.* Placebo)												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	75	23	–	MD **4.71 lower** (6.65 lower to 2.77 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM + placebo WCM *vs.* placebo CHM + WCM)												
1	randomised trials	not serious	not serious	not serious	not serious	none	32	31	–	MD **2.33 higher** (1.93 lower to 6.59 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM *vs.* WCM)												
14	randomised trials	not serious	serious[c]	not serious	not serious	none	624	601	–	MD **0.44 higher** (0.11 lower to 0.99 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM_{10} *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	36	27	–	MD **0.79 higher** (2.06 lower to 3.64 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_2 *vs.* WCM_1)												
6	randomised trials	not serious	not serious	not serious	not serious	none	224	220	–	MD **0.09 higher** (0.33 lower to 0.52 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_6 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	131	122	–	MD **2.20 lower** (4.32 lower to 0.08 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_6 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	30	30	–	MD **0.12 lower** (4.32 lower to 0.08 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_5 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	30	30	–	MD **0.75 higher** (1.65 lower to 1.41 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_5 *vs.* WCM_2)												
1	randomised trials	not serious	not serious	not serious	not serious	none	28	29	–	MD **0.75 higher** (0.59 lower to 2.09 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_3 *vs.* WCM_1)												
2	randomised trials	not serious	not serious	not serious	not serious	none	103	101	–	MD **1.72 higher** (0.22 higher to 3.23 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM + WCM *vs.* WCM)												
11	randomised trials	not serious	serious[c]	not serious	not serious	none	415	414	–	MD **2.51 lower** (3.24 lower to 1.77 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM_1 + WCM_1 *vs.* WCM_1)												
5	randomised trials	not serious	not serious	not serious	not serious	none	193	193	–	MD **2.16 lower** (2.86 lower to 1.46 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_2 + WCM_1 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	30	30	–	MD **1.10 lower** (2.37 lower to 0.17 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_3 + WCM_1 *vs.* WCM_1)												
3	randomised trials	not serious	not serious	not serious	not serious	none	98	96	–	MD **3.01 lower** (3.88 lower to 2.13 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_3 + WCM_2 *vs.* WCM_2)												
1	randomised trials	not serious	not serious	not serious	not serious	none	60	60	–	MD **4.08 higher** (4.93 lower to 3.23 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

(*continued on next page*)

Table 3 (*continued*)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trial	Control	**Relative (95% CI)**	**Absolute (95% CI)**		
The Hamilton Rating Scale for Depression (CHM_9 + WCM_1 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	34	35	–	MD **1.25 lower** (2.39 lower to 0.11 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM + WCM *vs.* placebo CHM + WCM)												
7	randomised trials	not serious	serious[c]	not serious	not serious	none	279	285	–	MD **2.50 lower** (3.72 lower to 1.29 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
The Hamilton Rating Scale for Depression (CHM_1 + WCM_1 *vs.* placebo CHM_1 + WCM_1)												
3	randomised trials	not serious	not serious	not serious	not serious	none	214	226	–	MD **1.95 lower** (2.77 lower to 1.12 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_5 + WCM_1 *vs.* placebo CHM_5 + WCM_1)												
1	randomised trials	not serious	not serious	not serious	not serious	none	32	33	–	MD **4.31 lower** (8.24 lower to 0.38 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
The Hamilton Rating Scale for Depression (CHM_7 + WCM_1 *vs.* placebo CHM_7 + WCM_1)												
2	randomised trials	not serious	not serious	not serious	not serious	none	33	26	–	MD **3.66 lower** (6.18 lower to 1.14 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Total Effective Rate (CHM *vs.* Placebo)												
3	randomised trials	serious[a]	not serious	not serious	serious[d]	none	106/135 (78.5%)	32/93 (34.4%)	**RR 2.15** (1.61–2.88)	**396 more per 1000** (from 210 more to 647 more)	⊕⊕◯◯ LOW	IMPORTANT
Total Effective Rate (CHM_1 *vs.* placebo)												
1	randomised trials	serious[b]	not serious	not serious	serious[d]	none	52/60 (86.7%)	10/22 (45.5%)	**RR 1.91** (1.19–3.05)	**414 more per 1000** (from 86 more to 932 more)	⊕⊕◯◯ LOW	IMPORTANT
Total Effective Rate (CHM_3 *vs.* placebo)												
1	randomised trials	serious[b]	not serious	not serious	serious[d]	none	54/75 (72.0%)	22/71 (31.0%)	**RR 2.32** (1.60–3.38)	**409 more per 1000** (from 186 more to 737 more)	⊕⊕◯◯ LOW	IMPORTANT
Total Effective Rate (CHM vs. WCM)												
17	randomised trials	not serious	not serious	not serious	not serious	none	646/774 (83.5%)	622/748 (83.2%)	**RR 0.99** (0.95–1.02)	**8 fewer per 1000** (from 42 fewer to 17 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total Effective Rate (CHM_4 *vs.* WCM_1)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	70/82 (85.4%)	66/82 (80.5%)	**RR 1.06** (0.92–1.21)	**48 more per 1000** (from 64 fewer to 169 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_{10} *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	35/36 (97.2%)	27/27 (100.0%)	**RR 0.98** (0.90–1.06)	**20 fewer per 1000** (from 100 fewer to 60 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_2 *vs.* WCM_1)												
6	randomised trials	not serious	not serious	not serious	not serious	none	201/224 (89.7%)	203/222 (91.4%)	**RR 0.98** (0.94–1.03)	**18 fewer per 1000** (from 55 fewer to 27 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total Effective Rate (CHM_6 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	105/131 (80.2%)	83/122 (68.0%)	**RR 1.18** (1.02–1.37)	**122 more per 1000** (from 14 more to 252 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_6 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	24/30 (80.0%)	22/30 (73.3%)	**RR 1.09** (0.82–1.44)	**66 more per 1000** (from 132 fewer to 323 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_5 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	23/30 (76.7%)	25/30 (83.3%)	**RR 0.92** (0.71–1.19)	**67 fewer per 1000** (from 242 fewer to 158 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_5 *vs.* WCM_2)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	44/58 (75.9%)	44/52 (84.6%)	**RR 0.90** (0.74–1.08)	**85 fewer per 1000** (from 220 fewer to 68 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_3 *vs.* WCM_1)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	81/103 (78.6%)	90/103 (87.4%)	**RR 0.93** (0.81–1.06)	**61 fewer per 1000** (from 166 fewer to 52 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_1 *vs.* WCM_1)												

(*continued on next page*)

Table 3 (*continued*)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trial	Control	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	serious[d]	none	25/30 (83.3%)	22/30 (73.3%)	**RR 1.14** (0.87–1.49)	**103 more per 1000** (from 95 fewer to 359 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_8 *vs.* WCM_2)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	38/50 (76.0%)	40/50 (80.0%)	**RR 0.95** (0.77–1.17)	**40 fewer per 1000** (from 184 fewer to 136 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM + WCM *vs.* WCM)												
12	randomised trials	not serious	not serious	not serious	not serious	none	444/483 (91.9%)	369/481 (76.7%)	**RR 1.16** (1.07–1.27)	**123 more per 1000** (from 54 more to 207 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total Effective Rate (CHM_1 + WCM_1 *vs.* WCM_1)												
5	randomised trials	not serious	not serious	not serious	not serious	none	176/193 (91.2%)	145/193 (75.1%)	**RR 1.18** (1.07–1.31)	**135 more per 1000** (from 53 more to 233 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total Effective Rate (CHM_2 + WCM_1 *vs.* WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	29/30 (96.7%)	28/30 (93.3%)	**RR 1.04** (0.92–1.16)	**37 more per 1000** (from 75 fewer to 149 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_3 + WCM_1 *vs.* WCM_1)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	58/68 (85.3%)	40/66 (60.6%)	**RR 1.38** (1.12–1.71)	**230 more per 1000** (from 73 more to 430 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_3 + WCM_2 *vs.* WCM_2)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	107/120 (89.2%)	88/120 (73.3%)	**RR 1.22** (1.08–1.38)	**161 more per 1000** (from 59 more to 279 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_4 + WCM_2 *vs.* WCM_2)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	41/42 (97.6%)	32/42 (76.2%)	**RR 1.28** (1.07–1.53)	**213 more per 1000** (from 53 more to 404 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM + WCM *vs.* placebo CHM + WCM)												
3	randomised trials	not serious	not serious	not serious	not serious	none	134/154 (87.0%)	121/161 (75.2%)	**RR 1.14** (1.03–1.26)	**105 more per 1000** (from 23 more to 195 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total Effective Rate (CHM_1 + WCM_1 *vs.* placebo CHM_1 + WCM_1)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	106/122 (86.9%)	96/128 (75.0%)	**RR 1.14** (1.01–1.27)	**105 more per 1000** (from 8 more to 203 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total Effective Rate (CHM_5 + WCM_1 *vs.* placebo CHM_5 + WCM_1)												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	28/32 (87.5%)	25/33 (75.8%)	**RR 1.16** (0.91–1.46)	**121 more per 1000** (from 68 fewer to 348 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse events (CHM *vs.* Placebo)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	17/157 (10.8%)	12/131 (9.2%)	**RR 1.18** (0.59–2.38)	**16 more per 1000** (from 38 fewer to 126 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse events (CHM *vs.* WCM)												
12	randomised trials	not serious	not serious	not serious	not serious	none	151/594 (25.4%)	412/583 (70.7%)	**RR 0.36** (0.31–0.42)	**452 fewer per 1000** (from 488 fewer to 410 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse events (CHM + WCM *vs.* WCM)												
17	randomised trials	not serious	not serious	not serious	not serious	none	296/754 (39.3%)	468/764 (61.3%)	**RR 0.64** (0.58–0.71)	**221 fewer per 1000** (from 257 fewer to 178 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **MD:** Mean difference.

Explanations.

a. Unclear allocation concealment in all studies, participants and personnel blinded in one study, outcome assessors blinded in one study.

b. Allocation concealment and blinding were unclear.

c. The statistical test for heterogeneity shows a low P-value and the I^2 is large.

d. The number of events is small.

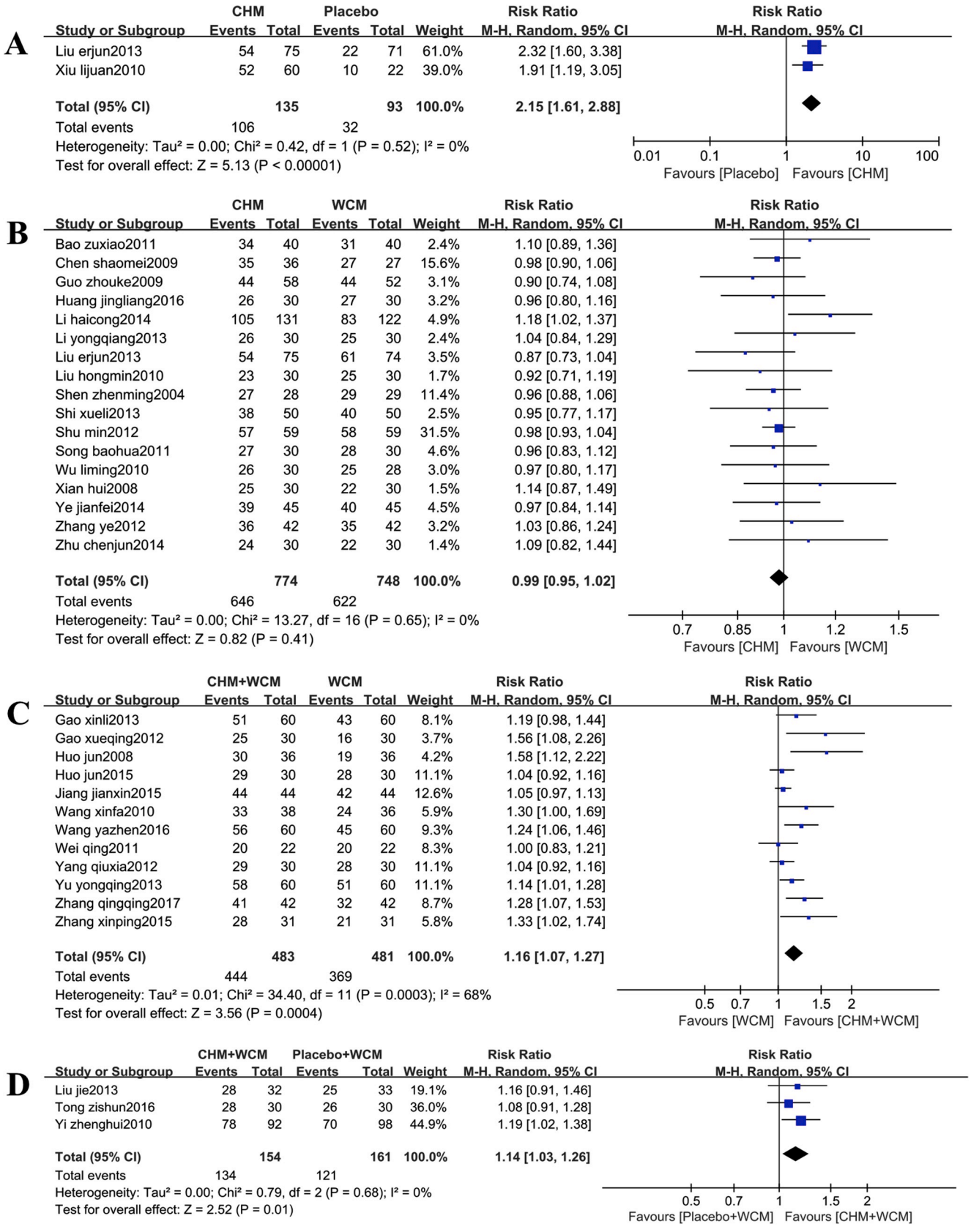

Fig. 3. Forest plot of TER: (A) CHM *vs.* placebo; (B) CHM *vs.* WCM; (C) CHM + WCM *vs.* WCM; (D) CHM + WCM *vs.* placebo CHM + WCM. (CHM, Chinese herbal medicine; WCM, western conventional medications; TER, total effective rate).

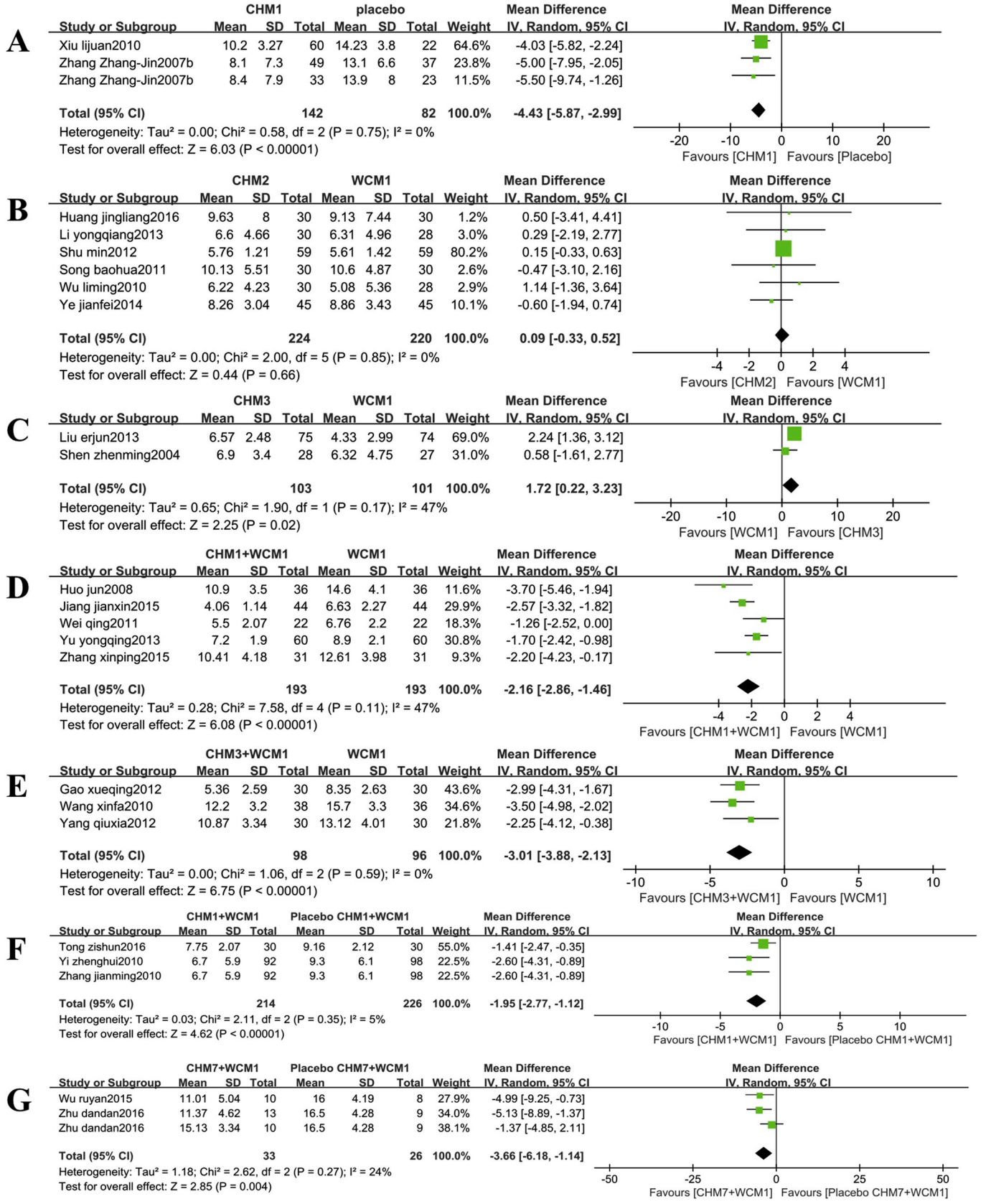

Fig. 4. Forest plot of HAMD-17: (A) CHM_1 *vs.* placebo; (B) CHM_2 *vs.* WCM_1; (C). CHM_3 *vs.* WCM_1; (D) CHM_1 + WCM_1 *vs.* WCM_1; (E) CHM_3 + WCM_1 *vs.* WCM_1; (F) CHM_1 + WCM_1 *vs.* placebo CHM_1 + WCM_1;(G) CHM_7 + WCM_1 *vs.* placebo CHM_7 + WCM_1. (CHM, Chinese herbal medicine; WCM, western conventional medications; HAMD-17, the Hamilton Rating Scale for Depression 17 items).

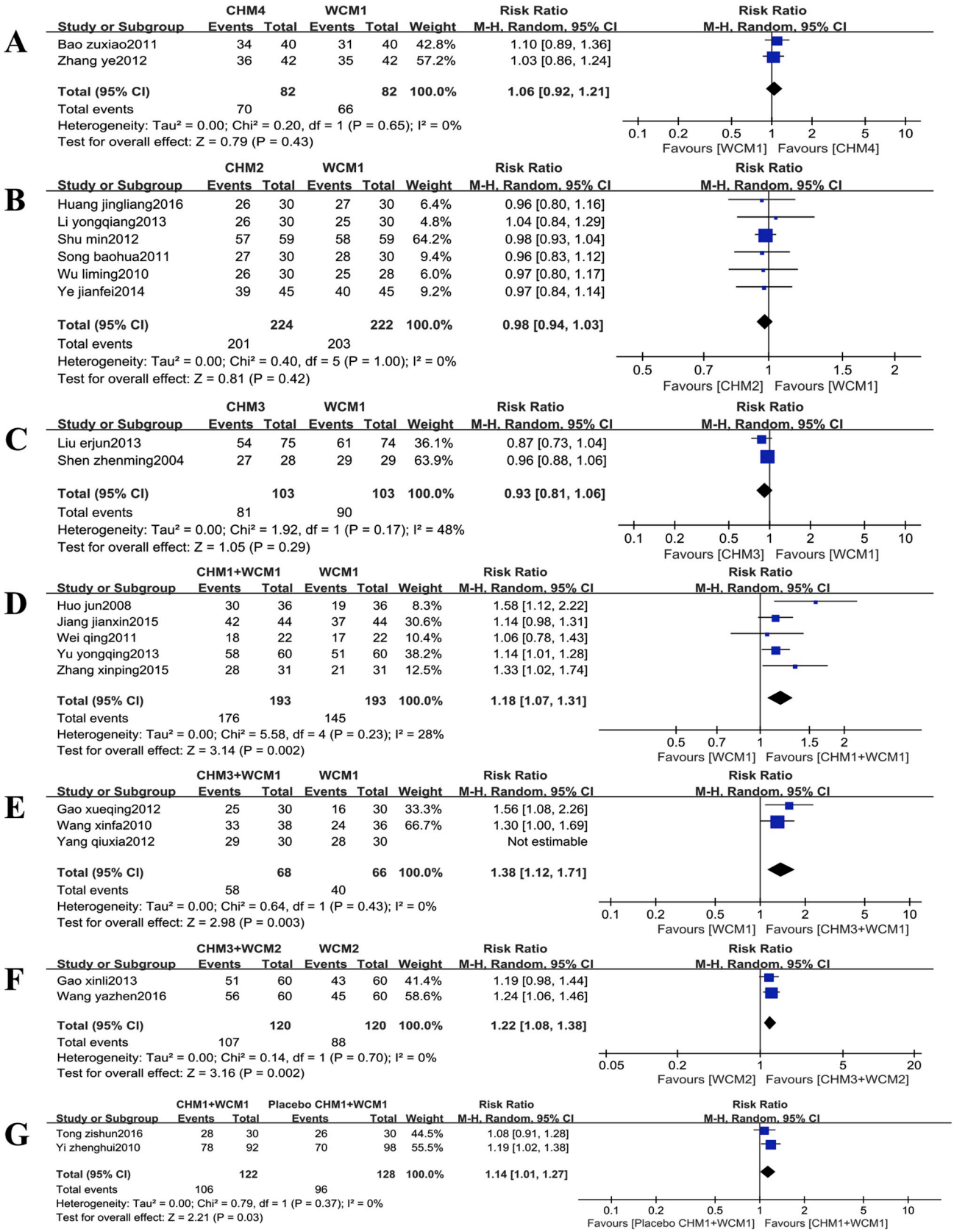

Fig. 5. Forest plot of TER: (A) CHM_4 *vs.* WCM_1; (B) CHM_2 *vs.* WCM_1; (C) CHM_3 *vs.* WCM_1; (D) CHM_1 + WCM_1 *vs.* WCM_1; (E) CHM_3 + WCM_1 *vs.* WCM_1; (F) CHM_3 + WCM_2 *vs.* WCM_2; (G) CHM_1 + WCM_1 *vs.* placebo CHM_1 + WCM_1. (CHM, Chinese herbal medicine; WCM, western conventional medications; TER, total effective rate).

Lei, 2012; Wang et al., 2010; Yang et al., 2012) showed there was no significant difference between CHM_3 plus WCM_1 and WCM_1 in TER (RR = 1.25, 95% CI (0.89, 1.75), P = 0.19, I^2 = 83%). Sensitivity analysis showed that the heterogeneity declined after removing one study (Yang et al., 2012), which only included elder patients. The remaining two studies (Gao and Lei, 2012; Wang et al., 2010) indicated that CHM_3 plus WCM_1 was superior to WCM_1 alone in TER (RR = 1.38, 95% CI (1.12, 1.71), P = 0.003, I^2 = 0%, Fig. 5E, Certainty of evidence: Moderate, Table 3).

3.5.19. CHM_3 + WCM_2 vs. WCM_2

One study (Wang et al., 2016) indicated that CHM_3 plus WCM_2 was superior to WCM_2 alone in HAMD-17 (MID = 4, MD = −4.08, 95% CI (−4.93, −3.23), P < 0.00001, Certainty of evidence: High, Table 3). Pooled analysis of 2 studies (Gao et al., 2013; Wang et al., 2016) indicated that CHM_3 plus WCM_2 was superior to WCM_2 alone in TER (RR = 1.22, 95% CI (1.08, 1.38), P = 0.002, I^2 = 0%, Fig. 5F, Certainty of evidence: Moderate, Table 3).

3.5.20. CHM_9 + WCM_1 vs. WCM_1

One study (Mao et al., 2013) indicated that CHM_9 plus WCM_1 had comparable clinically effects with WCM_1 alone according to HAMD-17 (MID = 4, MD = −1.25, 95% CI (−2.39, −0.11), P = 0.03, Certainty of evidence: High, Table 3).

3.5.21. CHM_4 + WCM_2 vs. WCM_2

One study (Zhang and Meng, 2017) indicated that CHM_4 plus WCM_2 was superior to WCM_2 alone in TER (RR = 1.28, 95% CI (1.07, 1.53), P = 0.006, Certainty of evidence: Moderate, Table 3).

3.5.22. CHM + WCM vs. placebo CHM + WCM

Seven studies (Tong et al., 2016; Yi et al., 2010; Zhang and Zhu, 2010; Zhang et al., 2007a; Liu et al., 2013b; Wu et al., 2015; Zhu et al., 2016) compared the antidepressant effects of CHM plus WCM with that of placebo CHM plus WCM. Pooled analysis of 7 studies showed that CHM plus WCM had comparable clinically effects with placebo CHM plus WCM according to HAMD-17 (MID = 4, MD = −2.50, 95% CI (−3.72, −1.29), P < 0.0001, I^2 = 53%, Fig. 2D, Certainty of evidence: Moderate, Table 3). Three studies indicated that CHM plus WCM was superior to placebo CHM plus WCM in terms of TER (RR = 1.14, 95% CI (1.03, 1.26), P = 0.01, I^2 = 0%, Fig. 3D, Certainty of evidence: High, Table 3).

3.5.23. CHM_1 + WCM_1 vs. placebo CHM_1 + WCM_1

Pooled analysis of 3 studies (Tong et al., 2016; Yi et al., 2010; Zhang and Zhu, 2010) indicated that CHM_1 plus WCM_1 had comparable clinically effects with placebo CHM_1 plus WCM_1 in terms of HAMD-17 (MID = 4, MD = −1.95, 95% CI (−2.77, −1.12), P < 0.00001, I^2 = 5%, Fig. 4F, Certainty of evidence: High, Table 3). Pooled analysis of 2 studies (Tong et al., 2016; Yi et al., 2010) indicated that CHM_1 plus WCM_1 was superior to placebo CHM_1 plus WCM_1 in terms of TER (RR = 1.14, 95% CI (1.01, 1.27), P = 0.03, I^2 = 0%, Fig. 5G, Certainty of evidence: Moderate, Table 3).

3.5.24. CHM_1 + WCM_3 vs. placebo CHM_1 + WCM_3

One study (Zhang et al., 2007a) showed there was no significant difference between CHM_1 plus WCM_3 and placebo CHM_1 plus WCM_3 in terms of HAMD-17 (P > 0.05).

3.5.25. CHM_5 + WCM_1 vs. placebo CHM_5 + WCM_1

One study (Liu et al., 2013b) indicated that CHM_5 plus WCM_1 was superior to placebo CHM_5 plus WCM_1 in terms of HAMD-17 (MID = 4, MD = −4.31, 95% CI (−8.24, −0.38), P = 0.03, Certainty of evidence: High, Table 3), while there was no group difference in TER (RR = 1.16, 95% CI (0.91, 1.46), P = 0.23, Certainty of evidence: Moderate, Table 3).

3.5.26. CHM_7 + WCM_1 vs. placebo CHM_7 + WCM_1

Pooled analysis of 2 studies (Wu et al., 2015; Zhu et al., 2016) indicated that CHM_7 plus WCM_1 had comparable clinically effects with placebo CHM_7 plus WCM_1 according to HAMD-17 (MID = 4, MD = −3.66, 95% CI (−6.18, −1.14), P = 0.004, I^2 = 24%, Fig. 4G, Certainty of evidence: High, Table 3).

3.5.27. Adverse events

Adverse events were reported in 33 studies, analyzed but not observed in 2 studies (Mao et al., 2013; Zhang et al., 2015), and not analyzed in 5 studies (Xiu et al., 2010; Liu et al., 2010; Xian et al., 2008; Zhu et al., 2014, 2016). Adverse events of 10/33 (30.30%) studies were reported by physicians, of 3/33 (9.09%) were reported by patients themselves, of 14/33 (42.42%) reported by physicians and patients, and it was unclear in 6/33 (18.18%) studies.

In the 2 placebo-controlled trials (Liu et al., 2013a; Zhang et al., 2007b), 17/157 (10.82%) CHM participants and 12/131 (9.16%) placebo participants suffered from adverse events (P > 0.05, Certainty of evidence: Moderate, Table 3). In the 12 trials (Bao et al., 2011; Huang et al., 2016; Li et al., 2013, 2014; Luo et al., 2006; Liu et al., 2013a; Shu and Zhang, 2012; Song et al., 2011; Shi et al., 2013; Wu et al., 2010; Ye et al., 2014; Zhang et al., 2012) of single CHM-treated, a total of 151/594 (25.42%) participants suffered from adverse events in CHM-treated groups and 412/583 (70.67%) participants did so in WCM-treated groups (P < 0.01, Certainty of evidence: High, Table 3). In the 17 trials (Gao and Lei, 2012; Gao et al., 2013; Huo and Fu, 2015; Huo et al., 2008; Jiang et al., 2015; Liu et al., 2013b; Wu et al., 2015; Tong et al., 2016; Wei and Wei, 2011; Wang et al., 2010, 2016; Yang et al., 2012; Yu and Wu, 2013; Yi et al., 2010; Zhang and Meng, 2017; Zhang and Zhu, 2010; Zhang et al., 2007a) of the combination of CHM and WCM, a total of 296/754 (39.3%) participants suffered from adverse events in the groups treated with CHM plus WCM, and 468/764 (61.3%) participants did so in WCM-treated groups (P < 0.01, Certainty of evidence: High, Table 3). Three studies (Chen et al., 2009; Guo et al., 2009; Shen et al., 2004) indicated a lower rate of adverse events in CHM-treated groups when compared with WCM-treated groups (P < 0.05).

In the CHM-treated groups, dizziness, headache, nausea and anorexia were the most frequently occurring adverse events, affecting 36/174 (20.70%), 22/174 (12.64%), 21/174 (12.07%) and 16/174 (9.20%) participants, respectively.

In the WCM-treated groups, gastrointestinal discomfortable symptoms (dry mouth, nausea, constipation, vomiting, anorexia and diarrhea) were the most frequently occurring adverse events, affecting 417/848 (47.17%) participants. Neurological symptoms (dizziness, headache, insomnia, drowsiness and anxious) were also occurred frequently, affecting 241/848 (28.42%) participants.

4. Discussion

4.1. Summary of evidence

This study is an updated systematic review of the efficacy and safety of CHM for depression. Forty studies with 3549 subjects were identified. The methodological quality of included RCTs was moderate. The main findings were that: (1) the CHM plus WCM-treated groups were superior to the WCM-treated groups for improving the TER (Certainty of evidence: High), while CHM plus WCM had comparable clinically effects with WCM in terms of the severity of depression (Certainty of evidence: Moderate); (2) there was no difference between the CHM-treated and the WCM-treated groups in improving the severity of depression (Certainty of evidence: Moderate) and TER (Certainty of evidence: High); (3) when compared with placebo, CHM were more beneficial in improving the severity of depression (Certainty of evidence: Moderate) and TER (Certainty of evidence: Low); (4) CHM were generally safe; CHM also can improve tolerance of WCM leading to lower adverse events rate of the CHM plus WCM-treated group when

compared with WCM monotherapy group.

4.2. Limitation

Firstly, some methodological limitations exist in the primary studies. Only two studies (Xian et al., 2008; Wu et al., 2015) reported the concealment of allocation. Trials with inadequate or unclear concealment of allocation had average 18% more "beneficial" effect than trials with adequate concealment (Higgins and Green, 2012). Blinding is an essential method to avoid performance bias and detection bias. However, some studies were unable to be blinded, due to the special color, smell and taste of CHM. Only 8 studies reported double blinding of participants and personnel and 7 studies reported the blinding of outcome assessment. Second, most clinical trials did not conduct formal pretrial sample size calculation and majority of the included trials had relatively small sample sizes. The risk of over estimating therapeutic efficacy may exist in trials with insufficient statistical power (Kjaergard et al., 2001). Third, only three studies (Liu et al., 2010; Huo and Fu, 2015; Wang et al., 2016) describe the duration of follow-up, which ranged from 12 weeks to 6 months, making it difficult to assess the long-term efficacy of CHM treatment for depression. Fourth, we searched for papers published in Chinese or English database only, thus the eligible studies published in other languages may be left out, which may limit the generalizability of the findings. Fifth, across outcomes were combined through converting other units into the unit of the most commonly used instrument, which may increase computational error in the data processing. Sixth, a large variety of CHM were used as interventions in the included studies, with a great deal of variation in the composition, dosage, and the duration of treatment. The effectiveness of WCM used in comparisons were not all similar. Though we have categorized the CHM by the main components or the combinations of main components and categorized the WCM by different antidepressant effectiveness, the heterogeneity still existed in some outcomes, which would influence the reliability of the relevant results.

4.3. Implication for practice

The finding from the present systematic review revealed that applying CHM as monotherapy or adjuvant therapy may be beneficial for depression patients and be generally safe. *Radix Bupleuri, Radix Angelicae Sinensis, Poria, Radix Glycyrrhizae, Rhizoma Cyperi, Rhizoma Atractylodis Macrocephalae, Fructus Gardeniae, Radix Polygalae, Radix Curcumae,* and *Semen Ziziphi Spinosae*were the most commonly used herbs in prescriptions. They exerted the function of soothing the liver, invigorating spleen and promoting blood circulation and should be considered further in the development of Chinese herbal prescriptions for depression. TCM is characterized by syndrome differentiation and individualized treatment planning to optimize outcomes (Yu et al., 2017; Jiang et al., 2012). TCM syndrome differentiation is a unique TCM concept which is the essential guide for TCM therapy. It summarizes and differentiates the nature, location, and pattern of diseases. Based on each individual pattern, the precisely tailoring Chinese herbal prescription for individuals can maximize its effectiveness (Fu et al., 2013). One example of high-quality study published in JAMA (Bensoussan et al., 1998) indicated a more significant effect of using the individualized CHM for the treatment of irritable bowel syndrome compared with prescribing a common hypnotic prescription. These treatment principles together with experiential knowledge of the high-frequency CHM used for depression can guide CHM treatment planning for depression and thus improving the clinical effectiveness and safety.

4.4. Implication for research

In order to overcome methodology quality issues, further RCTs of CHM for depression should take a rigor standard design into consideration. First, the protocol of clinical trials must register in clinical trials registry platform and the requirement of Clinical Trial Data Sharing (Taichman et al., 2016) by the International Committee of Medical Journal Editors should be followed. Second, the CONSORT 2010 statement (Schulz et al., 2010), CONSORT for TCM (Bian et al., 2011), and RCTs investigating CHM (Flower et al., 2012) should be used as guidelines when designing and reporting RCTs for CHM. Third, adequate sample size is of great importance in methodologic quality, intervention effects, and publication bias (Kjaergard et al., 2001). Thus, it is necessary to conduct formal pretrial sample size calculation. Fourth, trials with short duration follow-up cannot scientifically assess the long-term efficacy of CHM for depression. Therefore, trials with optimum duration of follow-up were encouraged.

5. Conclusion

The present finding indicated that CHM provided statistically significant benefits for depression. CHM were generally safe and well tolerated in depression patients. Therefore, the findings of present systematic review, at least to a certain extent, provided supporting evidence for the routine use of CHM for depression.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.07.003.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association Press, Washington (DC). https://doi.org/10.1007/978-0-387-79061-9_113.

Bao, Z.X., Zhao, G.P., Sun, W., Chen, B.J., 2011. Clinical curative effects of Kaixin powder on. Depression with mild or moderate degree. Chin. Arch. Tradit. Chin. Med. (5), 987–988. https://doi.org/10.13193/j.archtcm.2011.05.52.baozx.042. (in Chinese).

Bech, P., Paykel, E., Sireling, L., Yiend, J., 2015. Rating scales in general practice depression: psychometric analyses of the clinical interview for depression and the Hamilton rating scale. J. Affect. Disord. 171, 68–73. https://doi.org/10.1016/j.jad.2014.09.013.

Bensoussan, A., Talley, N.J., Hing, M., Menzies, R., Guo, A., Ngu, M., 1998 Nov 11. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. J. Am. Med. Assoc. 280 (18), 1585–1589.

Bian, Z., LiuB, Moher, D., Wu, T., Li, Y., Shang, H., Cheng, C., 2011. Consolidated. standardsof reporting trials (CONSORT) for traditional Chinese medicine: current situationand future development. Front. Med. 5, 171–177. https://doi.org/10.1007/s11684-011-0132-z.

Bouchard, J.M., Delaunay, J., Delisle, J.P., Grasset, N., Mermberg, P.F., Molczadzki, M., et al., 1987 Nov. Citalopram versus maprotiline: a controlled, clinical multicentre trial in depressed patients. Acta Psychiatr. Scand. 76 (5), 583–592.

Chan, K., Shaw, D., Simmonds, M.S., Leon, C.J., Xu, Q., Lu, A., et al., 2012. Good practice. in. reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materiamedica. J. Ethnopharmacol. 140, 469–475. https://doi.org/10.1016/j.jep.2012.01.038.

Chen, G., Guo, X., 2017. Neurobiology of Chinese herbal medicine on major depressive. Disorder. Int Rev Neurobiol 135, 77. https://doi.org/10.1016/bs.irn.2017.02.005.

Chen, S.M., Zhang, X.L., Lin, A.J., Feng, G.Z., 2009. Clinical observation on Wangyou. prescription for treating depression. J. Liaoning Univ. Tradit. Chin. Med. 8, 92–94. https://doi.org/10.13194/j.jlunivtcm.2009.08.94.chenshm.168. (in Chinese).

Chen, X.S., 2013. A Comparative Study on the Effects of Kaixinsan on Behavior and NE and 5-HT in Stress-Induced Depression Rats. Yunnan University of Traditional Chinese Medicine (in Chinese).

Dang, H., Sun, L., Liu, X., Peng, B., Wang, Q., Jia, W., et al., 2009. Preventive action of Kai Xin San aqueous extract on depressive-like symptoms and cognition deficit induced by chronic mild stress. Exp. Biol. Med. 234, 785–793. https://doi.org/10.3181/0812-RM-354.

Davidson, J., Turnbull, C.D., Strickland, R., Miller, R., Graves, K., 1986. The Montgomery-Asberg Depression Scale: reliability and validity. Acta Psychiatr. Scand. 73, 544–548. https://doi.org/10.1111/j.1600-0447.1986.tb02723.x.

Demyttenaere, K., Hemels, M.E., Hudry, J., Annemans, L., 2005 Jan. A cost-effectiveness model of escitalopram, citalopram,and venlafaxine as first-line treatment for major depressive disorder in Belgium. Clin. Ther. 27 (1), 111–124. https://doi.org/10.1016/j.clinthera.2005.01.001.

Do Rego, J.C., Benkiki, N., Chosson, E., Kabouche, Z., Seguin, E., Costentin, J., 2007. Antidepressant-like effect of hyperfoliatin, a polyisoprenylated phloroglucinol derivative from Hypericum perfoliatum (Clusiaceae) is associated with an inhibition of neuronal monoamines uptake. Eur. J. Pharmacol. 569 (3), 197–203. https://doi.org/10.1016/J.EJPAR.2007.05.008.

Fu, D.L., Lu, L., Zhu, W., Li, J.H., Li, H.Q., Liu, A.J., Xie, C., Zheng, G.Q., 2013 Jun 21.

Xiaoxuming decoction for acute ischemic stroke: a systematic review and meta-analysis. J. Ethnopharmacol. 148 (1), 1–13. https://doi.org/10.1016/j.jep.2013.04.002.
Flower, A., Witt, C., Liu, J.P., Ulrich-Merzenich, G., Yu, H., Lewith, G., 2012. Guidelines for. randomised controlled trials investigating Chinese herbal medicine. J. Ethnopharmacol. 140, 550–554. https://doi.org/10.1016/j.jep.2011.12.017.
François, C., Toumi, M., Aakhus, A.M., Hansen, K., 2003. A pharmacoeconomic evaluation of escitalopram, a new selective serotonin reuptake inhibitor. Comparison of cost-effectiveness between escitalopram, citalopram, fluoxetine, and venlafaxine for the treatment of depression in Norway. Eur. J. Health Econ. 4 (1), 12–19. https://doi.org/10.1007/s10198-002-0139-0.
Gao, X.L., Ma, L., Yan, Y.J., Ma, C.S., Qiao, J.G., 2013. Combine use of traditional Chinese and. western medicine for treating 60 cases of depression. Henan Tradit. Chin. Med. 33 (6), 943–944. https://doi.org/10.16367/j.issn.1003-5028.2013.06.094. (in Chinese).
Gao, X.Q., Lei, F.Y., 2012. Clinical observation on combine use of Jieyu Ningxin decoction. and Flupentixol and Melitracen for depression. Chin. J. Inform. TCM 19 (9), 76–77. https://doi.org/10.3969/j.issn.1005-5304.2012.09.029. (in Chinese).
Guo, C., Zheng, Q.M., Zheng, H.C., 2005. The study of antidepressant activity of the total flavonoids product from Hypericum sampsonii Hance. J. Pharm. Pract. 23 (6), 345–347. https://doi.org/10.3969/j.issn.1006-0111.2005.06.009. (in Chinese).
Guo, Z.K., Lv, Q., Zhang, C.L., Kong, F.X., 2009. The effect of yu-le decoction to major depression of stagnated heat type of heart-liver and level change of 5-HT and NE in the blood plasma. Chin. Arch. Tradit. Chin. Med. (8), 1720–1726. https://doi.org/10.13193/j.archtcm.2009.08.154.gouzhk.023. (in Chinese).
Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare, revised Bethesda, MD, pp. 217–222.
Guyatt, G., Oxman, A.D., Sultan, S., Brozek, J., Glasziou, P., Guyatt, G., et al., 2013. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J. Clin. Epidemiol. 66, 151–157. https://doi.org/10.1016/j.jclinepi.2012.01.006.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.
Huang, J.L., Wu, H.Y., Zhang, X.Y., 2016. Clinical observation on Shugan Jieyu capsule for treating depression. Guangming, J. Chin. Med. 31 (20), 2973–2974. https://doi.org/10.3969/j.issn.1003-8914.2016.20.030. (in Chinese).
Higgins, J.P.T.Altman, D.G.Sterne, J.A.C.The Cochrane Collaboration, Assessing risk of bias in. Included studes. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated march 2011). Chapter 8. www.cochrane-handbook.org, Accessed date: 25 April 2018.
Higgins, J.P.T., Green, S.R., 2012. Cochrane Handbook for Systematic Reviews of. Interventions. Version 5. 0. 1. The Cochrane Collaboration, Oxford, UK Updated March 2011. http://www.cochrane-handbook.org/.
Hu, Y., Zhou, X.J., Liu, P., Dong, X.Z., Mu, L.H., Chen, Y.B., et al., 2012. Antidepressant and. neuroprotective effect of the Chinese herb kaixinsan against lentiviral shRNA knockdown brain-derived neurotrophic factor-induced injury in vitro and in vivo. J. Affect. Disord. 141, 308–314. https://doi.org/10.1159/000358089.
Huo, J., Fu, H.P., Yang, J., Li, A.L., 2008. The clinical research of depressive disorder treated in. dan-zhi decoction for ease combined fluoxetine. J. Henan Univ. Chin. Med. 23 (3), 38–39. https://doi.org/10.3969/j.issn.1674-8999.2008.03.020. (in Chinese).
Huo, J., Fu, H.P., 2015. Combine use of Shugan Jieyu capsule and Paroxetine for treating 30. cases of depression. Tradit. Chin. Med. Res. (8), 30–32. https://doi.org/10.3969/j.issn.1001-6910.2015.08.14. (in Chinese).
Jiang, J.X., Zhou, Y., Yang, Y., Liang, L., 2015. The clinical research of depressive disorder. treated in Modified Dan-zhi decoction combined Fluoxetine. Modern J. Integr. Tradit. Chin. West Med. (33), 3715–3717. https://doi.org/10.3969/j.issn.1008-8849.2015.33.026. (in Chinese).
Jiang, M., Lu, C., Zhang, C., Yang, J., Tan, Y., Lu, A., Chan, K., 2012. Syndrome differentiation in modern research of traditional Chinese medicine. J. Ethnopharmacol. 140, 634–642. https://doi.org/10.1016/j.jep.2012.01.033.
Ji, Y., Shang, F., Sun, D.Y., Shan, D.H., Kang, T.G., Dong, P., 2009. Effect of guipi decoction on serum il-1β and hippocampus il-1r i expression of depression model rats. Chin. J. Inform. TCM 16 (8), 28–29 (in Chinese).
Keltner, N.L., Mcafee, K.M., Taylor, C.L., 2002. Mechanisms and treatments of SSRI- induced sexual dysfunction. Perspect. Psychiatr. Care 38 (3), 111–116. https://doi.org/10.1111/j.1744-6163.2002.tb00665.x.
Kennedy, S.H., Lam, R.W., McIntyre, R.S., Tourjman, S.V., Bhat, V., Blier, P., et al., 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can. J. Psychiatr. 61, 540–560. https://doi.org/10.1177/0706743716659417.
Khan, A., Khan, S.R., Shankles, E.B., Polissar, N.L., 2002. Relative sensitivity of the. Montgomery-Asberg depression rating scale, the Hamilton depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials: a replication analysis. Int. Clin. Psychopharmacol. 17 (6), 281–285. https://doi.org/10.1097/00004850-200211000-00003.
Kim, J.H., Kim, S.Y., Lee, S.Y., Jang, C.G., 2007. Antidepressant- like effects of Albizzia julibrissin in mice: involvement of the 5-HT1A receptor system. Pharmacol. Biochem. Behav. 87, 41–47. https://doi.org/10.1016/j.pbb.2007.03.018.
Kjaergard, L.L., Villumsen, J., Gluud, C., 2001. Reported methodologic quality and. discrepancies between large and small randomized trials in meta-analyses. Ann. Intern. Med. 135, 982–989. https://doi.org/10.7326/0003-4819-135-11-200112040-00010.
Kroenke, K., West, S.L., Swindle, R., Gilsenan, A., Eckert, G.J., Dolor, R., et al., 2001 Dec 19. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. J. Am. Med. Assoc. 286 (23), 2947–2955.
Kwon, S., Lee, B., Kim, M., Lee, H., Park, H.J., Hahm, D.H., 2010. Antidepressant-like effect of the methanolic extract from Bupleurum falcatum in the tail suspension test. Prog. Neuropsychopharmacol. Biol. Psychiatr. 34 (2), 265–270. https://doi.org/10.1016/j.pnpbp.2009.11.015.
Li, D.Q., Huang, P., Xiong, B., Feng, Y.B., Zhang, J.M., 2008. A comparative study of Deanxit and paroxetine in the treatment of anxiety/depression in cardiovascular medicine. Chin. J. Cardiovasc. Rev. 6 (11), 846–847. https://doi.org/10.3969/j.issn.1672-5301.2008.11.018.
Li, D.S., Yuang, L., Liu, Q., Wu, J.H., Zhang, Z.H., Lü, Y.J., 2015. Effect of baihe zhimu decoction on camp signal transduction pathway of depression rats. Med. J. Wuhan Univ. 36 (6), 867–871. https://doi.org/10.14188/j.1671-8852.2015.06.006. (in Chinese).
Li, H.C., Li, Q.B., Yang, X.Q., Wang, Y., Tian, X., Chen, X.G., 2014. Clinical study on Gui Pi Tang. treating the depression and improving the life quality in elderly patients. China J. Tradit. Chin. Med. Ph. (6), 1855–1859 (in Chinese).
Li, Y.Q., Chen, P.X., Luo, H.C., 2013. Control study of effects of shugan jieyu capsule and. paroxetine on treatment of depression. Chin. J. Trauma. Disabil. Med. (8), 71–72. https://doi.org/10.3969/j.issn.1673-6567.2013.08.044. (in Chinese).
Liu, E.J., Wang, L.Z., Zhao, F.G., Zhang, W.L., Zhao, W.B., Bai, Y.P., 2013a. A research on the. clinical effect of Shugan Jianwei Anshen decoction on the treatment of depression. Hebei J. Tradit. Chin. Med. 35 (5), 655–658. https://doi.org/10.3969/j.issn.1002-2619.2013.05.006. (in Chinese).
Liu, H.M., Li, J.F., Xiao, S.F., 2010. The effect of yule powder preparation for infusion on cognition ability of depression patient. J. Chin. Med. 25 (1), 127–130. https://doi.org/10.16368/j.issn.1674-8999.2010.01.045. (in Chinese).
Liu, J., Jia, H.X., Wang, J.Q., Xu, Y., Tian, J.Z., Shi, J., 2013b. Treatment of refractory depression. patients of yin deficiency inner heat syndrome by jieyu granule combined paroxetine: an efficacy observation. Chin. J. Integr. Tradit. West. Med. 33 (4), 462–465. https://doi.org/10.7661/CJIM.2013.4.462. (in Chinese).
Luo, H.C., Qian, R.Q., Zhao, X.Y., BI, J., Xin, H.L., Jiang, X.Z., 2006. Clinical observation on Danzhi Xiaoyao powder for treating depression. Chin. J. Integr. Tradit. West. Med. 26 (3), 212–214. https://doi.org/10.7661/CJIM.2006.3.212. (in Chinese).
Mao, Z.X., Yang, Y., Li, G.Q., Ma, J., Wang, Y., 2013. Comparative trial of a combined therapy. (yangyin-Qinggan decoction combined with paroxetine) versus monotherapy on depressive patients with somatic symptoms. Int. J. Tradit. Chin. Med. 25 (1), 52–55. https://doi.org/10.3969/j.issn.1672-0369.2013.20.044. (in Chinese).
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int. J. Surg. 8, 336–341. https://doi.org/10.1016/j.ijsu.2010.02.007.
Montgomery, Asberg, 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389. https://doi.org/10.1192/bjp.134.4.382.
Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease: A Comprehensive. Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard University Press, Cambridge.
Psychological Branch of Chinese Medical Association, 2001. China Classification and Diagnostic Criteria for Mental Disorder (CCMD-3). Shandong Science and Technology Press, Jinan, pp. 83–90 (in Chinese).
Qian, Z., Wang, S.L., Tao, W.W., Long, H.Y., Wang, J.W., 2016. Effects of Jiaotaiwan on depressive-like behavior in mice after lipopolysaccharide administration. Metab. Brain Dis. 32 (2), 415–426. https://doi.org/10.1007/s11011-016-9925-8.
Qin, F., Wu, X.A., Tang, Y., Huang, Q., Zhang, Z.J., Yuan, J.H., 2011. Meta-analysis. of. randomized controlled trials to assess the effectiveness and safety of free and easy wanderer plus, a polyherbal preparation for depressive disorders. J. Psychiatr. Res. 45 (11), 1518–1524. https://doi.org/10.1016/j.jpsychires.2011.06.018.
Ren, L., Chen, G., 2017. Rapid antidepressant effects of Yueju: a new look at the function and. mechanism of an old herbal medicine. J. Ethnopharmacol. 203, 226–232. https://doi.org/10.1016/j.jep.2017.03.042.
Ren, L.X., Luo, Y.F., Li, X., Zuo, D.Y., Wu, Y.L., 2006. Antidepres- sant-like effects of sarsasapogenin from Anemarrhena aspho- deloides Bunge (Liliaceae). Biol. Pharm. Bull. 29, 2304–2306. https://doi.org/10.1248/bpb.29.2304.
Saxena, S., Saraceno, B., 1993. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines. WHOhttps://doi.org/10.1097/00003246-198012000-00001.
Schulz, K.F., Altman, D.G., Moher, D., Group CONSORT, 2010. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. Open Med. 4, e60–e68. https://doi.org/10.1097/AOG.0b013e3181d9d421.
Shen, Z.M., Zhu, M.L., Zhao, A.Q., Yu, Z.J., Wang, L.P., Jiang, T., 2004. Comparative observation on efficacy of jieyu pill and maprotiline in treating depression. Chin. J. Integr. Tradit. West. Med. 24 (5), 415–417. https://doi.org/10.3321/j.issn:1003-5370.2004.05.008. (in Chinese).
Shi, X.L., Jiang, C.L., Zhao, X.F., Zhang, Y.Q., 2013. Study on the effects of Albizia julibrissin flower on cognitive function and plasma 5-Ht,Ne and da in patients with depression: a randomized parallel controlled multicenter clinical trial. J. Pract. Tradit. Chin. Int. Med. (6), 18–20. https://doi.org/10.3969/j. issn.1671-7813.2013.03(x).09. (in Chinese).
Shu, M., Zhang, Q., 2012. Comparative study on efficacy and compliance of Shugan Jieyu. capsule in treating mild to moderate depressive disorder. Heb. Med. J. 34 (12), 1883–1884. https://doi.org/10.3969/j.issn.1002-7386.2012.12.078. (in Chinese).
Song, B.H., Wang, S.K., Dai, H., 2011. Effect of shugan jieyu capsule on mild to moderate. Depression. Mod. Pract. Med. 23 (9), 1025–1026. https://doi.org/10.3969/j.issn.1671-0800.2011.09.031. (in Chinese).
Sørensen, J., Stage, K.B., Damsbo, N., Le Lay, A., Hemels, M.E., 2007. A Danish cost-effectiveness model of escitalopram in comparison with citalopram and venlafaxine as first-line treatments for major depressive disorder in primary care. Nord. J. Psychiatry 61 (2), 100–108. https://doi.org/10.1080/08039480701226070.
Su, G.Y., Yang, J.Y., Wang, F., Xiong, Z.L., Hou, Y., Zhang, K., et al., 2014. Xiaochaihutang prevents depressive-like behaviour in rodents by enhancing the

serotonergic system. J. Pharm. Pharmacol. 66, 823–834. https://doi.org/10.1111/jphp.12201.
Szegedi, A., Wetzel, H., Angersbach, D., Dunbar, G.C., Schwarze, H., Philipp, M., Benkert, O., 1997 May. A double-blind study comparing paroxetine and maprotiline in depressed outpatients. Pharmacopsychiatry 30 (3), 97–105. https://doi.org/10.1055/s-2007-979490.
Taichman, D.B., Backus, J., Baethge, C., Bauchner, H., de Leeuw, P.W., Drazen, J.M., et al., 2016. Sharing clinical trial data: a proposal from the international committee of medical journal Editors. Ann. Intern. Med. 164, 505–506. https://doi.org/10.4103/0366-6999.173420.
Tang, J.L., Liu, B.Y., Ma, K.W., 2008. Traditional Chinese medicine. Lancet 372, 1938–1940. https://doi.org/10.1016/s0140-6736(08)61354-9.
Thorlund, K., Walter, S.D., Johnston, B.C., Furukawa, T.A., Guyatt, G.H., 2011. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. Res. Synth. Methods 2 (3), 188–203. https://doi.org/10.1002/jrsm.46.
Tong, Z.S., Liu, Y., Xu, Y., 2016. A randomized controlled trial of paroxetine combined with jiawei xiaoyaosan for patients with depression. Sichuan Ment. Health 29 (1), 31–34. https://doi.org/10.11886/j.issn.1007-3256.2016.01.008. (in Chinese).
Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., et al., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in star*d: implications for clinical practice. Am. J. Psychiatry 163 (1), 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.
Viana, A., do Rego, J.C., von Poser, G., Ferraz, A., Heckler, A.P., Costentin, J., et al., 2005 Dec. The antidepressant-like effect of Hypericum caprifoliatum Cham & Schlecht (Guttiferae) on forced swimming test results from an inhibition of neuronal monoamine uptake. Neuropharmacology 49 (7), 1042–1052. https://doi.org/10.1016/j.neuropharm.2005.06.002.
Wang, J.M., Feng, W.S., Cui, Y., Zhang, Y.Y., Wang, G.F., Zhou, G., et al., 2014. A comparative study on the antidepressant effects of alcohol extract of Rehmannia glutinosa and water extract of its residue. Chin. Pharmaceut. J. 49 (23), 2073–2076. https://doi.org/10.11669/cpj.2014.23.005. (in Chinese).
Wang, X., Feng, Q., Xiao, Y., Li, P., 2015. Radix Bupleuri ameliorates depression by increasing nerve growth factor and brain-derived neurotrophic factor. Int. J. Clin. Exp. Med. 8 (6), 9205–9217.
Wang, X.F., Liu, L., Han, X.Y., 2010. Study of jieyu wan combined with fluoxetine in the. treament of major depression disorders. China J. Health Psychol. 18 (8), 911–913. https://doi.org/10.13342/j.cnki.cjhp.2010.08.013. (in Chinese).
Wang, Y., Gao, S.M., Li, R., Zhang, M., Gao, S., Yu, C.Q., 2016a. Antidepressant-like effects of the Radix Bupleuri and Radix Paeoniae Alba drug pair. Neurosci. Lett. 633, 14–20. https://doi.org/10.1016/j.neulet.2016.09.001.
Wang, Y., Li, M., Liang, Y., Yang, Y., Liu, Z., Yao, K., et al., 2017. Chinese herbal medicine for the treatment of depression: applications, efficacies and mechanisms. Curr. Pharmaceut. Des. 23 (34). https://doi.org/10.2174/1381612823666170918120018.
Wang, Y.Z., Zhong, W.W., Chen, J.Y., 2016b. Clinical observation on combine use of traditional. Chinese and western medicine for treating 60 cases of depression. Health Everyone 18 (in Chinese).
Wei, Q., Wei, X.H., 2011. Clinical observation on shugan bushen jieyu decoction plus maprotiline for 22 cases of depression. 1668-1667. J. Tradit. Chin. Med. 52 (19). https://doi.org/10.1038/cdd.2010.68. (in Chinese).
WHO Global Report, 2016. http://www.who.int/mediacentre/factsheets/fs369/en/.
Wu, L.M., Peng, Y.H., Lv, M.W., 2010. Clinical study of Shugan Jieyu capsule in treating mild to moderate depressive episode. Guangming, J. Chin. Med. 25 (12), 2259–2261. https://doi.org/10.3969/j.issn.1003-8914.2010.12.070. (in Chinese).
Wu, R.Y., Zhu, D.D., Xia, Y.C., Wang, H.S., Tao, W.W., Xue, W.D., et al., 2015. A role of yueju in fast-onset antidepressant action on major depressive disorder and serum bdnf expression: a randomly double-blind, fluoxetine-adjunct, placebo-controlled, pilot clinical study. Neuropsychiatric Dis. Treat. 11, 2013–2021. https://doi.org/10.2147/NDT.S86585.
Xian, H., Tang, Q.S., Zhao, J., 2008. Treatment of depression of liver-qistagnation and. spleen-deficiency type with therapy of soothing liver and invigorating spleen. J. Beijing Univ. Tradit. Chin. Med 31 (12), 856–859. https://doi.org/10.3321/j.issn:1006-2157.2008.12.017. (in Chinese).
Xiu, L.J., Sun, D.Z., Yang, Y.X., Jiao, J.P., Wei, P.K., 2010. Clinical effects of Bailong Jieyu granule on depression. 77-77. Chin. J. Inform Tradit. Chin. 17 (10). https://doi.org/10.3969/j.issn.1005-5304.2010.10.038. (in Chinese).
Xu, C.J., Teng, J.J., Chen, W.D., Ge, Q., Yang, Z.Q., Yu, C.Y., et al., 2010. 20 (S)-protopanaxadiol, an active ginseng metabolite, exhibits strong antidepressant-like effects in animal tests. Prog. Neuropsychopharmacol. Biol. Psychiatr. 34, 1402–1411. https://doi.org/10.1016/j.pnpbp.2010.07.010.
Xu, Q., Bauer, R., Hendry, B.M., Fan, T.P., Zhao, Z., Duez, P., et al., 2013. The quest for. modernization of traditional Chinese medicine. BMC Complement Altern. Med. (13), 132. https://doi.org/10.1186/1472-6882-13-132.
Xu, Q., Pan, Y., Yi, L.T., Li, Y.C., Mo, S.F., Jiang, F.X., et al., 2008 Jun. Antidepressant-like effects of psoralen isolated from the seeds of Psoralea corylifolia in the mouse forced swimming test. Biol. Pharm. Bull. 31 (6), 1109–1114. https://doi.org/10.1248/bpb.31.1109.
Yang, Q.X., Wang, R.S., Fan, H.Z., 2012. Clinical study on Jieyu pill plus Citalopram treating. the depression in 30 elderly patients. Tradit. Chin. Med. Res. 25 (4), 28–29. https://doi.org/10.3969/j.issn.1001-6910.2012.04.012. (in Chinese).
Ye, J.F., Lin, Y., Xia, J.M., 2014. Comparative study of Shugan Jieyu capsule and Sertraline in the treatment of senile depression. Chin. Tradit. Patent Med. 36 (5), 1104–1105. https://doi.org/10.3969/j.issn.1001-1528.2014.05.054. (in Chinese).
Ye, L., Hu, Z., Du, G., Zhang, J., Dong, Q., Fu, F., Tian, J., 2012. Antidepressant-like effects of the extract from Cimicifuga foetida L. J. Ethnopharmacol. 144, 683–691. https://doi.org/10.1016/j.jep.2012.10.013.
Yeung, W.F., Chung, K.F., Ng, K.Y., Yu, Y.M., Ziea, E.T., Ng, B.F., 2014. A systematic review. on the efficacy, safety and types of Chinese herbal medicine for depression. J. Psychiatr. Res. 57 (1), 165–175. https://doi.org/10.1016/j.jpsychires.2014.05.016.
Yi, R., Zhu, C., Wu, J., Zheng, R., Cao, H., 2015. Comparison between herbal medicine and fluoxetine for depression: a systematic review of randomized controlled trials. Complement. Ther. Med. 23 (5), 674–684. https://doi.org/10.1016/j.ctim.2015.07.002.
Yi, Z.H., Zhu, L.P., Long, B., Yao, P.F., Zhao, G.X., Shen, A.Z., et al., 2010. Clinical observation. on treatment of major depressive disorder by paroxetine combined with chaihu xiaoyao mixture. Chin. J. Integr. Tradit. West. Med. 30 (30), 1257–1260 (in Chinese).
Yu, W., Ma, M., Chen, X., Min, J., Li, L., Zheng, Y., Li, Y., et al., 2017. Traditional Chinese medicine and constitutional medicine in China, Japan and Korea: acomparative study. Am. J. Chin. Med. 45, 1–12. https://doi.org/10.1142/S0192415X1750001X.
Yu, Y.Q., Wu, H.G., 2013. Clinical observation on combine use of Xiaoyao Powder and Sertraline Hydrochloride for treating 60 cases of depression. Guiding J. Tradit. Chin. Med Pharm. (9), 53–54. https://doi.org/10.3969/j.issn.1672-951X.2013.09.024. (in Chinese).
Zhang, H.C., Chen, Y.Y., Wang, W.R., Fu, X., 2018. Serum metabolomics study of chaihu-baishao on depression in rats. Inform. on TCM 35 (1), 34–37. https://doi.org/10.19656/j.cnki.1002-2406.180011. (in Chinese).
Zhang, J.M., Zhu, L.P., 2010. Adverse reactions of Chaihu Xiaoyao mixture in treatment of. depressive disorder. Chin. J. N. Drugs Clin. Remedies 29 (6), 472–475 (in Chinese).
Zhang, Q.Q., Meng, Y., 2017. Clinical research of Yangxin Tang combined with escitalopram in the treatment of depression. J. Chin. Med. 32 (6), 1011–1014. https://doi.org/10.16368/j.issn.1674-8999.2017.06.265. (in Chinese).
Zhang, X.P., Zhuang, J.J., Wu, M., 2015. Mild to moderate depression randomized controlled study jiawei xiaoyao capsules combined with western medicine. J. Pract. Tradit. Chin. Intern. Med. (8), 69–71. https://doi.org/10.13729/j.issn.1671-7813.2015.08.35. (in Chinese).
Zhang, Y., Chen, J., Yang, L.Q., Lin, Y., Li, X.T., Wu, X.Q., 2012. Clinical efficacy of Qishen Fukang capsule and fluoxetine in treating first-episode depression. Shaanxi J. Tradit. Chin. Med. 33 (8), 1028–1032. https://doi.org/10.3969/j.issn.1000-7369.2012.08.057. (in Chinese).
Zhang, Z.J., Kang, W.H., Li, Q., Tan, Q.R., 2007b. The beneficial effects of the herbal medicine. free and easy wanderer plus (fewp) for mood disorders: double-blind, placebo-controlled studies. J. Psychiatr. Res. 41 (10), 828–836. https://doi.org/10.1016/j.jpsychires.2006.08.002.
Zhang, Z.J., Kang, W.H., Tan, Q.R., Li, Q., Gao, C.G., Zhang, F.G., et al., 2007a. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. J. Psychiatr. Res. 41 (3–4), 360–369. https://doi.org/10.1016/j.jpsychires.2005.06.002.
Zhu, C.J., Li, X., Qu, M., 2014. Guipi decoction for treating 30 cases of heart-spleen. Deficiency depression. Chin. J. Exp. Tradit. Med. Formulae 20 (16), 209–213. https://doi.org/10.13422/j.cnki.syfjx.2014160209. (in Chinese).
Zhu, D.D., Wu, R.Y., Zhou, X., Xia, Y.C., Tai, W.T., Chen, G., 2016. Rapid antidepressant effects of yueju pill on major depression. Liaoning J. Tradit. Chin. Med. (2), 311–313. https://doi.org/10.13192/j.issn.1000-1719.2016.02.035. (in Chinese).
Zhu, W., Ma, S., Qu, R., Kang, D., Liu, Y., 2006. Antidepressant effect of baicalin extracted from the root of Scutellaria baicalensis in mice and rats. Pharm. Biol. 44, 503–510.
Zimmerman, M., Martinez, J.H., Young, D., Chelminski, I., Dalrymple, K., 2013. Severity. Classification on the Hamilton depression rating scale. J. Affect. Disord. 150, 384–388. https://doi.org/10.1016/j.jad.2013.04.028.
Zung, W.W., Gianturco, J.A., 1971. Personality dimension and the self-rating depression scale. J. Clin. Psychol. 27, 247–248. https://doi.org/10.1002/1097-4679(197104)27:23.0.CO;2-6.