Journal of Psychiatric Research 57 (2014) 165–175

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

# A systematic review on the efficacy, safety and types of Chinese herbal medicine for depression

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ARTICLE INFO

*Article history:*
Received 12 March 2014
Received in revised form
5 May 2014
Accepted 28 May 2014

*Keywords:*
Chinese herbal medicine
TCM
Depression
Systematic review
Meta-analysis

ABSTRACT

Chinese herbal medicine (CHM) is one of the commonly used complementary and alternative medicine therapies for major depressive disorder. The objective of this study was to review the efficacy, safety and types of CHM for depression. We systematically searched key databases (9 Chinese and 7 English) up until May 2013 for randomized controlled trials (RCTs) and examined 7 systematic reviews for additional articles. Methodological quality was assessed by modified Jadad scale and Cochrane's risk of bias assessment. Only studies with moderate methodological quality, defined as modified Jadad scale score $\geq$3, were included in meta-analysis for efficacy. Of the 296 RCTs that were assessed in details, 278 (93.9%) had modified Jadad scale score < 3, and only 21 scored $\geq$ 3. The frequently used formulas were Xiao Yao decoction, Chaihu Shugan decoction and Ganmai Dazao decoction; while Chaihu, Bai Shao and Fu Ling were the frequently used single herb. Meta-analyses showed that CHM monotherapy was better than placebo and as effective as antidepressants in reducing Hamilton Depression Rating Scale (HDRS) score (CHM vs. placebo: mean difference: −7.97, 95% CI: −10.25 to −5.70, $P < 0.00001$, 2 studies; CHM vs. antidepressants: mean difference: 0.01, 95% CI: −0.28 to 0.30, $P = 0.95$, 7 studies). CHM were associated with less adverse events than antidepressants, and adding CHM to antidepressants reduced adverse events. Despite the overall positive results, due to the small number of studies with sufficient methodological quality, it is premature to accurately conclude the benefits and risks of CHM for depression.


## 1. Objectives of the study and background

According to the Global Burden of Disease Study 2010, major depressive disorder (MDD) was ranked the second leading cause of years lived with disability, after low back pain, accounting for 8.2% of all years lived with disability (Ferrari et al., 2013). The World Mental Health Survey Initiative showed that the average lifetime prevalence for major depressive episode based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV, American Psychiatric Association, 1994) was 14.6% in 10 high-income countries and 11.1% in 8 low- to middle-income countries (Bromet et al., 2011). MDD not only affects individuals' work, school and daily life, but it also affects their life satisfaction and perceived well-being. As the number of people with depression is rapidly increasing across the world (Baxter et al., 2014), more effective treatments should be identified in order to reduce the potential harms MDD brings to sufferers' lives.

Pharmacotherapy is currently the most commonly used treatment for MDD because of its reported effectiveness. However, complaints such us nausea, headache, insomnia, agitation, weight gain daytime somnolence and sexual dysfunction are often reported during the course of treatment, leading to treatment termination in some patients. Psychological treatments for depression are also commonly used. Despite its proven effectiveness, the use of psychotherapy is limited by its time-intensive nature, limited access to skilled providers, high cost, and requirement of patients' participation and motivation. According to the World Health Organization Mental Health Atlas 2011, psychosocial interventions were not readily available in more than half of the countries surveyed, especially the low income countries (World Health Organization, 2011). Faced with the limitations of the

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http://dx.doi.org/10.1016/j.jpsychires.2014.05.016
0022-3956/

currently available treatments, the use of complementary and alternative medicine for depression is common. A national representative survey in the United States found that 53.6% of people with self-reported depression reported using some forms of complementary and alternative therapies to treat depression during the past 12 months (Kessler et al., 2001). A large number of studies have been performed to examine the effectiveness of complementary and alternative therapies for mood disorders (Qureshi and Al-Bedah, 2013), suggesting that there is a demand for treatments other than pharmacotherapy and psychotherapy.

Chinese herbal medicine is one of the most commonly used modalities of complementary and alternative medicine therapies, especially in Chinese culture (Hsu et al., 2008). There have been previous systematic reviews on specific CHM formulas, including Chaihu-Shugan-San (Wang et al., 2012) and Xiao-Yao-San (Qin et al., 2011; Zhang et al., 2012). These reviews were limited by the poor methodological quality of the studies included in analysis and the grouping of bipolar disorder as depression. There were two other systematic reviews on CHM for depression (Butler and Pilkington, 2013; Zhao et al., 2009). The review by Butler and Pilkington (2013) was based on previous systematic reviews supplemented by an update search of English databases, whereas the study by Zhao et al. (2009) searched only one Chinese database. In addition, the pattern of CHM use for depression was not examined in previous reviews. In view of the shortcomings of previous studies, this systematic review aimed to: (1) summarize the efficacy and safety of CHM, as either monotherapy or adjunct therapy, in treating depression, with attention to studies with better methodological quality and (2) determine the most commonly used CHM formulas and single herbs for the treatment of depression.

## 2. Materials and methods

Nine Chinese language databases (China Journals Full-text Database, China Proceedings of Conference Full-text Database, Chinese Biomedical Literature Database, China Doctor Dissertations Full-text Database, China Master Theses Full-text Database, Chinese Science and Technology Documents Database, Chinese Dissertation Document Bibliography Database, Taiwan Electronic Periodical Services, and WanFang Database) and seven English language databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine, PsycINFO and ProQuest Dissertations and Theses A&I) were searched by two researchers independently up until May 2013 using the grouped terms (depression* OR depressive* OR dysthymia* OR mood disorder* OR "affective disorder*" OR "affective symptoms" OR MDD) AND (Chinese herb* OR herbal medicine* OR traditional Chinese medicine* OR TCM OR Chai-Hu-Shu-Gan-San OR ChaiHuShuGan* OR Xiao-Yao-San OR Xiao Yao* OR Ban-Xia-Hou-Pu-Tang OR Ban Xia Hou Pu* OR Gan-Mai-Da-Zao-Tang OR GanMai DaZao* OR Gui-Pi-Tang OR GuiPi* OR Wen-Dan-Tang OR WenDan OR Yue-Ju-Wan OR Yue-Ju) and their equivalent Chinese terms. The reference lists of the included papers and previous systematic reviews (Kou and Chen, 2012; Wang et al., 2012; Qin et al., 2010; Qin et al., 2011; Butler and Pilkington, 2013; Zhao et al., 2009; Zhang et al., 2012) were further searched for relevant articles. We included saffron as a CHM because saffron has a long history of use in China despite its Persian origin. The use of saffron was documented in "Compendium of Materia Medica", one of the most respected Chinese medical texts written in 1578, which termed saffron as "foreign red flower" (Feng, 2014). The herb is now named as "Western red flower" in the pharmacopoeia of China (Ministry of Health of the People's Republic of China (2010)). There was no language restriction in our search.

Studies included in this review were randomized or quasi-randomized clinical trials that examined participants with depression according to one of the following diagnostic criteria: the DSM-IV (American Psychiatric Association, 1994), Research Diagnostic Criteria (RDC, Spitzer et al., 1989), Chinese Classification of Mental Disorders, Second-Revised/Third Edition (CCMD-2-R/3, Chinese Psychiatric Society, 2001) or other relevant criteria. The included studies should include one of the following comparisons: (1) CHM vs. placebo, antidepressants, psychotherapy, or routine care; (2) CHM in combination with antidepressants, psychotherapy, or routine care vs. antidepressants, psychotherapy, or routine care alone; and (3) CHM in combination with placebo antidepressants vs. antidepressants in combination with CHM placebo. In addition, at least one of the following outcome measures was used: (1) self-rating scales, (2) clinician-rated scales, or (3) effective rate, which was often defined as the proportion of subjects who had at least 30% reduction in depression score. Secondary outcome examined in this study was the occurrence of adverse events.

Two authors (KN and YY) searched the databases and selected the relevant publications independently. Any disagreement about the eligibility of a study was resolved by discussion, and consultation with the senior authors (WY and KC). One author extracted the data (KN) and the other (YY) checked the extracted data. For each study, we examined the study design, patients' characteristics including age, gender, and duration of depression, CHM treatment, control intervention and outcome parameter. We analyzed the methodological quality of the studies using the modified Jadad scale (Jadad et al., 1996; White and Ernst, 1999) and the Cochrane's risk of bias assessment (Higgins and Green, 2011). The modified Jadad scale score ranges from 1 to 5; points are awarded if study: is described as randomized, 1 point; has appropriate randomization method, 1 point; is described as subject-blinded, 1 point; is described as evaluator-blinded, 1 point; and has description of withdrawals and dropouts, 1 point. Studies with a modified Jadad score $\geq$3 were considered to be moderate-quality randomized controlled trials (RCTs) (Manchikanti et al., 2011). The risk of bias assessment appraises a study in six domains: adequate sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. Each domain can be rated as "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (uncertain risk). A meta-analysis for efficacy would be performed only if studies were similar in clinical characteristics and had moderate methodological quality (modified Jadad score $\geq$ 3). Data were summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary outcome; mean difference (MD) or standardized mean difference (SMD), if different studies measured the same outcome in different scales, with 95% CI was used for continuous outcome. The incidence of any adverse events was summarized using rate ratio (RaR).

## 3. Results

### 3.1. Description of the paper selection process and overview of the reviewed studies

The search yielded 5097 potential titles, of which 929 were duplicate records and 3594 were excluded for reasons of irrelevance. The full text of 574 articles were retrieved for assessment, of which 278 were excluded for various reasons (Fig. 1). Full details of the excluded studies are available from the authors upon request. Of the remaining 296 studies that were examined in details, 104 studies used Western antidepressants as comparators, 108 studies on adjunctive CHM with antidepressants vs. antidepressants alone, while only seven studies used placebo control. The sample size of the 296 studies ranged from 30 to 1024, with a total of 24,876