REVIEW ARTICLE

Managing Depression with *Bupleurum chinense* Herbal Formula: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objectives: *Bupleurum chinense* (BC; Radix Bupleuri) formulae are widely used in herbal medicine clinical practice for major depressive disorder (MDD). This study provides an up-to-date and comprehensive systematic review and meta-analysis of BC formula for MDD.

Design: Randomized controlled trials were retrieved from English and Chinese databases, from their inceptions to March 2019. Included studies compared BC formula alone or as integrative medicine to selective serotonin reuptake inhibitor (SSRI) antidepressants. Studies included adults 18–65 years of age. People with other types of depression or physical comorbidities, such as poststroke depression, bipolar, and other mental or physical disorders, were excluded. Meta-analysis was performed using STATA software. Grading of Recommendations Assessment, Development, and Evaluation was also conducted to assess the quality of evidence.

Results: Thirty studies compared BC formula to antidepressants and 25 studies compared BC formula plus antidepressants to antidepressants alone. BC formula was more effective than antidepressants at improving depression severity measured on the Hamilton Rating Scale for Depression (HRSD) (standardized mean difference [SMD] -0.35 , 95% confidence interval [CI] -0.52 to -0.18 , $I^2 = 81.2\%$). Integrative use of BC formula plus SSRIs was also superior to SSRIs alone at improving HRSD scores (SMD -1.03 , 95% CI -1.43 to -0.62 , $I^2 = 94.2\%$). However, heterogeneity of the included studies was high and quality was low. The total number and severity of adverse events in the BC formula groups were less than that in the antidepressant groups.

Conclusions: BC formula alone or given as integrative medicine with antidepressants reduced depression severity. However, the evidence is low quality and at risk of bias. Well-designed studies are needed to validate the results we identified in this review.

Keywords: major depressive disorder, *Bupleurum chinense*, herbal medicine, systematic review, meta-analysis, randomized controlled trial

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Introduction

MAJOR DEPRESSIVE DISORDER (MDD), commonly referred to as depression, unipolar depression, or clinical depression, is one of the most common mood disorders affecting individuals and societies worldwide.^{1,2} It is associated with significant disability and mortality, and accounts for more than 40% of all mental disorders and substance abuse disorders.³ It is characterized by sadness, loss of interest, and decreased energy, as well as other symptoms, including reduced self-esteem, loss of confidence, inappropriate or excessive guilt, and thoughts of death or suicide.⁴

Depression is increasing in prevalence⁵ and is predicted to be the second most common burden of disease by 2020.⁶ The Global Burden of Disease Study reported that the disability-adjusted life years for MDD ranked 15th in 1990 and 11th in 2010.⁷ It is estimated that as many as 12% of the population, both in developed and developing countries, will experience depression in their lifetime.⁸

In primary care practice, people with depression are commonly prescribed antidepressants, such as selective serotonin reuptake inhibitors (SSRIs).^{9,10} However, these treatments often need to be maintained even after remission and patients can become noncompliant when using antidepressants.^{1,11–13} Noncompliance is sometimes due to adverse events, such as dry mouth, dizziness, gastrointestinal effects, sexual dysfunction, sedation, and weight gain.^{14–17} Discontinuing medication and noncompliance have been reported to be associated with increased risk of recurrence of depression and high medical costs.^{18,19}

People with depression often use herbal medicine to alleviate symptoms or to avoid adverse events caused by antidepressants. In addition, they often believe herbal medicines are safe.^{20,21} Research also indicates depression is an indicator and predictor of herbal medicine use.^{22,23} However, there is a lack of evidence showing a statistically significant benefit or reduction in harms of herbal medicine compared to antidepressants.^{24,25}

Research has revealed a variety of chemicals, pharmacological agents, and clinical benefits of herbs for depression.^{26,27} *Bupleurum chinense* DC (termed BC in this article) [Radix Bupleuri; Family: Apiaceae; Chinese name: Chai hu] is one of the most important herbs in Chinese medicine for depression and has been widely used in Asia and increasingly used in Western countries. Approximately, 74 compounds have been isolated from BC, including essential oils, triterpenoid saponins, polyacetylenes, flavonoids, lignans, fatty acids, and sterols.²⁸ BC is commonly combined with other herbal ingredients to make a formula (e.g., BC is combined with *Citrus reticulata*, *Ligusticum chuanxiong*, *Citrus aurantium*, *Paeonia lactiflora*, *Glycyrrhiza* spp., and *Cyperus rotundus* to make Chai hu shu gan san; or with *Angelica sinensis*, *P. lactiflora*, *Actinolydes macrocephala*, *Poria cocos*, *Glycyrrhiza* spp., *Mentha haplocalyx*, and *Zingiber officinale* to make Xiao yao san).

Previous systematic reviews of randomized controlled trials (RCTs) of BC formula, including Chai hu shu gan san and Xiao yao san, indicate that BC formula may be effective for depression, subclinical depression, including dysthymia, and secondary depression, such as poststroke depression.^{29,30} However, the results from previous reviews were limited by poor quality studies. This systematic review

provides an updated and focused assessment and analysis of the efficacy and safety of all types of BC formula for MDD compared to SSRI antidepressants.

Methods

We followed the methods described in the *Cochrane Handbook of Systematic Reviews*.³¹

Inclusion and exclusion criteria

This review is a part of a larger project initiated by the China–Australia International Research Centre for Chinese Medicine and a systematic review protocol is registered with PROSPERO (CRD42018091770). The inclusion and exclusion criteria were predefined by the review team before data extraction.

Participants. Included studies were prospective, parallel RCTs, with participants 18–65 years of age and diagnosed with depression based on established clinical guidelines, including the *Diagnostic and Statistical Manual of Mental Disorders* (DSM),⁴ the *Chinese Classification of Mental Disorders* (CCMD-3),³² and the *International Classification of Diseases* (ICD-10).³³ We excluded studies that included participants with other types of depression, such as bipolar disorder, dysthymia, depressive symptoms caused by other mental or physical disorders, or depression caused by another medical condition or a substance.

Interventions and comparators. We included studies that used oral BC formula alone or in combination with other herbs as the intervention. We chose SSRIs as the comparator in this review, because clinical guidelines recommend SSRIs to treat depression.^{16,34,35} We excluded studies that did not specify the type of antidepressants used as comparator.

Outcomes. Prespecified outcomes included clinician-rated scales, such as the Hamilton Rating Scale for Depression (HRSD),³⁶ and self-rated scales, such as the Zung's Self-Rating Depression Scale (SDS)³⁷ and the Montgomery-Asberg Depression Rating Scale.³⁸ These scales measure depression severity and related symptoms. Other outcomes included number of participants who relapsed or achieved remission, quality of life, functional capacity (e.g., social adjustment scales), suicidality, and adverse events.

Search strategy

We searched English and Chinese databases from their inception to March 2019. English databases included PubMed, Excerpta Medica Database (Embase), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Comparator Trials (CENTRAL), and Allied and Complementary Medicine Database (AMED). Chinese databases included China BioMedical Literature (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), and Wanfang.

Search terms were mapped to controlled vocabulary in three groups: (1) condition (depression, depressive disorder, unipolar depression, major depression, major depressive disorder, and related terms); (2) intervention type (Chinese herbal medicine, herbal medicine, *Bupleurum chinense*, and

related terms); and (3) study design (randomized controlled trials and related terms) (Supplementary Table S1).

In addition to electronic databases, we searched the reference lists of previous systematic reviews and their included studies. We also searched clinical trial registries for completed studies, including the United States National Institutes of Health register (ClinicalTrials.gov), the Chinese Clinical Trial Registry (ChiCTR), the European Union Clinical Trials Register (EU-CTR), and the Australian New Zealand Clinical Trials Registry (ANZCTR).

Data extraction

Search results from the English and Chinese databases were merged and duplicates were removed. Three reviewers (L.Y., J.L.S., and Y.M.D.) screened titles and abstracts and disagreements were resolved by discussion with a fourth reviewer (A.L.Z.). Full texts were obtained and screened against the inclusion criteria. Two reviewers (L.Y. and Y.M.D.) independently extracted data from relevant studies in EpiData software (EpiData Association, Odense, Denmark). Data checking and disagreements were resolved by discussion with a third reviewer J.L.S. Data included author names, publication year, title, journal, location, study design, diagnostic criteria, age, gender, intervention, comparator, outcome measures, treatment duration, sample size, dropouts, and adverse events.

Risk of bias

Two reviewers (L.Y. and Y.M.D.) independently used the risk of bias assessment tool from the Cochrane Handbook to assess risk of bias for each publication.³¹ A third reviewer (J.L.S.) resolved any disagreement about risk of bias. Potential publication bias was assessed using Funnel plots and Egger's test.

Data analysis

Studies were synthesized using meta-analysis. Continuous outcome data were analyzed using mean difference (MD) and 95% confidence intervals (CIs). When different versions of outcome measures were used, standardized mean difference (SMD) was used for data analysis. Statistical heterogeneity was assessed using the I^2 statistic. An I^2 over 50% was considered to be an indicator of substantial heterogeneity.³¹ Subgroup analyses were planned based on participant characteristics and study design, such as treatment duration, low risk of bias for sequence generation, and different versions of outcome measures.

Results

Characteristics of the included studies

Database searches identified 30,733 citations. After removing duplicates and excluding ineligible studies, we included a total of 55 RCTs (Fig. 1).^{39–93} Thirty of these RCTs (54.5%) compared BC formula to SSRIs, and 25 RCTs (45.5%) compared BC formula plus SSRIs to SSRIs alone (Table 1). All clinical studies were conducted in China and published from 2006 to 2017. Studies enrolled 5572 participants (sample size range: 46–480). Participants' ages ranged from 18 to 65 years. The duration of depression

ranged from 1 month to 15 years, including single and recurrent episodes. Treatment duration ranged from 2 to 12 weeks (Table 1).

All BC formula treatments were orally administered by the following herbal preparations: decoctions, oral solutions, capsules, granules, pills, and tablets. The studies used 49 BC formula and 103 different herbs. The most common formulae (including their modified forms) were *Xiao yao san/wan* (12 studies, 21.8%), *Chai hu shu gan san* (5 studies, 9.0%), *Suan zao ren tang* (2 studies, 3.6%), and *Bu shen shu gan hua yu tang* (2 studies, 3.6%) (Table 1).

The studies included the following SSRIs: fluoxetine (29 studies, 52.7%), paroxetine (16 studies, 29.1%), sertraline (7 studies, 12.7%), citalopram (2 studies, 3.6%), and escitalopram (1 study, 1.8%). All comparators were fixed dose and recommended by current clinical guidelines.^{16,34,94}

In terms of outcome measures, depression symptoms were commonly assessed using the HRSD (54 studies, 98.2%) and SDS (7 studies, 12.7%). Quality of life was assessed using the Short Form 36-Item Health Survey (SF-36) in one study (1.8%). Relapse and remission of depression, functional capacity, and suicidality were not assessed in the included studies. Adverse events were reported in 22 studies (40%). All events were considered mild (Table 4).

Risk of bias

All studies were described as randomized; however, only 14 (25.5%) described an appropriate method of random sequence generation and were judged at low risk of bias. Two (3.6%) described an appropriate method of allocation concealment, while 53 (96.4%) did not describe the details of allocation concealment, so were judged as having unclear risk of bias. Blinding of participants and personnel was reported in six studies (10.9%); these were judged to be at low risk of bias, while the remaining 49 studies (89.1%) were judged at high risk of bias. The method of blinding of outcome assessors was judged at low risk of bias in eight studies (14.5%). Outcome data were available for most studies, with 54 (98.1%) judged at low risk of bias. Selective outcome reporting was judged at unclear risk in all the studies because protocols were not available. Risk of bias assessment for each study is included in Table 1 and Figure 2.

Publication bias

Funnel plots and Egger's tests were reviewed for two comparisons. For BC formula versus SSRIs for HRSD, the funnel plot was asymmetrical and publication bias was detected (Egger's test $t = -2.37$, 95% CI -4.8 to -0.35 , $p = 0.025$). However, for BC formula plus SSRIs versus SSRIs for HRSD, the funnel plot was symmetrical and publication bias was not detected (Egger's test $t = -1.41$, 95% CI -15.27 to 2.91 , $p = 0.17$). The number of studies reporting other outcomes was less than 10, and funnel plot evaluation was not appropriate (Fig. 3).

BC Formula Versus SSRIs

Hamilton Rating Scale for Depression

Thirty of the 55 studies (3459 participants) used the HRSD to assess severity of depression (Table 1).^{39–41,45,49,50,53–55,57–61,63,64,68,69,71,76,81–85,87,88,90,92,93} Several versions of the HRSD,

FIG. 1. Flow chart of study selection process.

including HRSD-17 and HRSD-24, were used across these studies. Therefore, SMD was used to pool studies. After 2–12 weeks of treatment, significant reductions in the HRSD scores were seen in BC formula groups compared to SSRI groups (SMD -0.35 [-0.52 to -0.18]; $I^2=81.2\%$), although heterogeneity was substantial, and quality of the evidence was very low (Fig. 4 and Table 2).

In terms of studies judged at low risk of bias for sequence generation, there were no significant differences between BC formula and SSRIs after subgroup analysis. Treatment for 6 weeks or less in 20 studies favored BC formula (SMD -0.33 [-0.50 to -0.16]; $I^2=68.5\%$), as did treatment equal to or greater than 6 weeks in 10 studies (SMD -0.41 [-0.80 to -0.02]; $I^2=90.2\%$). BC formula reduced depression severity more than the SSRI fluoxetine (SMD -0.42 [-0.64 to -0.21]; $I^2=85.0\%$, 21 studies), but there was no statistical difference when compared to the SSRI paroxetine or sertraline. Subgrouping the HRSD version (Version 17) showed that BC formula was superior to SSRIs (SMD -0.25 [-0.47 to -0.04]; $I^2=67.8\%$, 11 studies), although it was not superior in the HRSD-24 subgroup (SMD -0.19 [-0.46 to 0.08]; $I^2=76.6\%$, 10 studies). Heterogeneity remained substantial after subgrouping and the reasons were not identifiable.

Zung's Self-Rating Depression Scale

The SDS was assessed in four studies comparing BC formula to SSRIs (283 participants).^{53,68,81,88} Treatment

duration ranged from 3 to 9 weeks. Two studies used fluoxetine as comparator, and the other two used paroxetine. After treatment, BC formula was superior to SSRIs (MD -1.53 [-3.03 to -0.03]; $I^2=23.8\%$); low quality evidence (Table 2).

Adverse events

Twelve (40.0%) of the studies comparing BC formula with SSRIs reported adverse events.^{40,45,49,50,55,57,58,63,71,85,87,92} People allocated BC formula interventions reported 125 adverse events and people allocated SSRIs reported 286 adverse events. Ten studies reported details about adverse events. In BC formula groups, 85 detailed adverse events were reported. Dry mouth (16 cases) and loss of appetite (16 cases) were the most common, followed by nausea (9 cases). In the SSRI groups, 196 detailed adverse events were reported, including dry mouth (53 cases), loss of appetite (31 cases), and nausea (14 cases). Two studies reported the nature of the events, but did not specify the number of adverse events in the SSRI group (Table 4).^{55,63}

BC Formula Plus SSRIs Versus SSRIs

Hamilton Rating Scale for Depression

Twenty-four studies, including 2041 participants, used the HRSD to compare the effects of BC formula plus SSRIs with the same SSRIs alone.^{43,44,46–48,51,52,56,62,65–67,70,72–75,77–80,86,89,91}

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

First author, year	Number of participants (I:C)	Intervention	Control	Outcomes	Treatment duration	Risk of bias (SG, AC, BPt, BPn, BOA, IOD, SG, Other) ^{a,b}
Cao, 2010 ³⁹	60 (30:30)	Chai hu jie yu tang 柴胡解郁汤, 1 package bid	Paroxetine, 20 mg qd	HRSD	5 weeks	U, U, H, H, H, L, U, L
Chen, 2014 ⁴⁰	65 (34:31)	Jia wei xiao yao capsule 加味逍遥胶囊, 3 capsules qd + placebo of Sertraline 25–50 mg qd	Sertraline 25–50 mg qd + placebo of Jia wei xiao yao capsule, 3 capsules qd	HRSD, AEs	8 weeks	L, L, L, L, L, U, L
Chen, 2016 ⁴¹	60 (30:30)	Modified Xiao yao san 逍遥散加减方, 1 package qd	Fluoxetine, 20 mg qd	HRSD	8 weeks	U, U, H, H, H, L, U, L
Cheng, 2008 ⁴²	72 (36:36)	Unnamed formula (Chen pi, Chao bai zhu, Dang shen, Zhi Gan cao, Qin ban xia, Fu ling, Mu xiang, Sha ren, Huo xiang, Hong po, Zi su, Pei lan, Bai dou kou, Chai hu, Zhi ke, He huan pi), 1 package qd + Paroxetine, 20–40 mg qd once per day	Paroxetine, 20–40 mg qd	SDS	6 weeks	U, U, H, H, H, L, U, L
Ding, 2006 ⁴³	70 (35:35)	Tong luo jie yu tang 通络开郁汤, 1 package qd + Sertraline, 50–100 mg qd	Sertraline, 50–100 mg qd	HRSD, TESS, AEs	8 weeks	L, U, H, H, H, L, U, L
Dong, 2016 ⁴⁴	142 (71:71)	Modified Zhi zi chi tang 加味栀子豉汤, 1 package qd + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD, SDS, AEs	12 weeks	U, U, H, H, H, L, U, L
Guo, 2011 ⁴⁵	72 (38:34)	Chai hu shu gan san combined with Gan mai da zao tang 柴胡疏肝散合甘麦大枣汤, 1 package bid	Fluoxetine, 20 mg qd	HRSD, AEs	4 weeks	L, U, H, H, H, L, U, L
Guo, 2010 ⁴⁶	60 (30:30)	Chai hu shu gan san 柴胡疏肝散, 1 package bid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
He, 2008 ⁴⁷	100 (50:50)	Modified Xiao yao san 逍遥散加减, 1 package qd + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD	4 weeks	U, U, H, H, H, U, U, L
Jiang, 2016 ⁴⁸	90 (45:45)	Modified Chai hu tang 加味柴胡汤, 1 package qd + Paroxetine, 20 mg qd	Paroxetine, 20 mg qd	HRSD, TESS, SF-36	8 weeks	L, U, H, H, H, L, U, L
Li, 2014 ⁴⁹	60 (30:30)	Modified Er xian tang 加味二仙汤, 1 package qd	Fluoxetine, 20 mg qd	HRSD, AEs	6 weeks	U, U, H, H, H, L, U, L
Li, 2013 ⁵⁰	150 (75:75)	Tang he chen qi tang combined with Xiao chai hu tang 桃核承气汤合小柴胡汤加减, 1 package bid	Fluoxetine, 20 mg qd	HRSD, AEs	6 weeks	U, U, H, H, H, L, U, L
Lian, 2013 ⁵¹	80 (40:40)	Dan zhi xiao yao san 丹栀逍遥散 1 package qd + Sertraline, 50–200 mg qd	Sertraline, 50–200 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Liang, 2010 ⁵²	76 (38:38)	Modified Xiao yao san 逍遥散加减, 1 package bid + Paroxetine, 20 mg qd	Paroxetine, 20 mg qd	HRSD, AEs	6 weeks	H, U, H, H, H, L, U, L

(continued)

TABLE 1. (CONTINUED)

First author, year	Number of participants (I:C)	Intervention	Control	Outcomes	Treatment duration	Risk of bias (SG, AC, BPt, BPn, BOA, IOD, SG, Other) ^{a,b}
Lin, 2011 ⁵³	60 (30:30)	Jia wei chai hu shu gan san 加味柴胡疏肝散, 1 package bid	Fluoxetine, 20 mg qd	HRSD, SDS	2–3 weeks (20 days)	U, U, H, H, H, L, U, L
Lin, 2011 ⁵⁴	60 (30:30)	Jie yu xing shen fang (formula) 解郁醒神方, 1 package qd	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Lin, 2013 ⁵⁵	480 (240:240)	Bu shen jie yu fang (formula) 补肾解郁方, 3 capsules tid	Fluoxetine, 20 mg qd	HRSD, AEs	12 weeks	U, U, H, H, L, U, L
Liu, 2011 ⁵⁶	80 (42:38)	Shu gan jie yu an shen fang (formula) 疏肝解郁安神方, 1 package qd + Citalopram, 20 mg qd	Citalopram, 20 mg qd	HRSD, AEs	8 weeks	L, U, H, H, H, L, U, L
Liu, 2011 ⁵⁷	455 (341:114)	Ke xin shu pian 可欣舒片, 50 mg tid + placebo of Fluoxetine, 100 mg qd	Fluoxetine 100 mg qd + placebo of Ke xin shu pian, 50 mg tid	HRSD, AEs	6 weeks	U, U, L, L, L, U, L
Lv, 2014 ⁵⁸	80 (40:40)	Jie yu ning shen tang 解郁宁神汤, 1 package bid	Fluoxetine, 20 mg qd	HRSD, AEs	6 weeks	U, U, H, H, H, L, U, L
Lv, 2011 ⁵⁹	48 (24:24)	Xiao yao san 逍遥散, 1 package bid	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Mai, 2011 ⁶⁰	78 (40:38)	Xiao yao san 逍遥散, 1 package bid	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Mai, 2017 ⁶¹	120 (76:44)	Bu zhong yi qi pills combined with Ban xia xie xin tang 补中益气丸合半夏泻心汤; Xiao chai hu tang 小柴胡汤; Dang gui si ni tang 当归四逆汤; Wen shi ben tun tang 温氏奔豚汤, 1 package qd	Sertraline, 50 mg qd	HRSD	4 weeks	U, U, H, H, H, L, U, L
Mao, 2012 ⁶²	60 (30:30)	Jie yu tang 解郁汤, 1 package bid + Fluoxetine, 20–60 mg qd	Fluoxetine, 20–60 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Ren, 2017 ⁶³	48 (24:24)	Jie yu pills 解郁丸, 4 g tid	Fluoxetine, 20 mg qd	HRSD, AEs	4 weeks	U, U, H, H, H, L, U, L
Song, 2011 ⁶⁴	60 (30:30)	Chai hu shu gan san 柴胡疏肝散, 1 package qd	Fluoxetine, 20 mg qd	HRSD	4 weeks	U, U, H, H, H, U, U, L
Tong, 2016 ⁶⁵	60 (30:30)	Modified Xiao yao san 加味逍遥散, 1 package bid + Paroxetine, 20–40 mg qd	Paroxetine, 20–40 mg qd + placebo of modified Xiao yao san, 1 package bid	HRSD, AEs	8 weeks	L, U, L, L, L, U, L
Wang, 2013 ⁶⁶	78 (39:39)	Yang yin qin gan tang 养阴清肝汤, 1 package bid + Paroxetine, 20 mg qd	Paroxetine, 20 mg qd	HRSD	8 weeks	U, U, H, H, H, L, U, L
Wang, 2016 ⁶⁷	70 (35:35)	Shu gan fang (formula) 舒肝方, 1 package bid + Escitalopram, 10 mg qd	Escitalopram, 10 mg qd	HRSD, SDS	4 weeks	U, U, H, H, H, L, U, L
Xu, 2007 ⁶⁸	60 (30:30)	Modified Dan zhi xiao yao san 加味丹栀逍遥散	Fluoxetine	HRSD, SDS	8 weeks	U, U, H, H, H, L, U, L
Xu, 2013 ⁶⁹	164 (82:82)	Bu shen shu gan hua yu tang 补肾疏肝化瘀汤, 1 package bid	Fluoxetine, 20 mg qd	HRSD	8 weeks	U, U, H, H, H, L, U, L
Yang, 2010 ⁷⁰	60 (30:30)	Bao shen tang 保神汤, 100 mL tid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD, AEs	6 weeks	U, U, H, H, H, L, U, L
Yang, 2012 ⁷¹	100 (50:50)	Er he xiao yao tang 二合逍遥汤, 1 package qd	Fluoxetine, 20–40 mg qd	HRSD, AEs	8 weeks	U, U, H, H, H, L, U, L

(continued)

TABLE 1. (CONTINUED)

First author, year	Number of participants (I:C)	Intervention	Control	Outcomes	Treatment duration	Risk of bias (SG, AC, BPT, BPn, BOA, IOD, SG, Other) ^{a,b}
Yao, 2014 ⁷²	78 (40:38)	Zhong yao yu xiao No. 1 中药郁消 I 号, 1 package bid + Paroxetine, 20 mg qd	Paroxetine, 20 mg qd	HRSD, TESS	6 weeks	L, U, H, H, H, L, U, L
Yi, 2010 ⁷³	190 (92:98)	Chai hu xiao yao he ji 柴胡逍遥合剂, 50 mL bid + Paroxetine, 20–40 mg qd	Paroxetine, 20–40 mg qd + placebo of Chai hu xiao yao he ji, 50 mL bid	HRSD, AEs	8 weeks	L, U, L, L, L, U, L
Yin, 2011 ⁷⁴	46 (23:23)	Xiao yao pills 逍遥丸, 6 g tid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD, TESS	4 weeks	U, U, H, H, H, L, U, L
Yu, 2011 ⁷⁵	80 (40:40)	An shen ding zhi tang 安神定志汤, 1 package bid + Sertraline 50 mg qd	Sertraline, 50 mg qd	HRSD, TESS	6 weeks	U, U, H, H, H, L, U, L
Yu, 2013 ⁷⁶	60 (30:30)	Unnamed formula (Chai hu, Bai shao yao, Ban xia, Shi cang pu, Chen pi, He huan hua), 1 package bid	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L
Zhang, 2009 ⁷⁷	72 (38:34)	Zhao ren bu xie tang 枣仁补血汤, 100 mL bid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD, AEs	4 weeks	L, U, H, H, H, L, U, L
Zhang, 2009 ⁷⁸	200 (100:100)	Jie yu he huan tang 解郁合欢汤, 1 package bid + Paroxetine, 20 mg qd	Paroxetine, 20 mg qd	HRSD	12 weeks	U, U, H, H, H, L, U, L
Zhang, 2009 ⁷⁹	62 (31:31)	Xiao yao pills 逍遥丸, 8 pills tid + Paroxetine, 20–40 mg qd	Paroxetine, 20–40 mg qd	HRSD, TESS, AEs	6 weeks	U, U, H, H, H, L, U, L
Zhang, 2014 ⁸⁰	60 (30:30)	Unnamed formula (Chai hu, Yu jin, Chuan xiong, Mu dan pi, Ban xia, Tian nan xin, Tu fu ling, Chen pi, Sheng di huang, Bai shao yao, Suan zao ren, Bai zi ren, Yuan zhi, Cao wu, Gou teng, Gan cao), 1 package qd + Sertraline, 50 mg qd	Sertraline, 50 mg qd	HRSD, TESS, AEs	8 weeks	H, U, H, H, L, U, L
Zhang, 2010 ⁸¹	63 (32:31)	Modified Chai hu long gu mu li tang 柴胡龙骨牡蛎汤加减, 1 package qd	Paroxetine, 20 mg qd	HRSD, SDS	6 weeks	U, U, H, H, H, L, U, L
Zhang, 2014 ⁸²	455 (341:114)	Jin xiang shu gan pian 金香疏肝片, 40 mg tid	Fluoxetine, 50 mg qd	HRSD	6 weeks	L, U, L, L, L, U, L
Zhang, 2013 ⁸³	64 (32:32)	Bu shen shu gan hua yu tang 补肾疏肝化痰汤, 150 mL bid	Paroxetine, 20 mg qd	HRSD	8 weeks	U, U, H, H, H, L, U, L
Zhang, 2009 ⁸⁴	60 (30:30)	Yu le shu he ji 郁乐疏合剂, 20 mL tid	Paroxetine, 20 md qd	HRSD	6 weeks	L, L, H, H, H, L, U, L
Zhao, 2016 ⁸⁵	76 (38:38)	Chai gui kai yu tang 柴桂开郁汤, 1 package bid	Paroxetine, 20 mg qd	HRSD, AEs	12 weeks	U, U, H, H, H, L, U, L
Zhao, 2006 ⁸⁶	87 (45:42)	Chai hu shu gan san 柴胡疏肝散, 1 package bid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD	4 weeks	L, U, H, H, H, L, U, L
Zhong, 2013 ⁸⁷	51 (26:25)	Unnamed formula (Chai hu, Xiang fu, Yu jin, Zhi zi, Dan shen, Chi shi, Suan zao ren, Chen pi, Huang lian, Bai shao yao, Sheng di huang, Sha ren, Da zao, Gan cao), 200 mL bid	Fluoxetine, 20 mg qd	HRSD, AEs	6 weeks	U, U, H, H, H, L, U, L

(continued)

TABLE 1. (CONTINUED)

First author, year	Number of participants (I:C)	Intervention	Control	Outcomes	Treatment duration	Risk of bias (SG, AC, BPt, BPn, BOA, IOD, SG, Other) ^{a,b}
Zhong, 2012 ⁸⁸	100 (50:50)	Chai hu long gu mu li tang 柴胡龙骨牡蛎汤, 1 package qd	Paroxetine, 20 mg	HRSD, SDS	8–9 weeks (60 days)	U, U, H, H, H, L, U, L
Zhou, 2012 ⁸⁹	60 (30:30)	Fu fang kuai wei shu gan pills 复方快胃舒肝丸, 1 package bid + Fluoxetine, 20 mg qd	Fluoxetine, 20 mg qd	HRSD, TESS	4 weeks	U, U, H, H, H, L, U, L
Zhou, 2013 ⁹⁰	127 (65:62)	Modified Xiao yao capsule 加味逍遥胶囊, 6 g bid	Sertraline, 20 mg qd	HRSD	8 weeks	L, U, L, L, L, L, U, L
Zhou, 2012 ⁹¹	80 (40:40)	Unnamed formula (Chai hu, Xiang fu, Yu jin, Bai zhu, Fu ling, Shi cang pu, Bo he, Zhen zhu mu), 1 package qd + Citalopram, 20 mg	Citalopram, 20 mg qd	HRSD	5–6 weeks (40 days)	L, U, H, H, H, L, U, L
Zhu, 2014 ⁹²	63 (32:31)	Suan zao ren tang 酸枣仁汤, 100 mL bid	Paroxetine, 20 mg qd	HRSD, AEs	4 weeks	U, U, H, H, H, L, U, L
Zong, 2014 ⁹³	60 (30:30)	Yi shen qing xin fang 益肾清心方, 150 mL tid	Fluoxetine, 20 mg qd	HRSD	6 weeks	U, U, H, H, H, L, U, L

^aRisk of bias abbreviations: SG, sequence generation; AC, allocation concealment; BPt, blinding of participants; BPn, blinding of personnel; BOA, blinding of outcome assessment; IOD, incomplete outcome data; SOR, selective outcome reporting; Other, defined as baseline balance for the HRSD and SDS scores.

^bRisk of bias judgments: L, low risk; U, unclear risk or no information available; H, high risk.

AEs, adverse events; bid, twice per day; C, control groups; HRSD, Hamilton Rating Scale for Depression; I, intervention groups; qd, once per day; RCT, randomized controlled trial; SDS, Zung Self-Rating Depression Scale; SF-36, 36-Item Short Form Health Survey; SSRIs, selective serotonin reuptake inhibitors; TESS, Toxic Exposure Surveillance System; tid, three times per day.

FIG. 2. Risk of bias.

FIG. 3. Funnel plots for publication bias. **(A)** BC formula versus SSRIs. **(B)** BC formula plus SSRIs versus SSRIs. BC, *Bupleurum chinense*; SSRIs, selective serotonin reuptake inhibitors.

FIG. 4. Forest plot comparing BC formula to SSRIs, in terms of Hamilton Rating Scale for Depression. Note that despite a significant difference between groups, studies had risk of bias, which should be considered when interpreting results from this figure.

After 4–12 weeks of treatment, BC formula plus SSRIs reduced the severity of depression more than SSRIs alone (SMD -1.03 [-1.43 to -0.62]; $I^2=94.2\%$; low quality evidence) (Fig. 5 and Table 3).

In nine studies at low risk of bias for sequence generation, subgrouping also showed that BC formula plus SSRIs was superior to SSRIs alone (SMD -0.90 [-1.38 to -0.43]; $I^2=90.0\%$). Treatment with BC formula for equal to or less than 6 weeks produced lower HRSD scores between groups (SMD -0.65 [-1.01 to -0.29]; $I^2=87.4\%$, 15 studies). Treatment for greater than 6 weeks had similar results (SMD -1.63 [-2.42 to -0.84]; $I^2=96.2\%$, 9 studies). Subgrouping by HRSD version (Version 17) showed that BC formula plus SSRIs was superior to SSRIs alone in 13 studies (SMD -0.67 [-0.87 to -0.47], $I^2=59.4\%$).

Zung's Self-Rating Depression Scale

Three studies, including 289 participants, used the SDS to compare BC formula plus SSRIs with SSRIs alone.^{42,44,67}

After 4–12 weeks of treatment, SDS scores in the BC formula plus SSRIs groups were significantly lower than those in the SSRI-alone groups (MD -7.19 points [-8.39 to -5.99]; $I^2=0.0\%$; low quality evidence (Table 3).

Short Form SF-36 Health Survey

One RCT evaluated 90 participants using the SF-36 to measure quality of life.⁴⁸ Individual health domains were not reported, but an aggregate score was given. BC formula plus paroxetine was superior to paroxetine after 8 weeks of treatment (MD 13.53 [9.82 – 17.24]) (Table 3).

Adverse events

Ten studies mentioned adverse events.^{43,44,52,56,65,70,73,77,79,80} In the BC formula plus SSRIs groups, 118 events were reported, while in the SSRI groups, 174 events were reported. Nine studies provided adverse event information. Diarrhea was the most common adverse event in the BC formula plus SSRIs

TABLE 2. SUMMARY OF FINDINGS OF *BUPLEURUM CHINENSE* VERSUS SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Outcomes	No. of participants (Studies)	Quality of the evidence (GRADE)	Anticipated absolute effects	
			Assumed risk	
			SSRIs	Risk difference with BC
Depressive symptoms (clinician rated) Hamilton Rating Scale for Depression Treatment duration: mean 6.4 weeks	3459 (30 RCTs)	⊕ ⊙ ⊙ ⊙ VERY LOW ^{1,2,3}	—	SMD 0.35 SD lower (0.52 lower to 0.18 lower)
Depressive symptoms (patient reported) Self-rating Depression Scale Treatment duration: mean 6.5 weeks	283 (4 RCTs)	⊕ ⊕ ⊙ ⊙ LOW ^{1,4}	The mean Self-rating Depression Scale was 35.12 points	MD 1.53 points lower (3.03 lower to 0.03 lower)
Quality of life			Not reported	
Adverse events			Not reported	

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹Downgraded one level for unclear sequence generation and allocation concealment, lack of blinding of participants and personnel.

²Downgrade one level for considerable statistical heterogeneity.

³Downgrade one level for publication bias.

⁴Downgrade one level for small sample size.

BC, *Bupleurum chinense*; CI, confidence interval; MD, mean difference; SD, standard deviation; SMD, standardized mean difference.

group (17 cases), while constipation was the most common adverse event in the comparator groups (22 cases). Other adverse events included hypersomnia, nausea, and vomiting (Table 4). Eight of the studies reported adverse events on the Toxic Exposure Surveillance System (TESS); after treatment, TESS was lower, indicating less severe and fewer adverse events in the integrative medicine group compared to SSRIs alone (MD −1.12 [−1.69 to −0.55] $I^2=93.2\%$) (Table 3).

Discussion

BC formula may be effective for improving clinical symptoms and alleviating depression severity. It also appears to be safe, with the number of adverse events in the BC formula groups being half that of the SSRI groups. In addition, meta-analyses for depression severity measured on the HRSD and SDS scales consistently indicated that BC formula has a promising effect when given alongside SSRIs or alone for reducing depression severity. However, heterogeneity and limitations in study methodology should be considered when interpreting these results. Meta-analysis showed that at the end of treatment, there was a significant difference in the HRSD and SDS scores between BC formula and SSRI groups, indicating a potentially clinically important effect.³¹ This result was consistent with previous systematic reviews of herbal medicine for depression.^{95–98}

Our review indicates that BC formula for depression is effective in the short term, similar to acute-phase treatment

with antidepressants.^{99,100} When BC formula was used as integrative medicine, the pooled results showed that it may reduce the severity of depression compared to SSRIs alone. The total number of adverse events in the BC formula groups was less than that in SSRI groups.

Improvements of BC formula groups, either integrative use or used alone, were more obvious after treatment for 6 and 12 weeks. Research indicates that a minimum of 8–10 weeks of treatment is needed for optimal symptom reduction.^{35,101}

Contemporary experimental research suggests that herbal compounds or compound combinations act on various targets and pathways to produce antidepressant effects. Pre-clinical studies have shown these herbs' antidepressant effects are related to their antioxidant and neurotransmitter properties.^{102,103} *Xiao yao san/wan* has reported antidepressant effects in preclinical studies.¹⁰⁴ *Chai hu shu gan san* has also shown its effects are comparable to the antidepressant drug fluoxetine.^{105,106} More research into key herbal compounds of *B. chinense* and BC formula in animal models or neuronal cells is needed to further elucidate the possible mechanisms of action of this herb.

Limitations of the study

Included studies were not free from bias. They also had methodological shortfalls, such as unclear sequence generation and allocation concealment, and a lack of blinding of participants and personnel. Considerable heterogeneity was

FIG. 5. Forest plot comparing BC formula plus SSRIs to SSRIs alone, in terms of Hamilton Rating Scale for Depression. Note that despite a significant difference between groups, studies had risk of bias, which should be considered when interpreting results from this figure.

also noted and could not be resolved by subgroup analysis. It may be due to variable etiologies, severity of depression, disease history, study protocols, and outcome measurements. The BC formula interventions were considered to be the same and therefore merged in meta-analysis. However, there were differences between studies in terms of treatment duration, other herbal ingredients, dosage, and medication compliance that may have contributed to heterogeneity.

Future studies

Future clinical studies of BC formula for MDD need rigorous methodology, including clearly stated methods of sequence generation and allocation concealment. Future studies should also publish their protocols and be registered with a clinical trial registry to minimize reporting bias and increase transparency in reporting of the results.

Cause of depression, severity, disease history, treatment preference, and expectancy should be taken into consideration when designing trials and selecting participants. Selecting similar participants, in terms of etiology, age range,

and severity, may help to achieve more comparable and reliable results. Assessing clinically important outcomes, such as relapse and remission of depression, quality of life, functional capacity, and suicidality, would provide a comprehensive understanding of the effect of BC formula. As for treatment expectancy, it may influence treatment effect and modify clinical decisions, and should be considered when designing trials and drawing conclusions.

Treatment duration in the included clinical trials ranged from 2 to 12 weeks and only a few reported follow-up data. Depression is a lifelong disease and should be monitored every 1–2 weeks during treatment. Follow-up assessment would provide long-term data and further strengthen the evidence.

Future clinical studies should also report the items required by the Consolidated Standards of Reporting Trials (CONSORT)¹⁰⁷ and its extensions for herbal medicine.^{108,109} Informative reporting of trial participants, reason for intervention selection, comparator, and results of validated outcome measures will provide high-level clinical evidence, and will benefit practitioners, researchers, patients, and knowledge translation.

TABLE 3. SUMMARY OF FINDINGS OF *BUPLEURUM CHINENSE* PLUS SELECTIVE SEROTONIN REUPTAKE INHIBITORS VERSUS SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Outcomes	No. of participants (Studies)	Quality of the evidence (GRADE)	Anticipated absolute effects	
			Assumed risk	
			SSRIs	Risk difference with BC
Depressive symptoms (clinician rated) Hamilton Rating Scale for Depression Treatment duration: mean 6.6 weeks	2041 (24 RCTs)	⊕ ⊕ ○ ○ LOW ^{1,2}	—	SMD 1.03 SD lower (1.43 lower to 0.62 lower)
Depressive symptoms (patient reported) Self-rating Depression Scale Treatment duration: mean 7.3 weeks	289 (3 RCTs)	⊕ ⊕ ○ ○ LOW ^{1,3}	The mean Self-rating Depression Scale was 44.90 points	MD 7.19 points lower (8.39 lower to 5.99 lower)
Quality of life Short Form SF-36 Health Survey Treatment duration: 8 weeks	90 (1 RCT)	⊕ ⊕ ○ ○ LOW ^{1,3}	The SF-36 was 60.68 points	MD 13.53 points higher (9.82 higher to 17.24 higher)
Adverse events TESS Treatment duration: 6.25 weeks	546 (8 RCTs)	⊕ ⊕ ○ ○ LOW ^{1,2}	The mean TESS was 4.51 points	MD 1.12 lower (1.69 lower to 0.55 lower)

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹Downgraded one level for unclear sequence generation and allocation concealment, lack of blinding of participants and personnel.

²Downgrade one level for considerable statistical heterogeneity.

³Downgrade one level for small sample size.

TABLE 4. ADVERSE EVENTS

Comparisons	No. of studies	Intervention group adverse events	Control group adverse events
BC formula vs. SSRIs	12	Total adverse events = 125 Most common events (number of cases) • Dry mouth (16) • Loss of appetite (16) • Nausea (9) • Headache (8) • Restlessness (5) • Hypersomnia (5) • Dizziness (4) • Hypersomnia (5) • Sweating (3) • Nasal congestion (3)	Total adverse events = 286 Most common events (number of cases) • Dry mouth (53) • Loss of appetite (31) • Nausea (14) • Constipation (12) • Dizziness (11) • Sweating (8) • Insomnia (7) • Nausea and loss of appetite (7) • Insomnia (5) • Hypersomnia (5)
BC formula plus SSRIs vs. SSRIs	10	Total adverse events = 118 Most common events (number of cases) • Diarrhea (17) • Nausea (14) • Constipation (12) • Hypersomnia (9) • Blurred vision (9) • Dry mouth (8) • Headache (7) • Nausea and vomiting (7) • Dizziness (7) • Sweating (7)	Total adverse events = 174 Most common events (number of cases) • Constipation (22) • Nausea and vomiting (18) • Nausea (15) • Hypersomnia (15) • Dry mouth (13) • Insomnia (11) • Diarrhea (11) • Blurred vision (11) • Sweating (11) • Headache (5)

Conclusions

BC formula alone or given as integrative medicine with SSRIs may reduce depression severity. The current evidence should be interpreted with caution due to bias and methodological shortfalls in the included studies, and heterogeneity in meta-analysis. BC formula does not appear to increase the risk of adverse events. New studies with rigorous methodologies in well-defined populations, including short- and long-term follow-up, will help validate the promising evidence identified in this review.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1

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