

# Nine traditional Chinese herbal formulas for the treatment of depression: an ethnopharmacology, phytochemistry, and pharmacology review

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**Abstract:** Depression is a major mental disorder, and is currently recognized as the second-leading cause of disability worldwide. However, the therapeutic effect of antidepressants remains unsatisfactory. For centuries, Chinese herbal formulas (CHF) have been widely used in the treatment of depression, achieving better therapeutic effects than placebo and having fewer side effects than conventional antidepressants. Here, we review the ethnopharmacology, phytochemistry, and pharmacology studies of nine common CHF: “banxia houpo” decoction, “chaihu shugansan”, “ganmaidazao” decoction, “kaixinsan”, “shuganjieyu” capsules, “sinisan”, “wuling” capsules, “xiaoyaosan”, and “yueju”. Eight clinical trials and seven meta-analyses have supported the theory that CHF are effective treatments for depression, decreasing Hamilton Depression Scale scores and showing few adverse effects. Evidence from 75 preclinical studies has also elucidated the multitarget and multipathway mechanisms underlying the antidepressant effect of the nine CHF. Decoctions, capsules, and pills all showed antidepressant effects, ranked in descending order of efficacy. According to traditional Chinese medicine theory, these CHF have flexible compatibility and mainly act by soothing the liver and relieving depression. This review highlights the effective treatment choices and candidate compounds for patients, practitioners, and researchers in the field of traditional Chinese medicine. In summary, the current evidence supports the efficacy of CHF in the treatment of depression, but additional large-scale randomized controlled clinical trials and sophisticated pharmacology studies should be performed.

**Keywords:** traditional Chinese medicine, Chinese herbal formula, antidepressant, phytochemistry, pharmacological bioactivity

## Introduction

Depression is a common chronic mental health problem,<sup>1-3</sup> with a global prevalence of 4.4%–5%.<sup>4</sup> It is characterized by a loss of interest in daily activities and feelings of low self-worth, disappointment, sadness, and hopelessness. According to the Global Burden of Disease Study 2013, major depressive disorder (MDD) is the second-leading global cause of years lived with disability.<sup>5</sup> The population-attributable risk for depression and all-cause death is 12.7%, and for depression and suicide it is 11.2%.<sup>6</sup> The economic burden of individuals with MDD in the US increased by 21.5% between 2005 and 2010 (from \$173.2 billion to \$210.5 billion, inflation-adjusted).<sup>7</sup> A recent meta-analysis of the prevalence of depressive symptoms in older Chinese adults from 1987 to 2012 reported an overall prevalence of 23.6%.<sup>8-10</sup>

Conventional antidepressants, such as selective reuptake inhibitors of serotonin (5-HT) or norepinephrine (NE), monoamine oxidase inhibitors, tricyclic antidepressants,

or *N*-methyl-D-aspartate receptor (NMDAR) antagonists, fail to help at least 40% of depressed patients.<sup>11</sup> Existing treatments for MDD usually take several weeks or months to achieve their therapeutic effects.<sup>12,13</sup> During this lag period, patients continue to have depressive symptoms and risk self-harm.<sup>12</sup> Despite this, there has been little notable progress in the development of drugs to treat depression over the last few decades.<sup>14</sup> Scientists are seeking new, improved therapeutic approaches to deal with depression, and the drive to develop next-generation drugs with improved safety profiles has intensified.<sup>15,16</sup>

Traditional Chinese medicine (TCM) is attracting increasing attention as a method for meeting the demands for higher remission rate, faster onset, persistent antidepressant action, and fewer adverse effects.<sup>17,18</sup> TCM is one of the oldest medical systems in the world, and includes Chinese herbal medicine, acupuncture, and massage. Herbal medicine has been used for the treatment of depression in People's Republic of China for centuries, and is becoming more frequently used in Western countries. "Yuzheng", meaning "depression syndrome", first appeared in the Ming Dynasty Tuan Yu's *Yi Xue Zheng Zhuan*, although discussions about depression can be traced back to *Huangdi Neijing (The Inner Canon of Huangdi)*.<sup>19</sup> Then, in the Eastern Han Dynasty, *Jingui Yaolue (Synopsis of Prescriptions of the Golden Chamber)* first described the symptoms of lily disease, globus hystericus, and "zangzao" syndrome, which are thought to belong to depression syndrome; this document also recorded "banxia houpo" decoction (BHD) and "ganmaidazao" decoction (GMDZD), both used very frequently for depression.<sup>20</sup>

Interestingly, modern TCM for the treatment of depression has started to be integrated into evidence-based medicine. A PubMed search revealed that the first randomized controlled trial (RCT) of Chinese herbal formulas (CHF) in depression investigated "gengnianle", a defined formula of Chinese medicinal herbs for the relief of perimenopausal depression.<sup>21</sup> The earliest herbal pharmacology study investigated BHD.<sup>22</sup> A systematic review of the treatment of menopausal symptoms started with the study of "erxian" decoction,<sup>23</sup> and the first meta-analysis was conducted on the clinical effects of "chaihu shugansan" (CSS).<sup>24</sup> Further studies showed that liver depression and chi stagnation were the main syndromes,<sup>25</sup> and that the main treatment principle is the regulation of chi, relief of depression, and empathy.<sup>26</sup>

Following *Synopsis of Prescriptions of the Golden Chamber*, numerous antidepressant CHF were recorded in ancient books. Although some systematic reviews summarized the most frequent antidepressant formulas and patterns of TCM use,<sup>25,27</sup> there have been no detailed descriptions of

effective and classical CHF available to date, which is a major impediment to the use of CHF in modern medical practice. Here, we introduce nine common and important antidepressant CHF with regard to their source, composition, chemical constituents, indications, TCM and antidepressant effects, mechanisms, and side effects from a review of ethnopharmacology, phytochemistry, and pharmacology studies.

## Materials and methods

Available references that recorded the use of the nine CHF in depression were analyzed via PubMed and Web of Science (from inception to June 2, 2016). Further comprehensive resources were searched for each CHF in PubMed, Web of Science, Science Direct, China National Knowledge Infrastructure, Wanfang Data, Chinese Scientific Journals Full-Text Database, and Google Scholar. Relevant TCM information was from <http://www.tcmwiki.com/w/TCM-Wiki> and the *Pharmacopoeia of the People's Republic of China* (2015).

Database searches included the following keywords: ("depression" or "depressive disorder" or "antidepressant") and ("Chinese prescription" or "Chinese formula" or "Chinese decoction" or "Chinese herbal formula" or each CHF by name). The keywords were modified for use with different databases. Full-text articles in English or Chinese were included.

## Results

The source, TCM effects, and syndromes of the nine most commonly prescribed CHF for treating depression are provided in Table 1. Photographs of each formula are presented in Figure 1. All correspond to the typical principles of TCM treatment of yuzheng according to their effects and Chinese-syndrome patterns, including soothing the liver, relieving depression, promoting the circulation of chi, and resolving phlegm. Importantly, we found a considerable amount of evidence-based research for most of the CHF we examined, meaning the results can be used to guide clinical practice and research in related fields.

### Banxia houpo decoction

#### Composition

Banxia (*Pinellia* rhizome) 12 g, "fuling" (*Poria*) 12 g, houpo (*Magnolia officinalis* cortex) 9 g, "shengjiang" (*Zingiber officinale* rhizome) 9 g, "suye" (*Perilla* folium) 6 g.

#### Chemical constituents

Zingiberol, guanosine, rosmarinic acid,<sup>28</sup> magnolol, honokiol,<sup>29</sup> volatile oils (including linalool, citral, nerolidol,

**Table 1** The source, TCM effects, and syndromes of the nine Chinese herbal formulas

Formula	Source	TCM effects	TCM syndromes
Banxia houpo decoction	<i>Jingui Yaolue (Synopsis of Prescriptions of the Golden Chamber)</i> <sup>22</sup>	Promote chi and eliminate stagnation, calm the adverse chi, and dissolve phlegm	Syndrome of phlegm-chi stagnation and binding
Chaihu shugansan	<i>Jingyue Quanshu (Complete Works of Zhang Jingyue)</i> <sup>24</sup>	Soothe the liver and regulate chi, promote blood circulation to relieve pain	Syndrome of liver-chi stagnation
Ganmaidazao decoction	<i>Jingui Yaolue (Synopsis of Prescriptions of the Golden Chamber)</i> <sup>48</sup>	Nourish the heart and tranquilize mind, regulate the function of the middle jiao, relieve spasms, and alleviate pain	Syndrome of heart-yin deficiency, heart–mind malnutrition, and liver-chi disharmony
Kaixinsan	<i>Beiji Qianjin Yaofang (Essential Prescriptions Worth a Thousand in Gold for Every Emergency)</i> <sup>53</sup>	Invigorate vital energy to nourish heart and tranquilize and sedate the mind	Syndrome of heart-chi deficiency, heart–kidney disharmony
Shuganjieyu capsules	Chengdu Kanghong Pharmaceuticals Co., Ltd, Chengdu, People's Republic of China (batch Z20080580) <sup>71</sup>	Soothe the liver and relieve depression, strengthen the spleen, and calm the nerves	Syndrome of liver-chi stagnation and spleen deficiency
Sinisan	<i>Shanghan Lun (Treatise on Febrile Diseases Caused by Cold)</i> <sup>76</sup>	Expel pathogens and resolve depression, soothe the liver, and regulate the spleen	Syndrome of yang-chi stagnation or syndrome of liver–spleen disharmony
Wuling capsules	Zhejiang Jolly Pharmaceuticals Co., Ltd (batch Z19990048) <sup>86</sup>	Tonify the kidney and brain, nourish the heart, and tranquilize the mind	Syndrome of heart–kidney disharmony or heart–spleen deficiency
Xiaoyaosan	<i>Pharmacy Taiping Huimin Heji Ju Fang (Prescriptions of the Bureau of Taiping People's Welfare)</i> <sup>100</sup>	Soothe the liver and strengthen the spleen, nourish blood, and regulate menstruation	Syndrome of liver-chi stagnation, blood deficiency, and spleen weakness
Yueju	<i>Danxi Xinfu (Danxi's Mastery of Medicine)</i> <sup>111</sup>	Regulate the flow of chi and relieve depression, regulate the function of the middle jiao, and remove chi stagnancy	Syndrome of six stagnancy (chi, dampness, fire, phlegm, blood, and food)

**Abbreviation:** TCM, traditional Chinese medicine.

caryophyllene, bisabolene, caryophyllene oxide, apiole,  $\alpha$ - and  $\beta$ -eudesmol, and  $\alpha$ -farnesene),<sup>30</sup> polysaccharides.<sup>31</sup>

### Pharmacology and bioactivity

A clinical report of 46 patients with globus hystericus showed that the modified BHD granule (BHD + “foshou” [*Citrus medica* var. *sarcodactylis* fructus] 15 g; 46 cases), taken at a dose of one pack three times a day, was more effective than Manyanshuning (sore-throat treatment; 49 cases) in reducing symptoms of depression and anxiety on Symptom Checklist 90 and improving patients' psychological state.<sup>32</sup>

A study using an orthogonal array showed that the interactions of the BHD constituents houpo  $\times$  suye and fuling  $\times$

suye were the core herb pairs to alleviate depression-like serotonergic and dopaminergic changes in mice.<sup>33</sup> Furthermore, aqueous and lipophilic extracts of BHD showed the greatest antidepressant effects, whereas the polyphenol fraction showed a moderate effect.<sup>22</sup> BHD reduced immobility time in the forced-swim test (FST) and tail-suspension test (TST), increased 5-HT and 5-hydroxyindoleacetic acid levels in the hippocampus and striatum, and decreased serum and liver malondialdehyde (MDA) levels in mice with a depression-like phenotype.<sup>34</sup> Ethanol and water extracts of BHD reduced c-Fos expression in cerebral regions of rats subjected to chronic mild stress (CMS) to a level comparable to that of fluoxetine.<sup>35</sup> BHD significantly



**Figure 1** The nine formulas examined in this review.

**Notes:** (A) Banxia houpo decoction; (B) chaihu shugansan; (C) ganmaidazao decoction; (D) kaixinsan; (E) shuganjieyu capsules; (F) sinisan; (G) wuling capsules; (H) xiaoyaosan; (I) yueju.

increased high-density lipoprotein levels, decreased serum triglyceride levels, improved the activity of splenic natural and lymphokine-activated killer cells, reduced the activity of liver SOD and nitric oxide synthase, and decreased the level of serum MDA by inhibiting lipid peroxidation in rats after CMS.<sup>36</sup> Furthermore, BHD normalized changes in the metabolites of rats after CMS, and exerted antidepressant effects by regulating amino acid and energy metabolism.<sup>37</sup>

### Indications and usage

BHD can be used to promote chi, calm adverse chi, eliminate stagnation, and dissolve phlegm. It is also used to treat the syndrome of phlegm-chi stagnation and binding, especially for globus hystericus<sup>32</sup> (which manifests as an obstruction in the throat that is hard to cough up or swallow), fullness and oppression in the chest and diaphragm, white fur on the tongue, and “wiry” pulse (which means a small, tense pulse).

### Dosage

Decocted in water for oral use; taken twice a day.

## Chaihu shugansan

### Composition

Chaihu (bupleuri radix) 6 g, “chenpi” (*Citrus reticulata* pericarp) 6 g, “chuanxiong” (*Ligusticum chuanxiong* rhizome) 4.5 g, “xiangfu” (*Cyperus* rhizome) 4.5 g, “zhiqiao” (*Citrus aurantium* fructus) 4.5 g, “shaoyao” (*Paeonia* radix) 4.5 g, “gancao” (*Glycyrrhiza* radix) 1.5 g.

### Chemical constituents

Synephrine, paeoniflorin, naringin, hesperidin, neohesperidin, saikosaponin A, glycyrrhizic acid, nobiletin, tangeretin, ferulic acid,<sup>38</sup> gallic acid, oxypaeoniflorin, albiflorin, liquiritin, benzoic acid, narirutin, meranzin hydrate, liquiritigenin, quercetin, benzoylpaeoniflorin, isoliquiritigenin, formononetin.<sup>39</sup>

### Pharmacology and bioactivity

An in vitro study suggested that the antioxidant activity of CSS contributes to its antidepressant effect. CSS showed a ferric-reducing antioxidant power equivalent to 0.24 mM FeSO<sub>4</sub>/g CSS aqueous extract and scavenging free radical activity.<sup>40</sup> A meta-analysis of ten RCTs with a total of 835 subjects showed CSS acts at multiple targets, without side effects. CSS, with or without combined antidepressant treatment, significantly improved symptoms of depression, with better efficacy and recovery rate than antidepressants alone.<sup>24</sup>

CSS reverses the stress-induced disruption of ERK5 and p-ERK1/2 activation in the rat hippocampus<sup>41,42</sup> and

increases the messenger RNA (mRNA)-expression ratio of ER $\alpha$  to ER $\beta$  in the rat hippocampus after CMS, but shows no significant change in estradiol levels or mRNA expression of ER $\alpha$  or GPR30.<sup>43</sup> CSS also inhibits the expression of the c-Jun N-terminal kinase via signal transduction involving stress-activated protein kinase in the hippocampus of rats after CMS.<sup>44</sup> Nevertheless, CSS upregulates the expression of 5-HT<sub>1A</sub>-receptor mRNA and cellular proliferation in the hippocampal dentate gyrus in epileptic rats with depression.<sup>45</sup> In addition, CSS inhibits lipid peroxidation, relieves oxidative injury, and regulates antioxidant capacity. Restrained mice treated with CSS have higher SOD and catalase activities in liver, lower MDA values, and higher glutathione levels in the blood compared with untreated restrained mice.<sup>40</sup> A urinary metabolomic study on rats after CMS showed that the therapeutic effect of CSS may involve reversal of energy and tryptophan-metabolism dysfunction, increase in bone density, and liver detoxification.<sup>46</sup> Furthermore, in depressed patients, CSS improves both clinical symptoms and impairments in cerebral blood flow in multiple regions, revealed by single-photon emission computed tomography.<sup>47</sup>

### Indications and usage

CSS is indicated to soothe the liver, regulate chi, and promote blood circulation to relieve pain. It can be used to treat the syndrome of liver-chi stagnation (manifesting as pain in the lateral thorax, pressure in the chest, and tendency to sigh), as well as depression or irritability, belching, abdominal fullness and distention, white fur on the tongue, or a “wiry” pulse.

### Precautions and side effects

In TCM theory, CSS should be used with caution in patients with yin deficiency. Like antidepressants (such as fluoxetine or melitracen-flupentixol), modified CSS can cause nausea, stomach upset, dry mouth, drowsiness, or insomnia. However, CSS ranks lower on the treatment-emergent side-effect scale than antidepressants, and does not affect patients' routine blood-examination results or hepatic or renal function.<sup>24</sup>

### Dosage

Decocted in water for oral use, or taken in its powder form; taken twice a day.

## Ganmaidazao decoction

### Composition

Gancao (*Glycyrrhiza* radix) 9 g, “xiaomai” (*Triticum aestivum* fructus) 9–15 g, 5–7 DZ (jujube [type of date] fructus).



## Chemical constituents

Known constituents are glycyrrhizic acid, isoliquiritin, and isoliquiritigenin, plus unknown extracts of three herbs: *triticum fructus*, *Glycyrrhiza*, and jujube.<sup>48</sup>

## Pharmacology and bioactivity

A meta-analysis of GMDZD for depression, including ten RCTs with a total of 968 subjects, suggested that GMDZD showed antidepressant action with few side effects. GMDZD in combination with antidepressants reduces side effects and enhances antidepressant efficacy.<sup>48</sup> Another study of modified GMDZD (43 patients) showed equivalent efficacy to melitracen–flupentixol (43 patients) in climacteric depression, and was more effective than melitracen–flupentixol in improving sleep quality, which may have been a result of adjusted levels of 5-HT, NE, estradiol, follicle-stimulating hormone, and luteotrophic hormone in climacteric depression.<sup>49</sup> Subchronic administration of GMDZD reduces CMS-induced depression-like behavior in rats, and this is associated with a reduction in glutamate levels and increased expression of NMDAR subunits (NR<sub>2A</sub> and NR<sub>2B</sub>) in the frontal cortex and hippocampus.<sup>50,51</sup>

## Indications and usage

GMDZD is used to nourish the heart, tranquilize the mind, regulate the function of the middle jiao, relieve spasms, and alleviate pain. It is also used to treat deficiency of heart yin, malnutrition of heart/mind, and disharmony of liver chi (which manifests as hysteria, climacteric syndrome, neurasthenia, or nocturnal fretfulness in infants), especially for zangzao syndrome (visceral irritation, in which female patients present with low mood, tendency to cry, possessive behavior, and frequent yawning).<sup>48</sup>

## Precautions and side effects

GMDZD is contraindicated in cases with excessive “phlegm fire” inside manic-depressive psychosis. Adverse events associated with modified GMDZD include dry mouth, constipation, melancholia, insomnia, irritability,<sup>48</sup> abdominal distension, and acid regurgitation.<sup>52</sup>

## Dosage

Decocted in water for oral use; taken three times a day.

## Kaixinsan

### Composition

“Rensheng” (ginseng radix and rhizome [GR]), “yuanzhi” (*Polygala* radix [PR]), “shichangpu” (*Acorus tatarinowii* rhizome [ATR]), fuling (*Poria* [PO]).

## Source

Kaixinsan (KXS) is known by different names, and has different dose-ratio compositions. For example, the ratio of GR:PR:ATR:PO is 1:1:25:50 in the formula KXS-652, 3:2:2:3 in “dingzhi xiaowan” (DZW-652) (both from *Essential Prescriptions Worth a Thousand in Gold for Every Emergency*), and 1:1:1:2 in KXS-984 (from *Prescriptions from the Heart of Medicine*).<sup>53</sup>

## Chemical constituents

Ginsenosides (27 in total, including R<sub>o</sub>, R<sub>a1</sub>, R<sub>b1</sub>, R<sub>b2</sub>, R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub>, R<sub>f</sub>, R<sub>g1</sub>, R<sub>g3</sub>, R<sub>g5</sub>, R<sub>g6</sub>, R<sub>h1</sub>, R<sub>h2</sub>, R<sub>oa</sub>, zingibroside R<sub>1</sub>, notoginsenoside R<sub>2</sub> and R<sub>4</sub>, and pseudoginsenoside R<sub>c1</sub>), *Polygala* saponins (arillatanoside A, tenuifolin), terpenoids (tumulosic acid, pachymic acid, dehydropachymic acid), oligosaccharide esters (18, including sibiricoses A<sub>1</sub> and A<sub>6</sub> and tenuifolisides A, B, C, E, G, H, I, K, L, M, and O), and other compounds, including 3,6'-disinapoyl sucrose, polygalaxanthone III, α- and β-asarone, and pachymic acid.<sup>53-55</sup>

## Pharmacology and bioactivity

A study in cultured astrocytes suggested that the antidepressant action of KXS is mediated by an increase in mRNA and protein expression and secretion of neurotrophic factors, including NGF, BDNF, and GDNF. Moreover, individual aqueous extracts of the four herbs that constitute KXS did not significantly influence the expression of neurotrophic factors, which suggests that these herbs act synergistically to produce their effects.<sup>56</sup> Furthermore, KXS attenuates cell death induced by BDNF knockdown (mediated by a lentiviral vector – LV-shBDNF-3) in primary hippocampal neurons; it also increased sucrose intake in the sucrose preference test, exploration in the open-field test, and learning ability in the Morris water maze in rats with an LV-shBDNF-3-induced depression-like phenotype. Western blot analysis has confirmed that KXS can reverse the LV-shBDNF-3-induced reduction in BDNF both in vitro and in vivo.<sup>57</sup> An optimized KXS with a GR:PR:ATR:PO ratio of 1:1:5:10 has shown a greater capability to promote neurofilament expression in pheochromocytoma (PC12) cells. Furthermore, the PKA inhibitor H89 significantly inhibited induced neurofilament-promoter activity, which indicated that the underlying mechanism was mediated by the PKA-signaling pathway.<sup>58</sup>

In patients after 2 and 4 weeks' treatment, Hamilton Depression Scale (HAM-D) scores were decreased significantly more after KXS (DZW-652, 40 cases, 60 g/day) than after fluoxetine (40 cases, 20 mg/day) in patients with mild or moderate depression. Also, after 8 weeks' treatment, the

clinical:control ratio was greater in the KXS group than in the fluoxetine group.<sup>59</sup>

KXS likely exerts its antidepressant and nootropic effects in CMS rat models of depression by modulating the hypothalamic–pituitary–adrenal (HPA) axis and monoaminergic and cholinergic systems. DZW-652 reduces depression-like behaviors in CMS rat models, increasing the sucrose preference index, increasing active avoidance and active movement distances in the two-way active avoidance test, and decreasing the prolonged latency of novelty-suppressed feeding. In addition, KXS significantly reduces CMS-induced elevation in serum levels of adrenocorticotrophic hormone, decreases hippocampal acetylcholinesterase expression, and upregulates monoaminergic neurotransmitters (dopamine, NE, and 5-HT) in the brain.<sup>60,61</sup> Another study showed that KXS increased 5-HT synthesis and reduced 5-HT reuptake. It significantly increased protein and mRNA expression of tryptophan hydroxylase during the 5-HT synthetic process in the hippocampus and prefrontal cortex of rat models of depression, and downregulated 5-HT transporter protein and mRNA levels.<sup>62</sup> It also regulates the activity of aralkylamine *N*-acetyltransferase (the penultimate and key enzyme in the hormone biosynthetic pathway) in the pineal body, melatonin biosynthesis, and the expression of the melatonin receptor Mel<sub>1A</sub> in rat models of depression.<sup>63,64</sup>

### Indications and usage

KXS invigorates vital energy to nourish the heart and tranquilize and sedate the mind. It can be used to treat the syndrome of heart-chi deficiency and disharmony of the heart and kidney, manifesting as sadness, insomnia, and amnesia.

### Precautions and side effects

It is relatively safe to take KXS orally. The observed adverse-effect level is 19.67 g/kg/day for mice, 73-fold higher than the currently recommended dose for a 60 kg human. Adverse effects in mice include slow movement, a decrease in aggression, anorexia, and weight loss.<sup>65</sup> In humans, adverse effects include dry mouth and abdominal distension, which alleviate spontaneously without any treatment.<sup>59</sup>

### Dosage

Decocted in water for oral use, taken twice a day.

## Shuganjieyu capsules

### Composition

Extracts of “guanye jinsitao” (*Hypericum perforatum*) and “ciwujia” (*Acanthopanax*).

### Chemical constituents

Twenty-two compounds were identified by ultraperformance liquid chromatography tandem mass spectrometry: neochlorogenic acid, syringin, chlorogenic acid, 1'-*O*-caffeoylquinic acid, 1',5'-, 3',5'-, and 4',5'-*O*-dicaffeoylquinic acid, eleutheroside E, rutin, hyperoside, isoquercitrin, isofraxidin, quercetin-3-β-D-arabinose, quercitrin, acetyl-hyperoside, quercetin, II3,II8-biapigenin, protopseudohypericin, hyperforin, adhyperforin, hypericin, and pseudohypericin.<sup>66</sup>

### Pharmacology and bioactivity

A systematic review of shuganjieyu capsules for mild-to-moderate depression included 15 RCTs with 1,240 patients, and concluded that the total effective rate and HAM-D scores of the shuganjieyu group were higher than those of the control group (paroxetine, citalopram, sertraline, fluoxetine, or melitracen–flupentixol), and the incidence of adverse drug reactions in the shuganjieyu group was also better than in the control group.<sup>67</sup> Another meta-analysis investigating MDD in adults comprised seven RCTs with 595 participants. The capsule was superior to placebo in terms of response and remission rates, and mean changes from baseline in the HAM-D and TCM-syndrome scales. Moreover, shuganjieyu plus venlafaxine had significantly higher response and remission rates than venlafaxine alone, and was superior to venlafaxine in terms of average change from baseline on the treatment-emergent symptom scale.<sup>68</sup> The capsule was also effective and safe in the treatment of geriatric depression.<sup>69</sup>

In rat models of depression, shuganjieyu capsules increased spontaneous activity, sucrose consumption, and sucrose preference, reduced immobility time in the FST, decreased the number of apoptotic cells, and decreased protein levels of caspase 3.<sup>70</sup> They also increased levels of p-CREB and BDNF expression in the medial prefrontal cortex and hippocampal CA3 region.<sup>71</sup>

### Indications and usage

Shuganjieyu capsules soothe the liver, relieve depression, strengthen the spleen, and calm the nerves. They are used for mild and moderate single-phase depression with the syndrome of liver-chi stagnation and spleen deficiency, manifesting as low spirits, falling interest, slow movement, sleep disorder, anxiety, irritability, indigestion, loss of appetite, fatigue, sweating, white or greasy tongue, and wiry or small pulse.

### Precautions and side effects

Nausea and vomiting, dry mouth, headache, dizziness, nasal congestion, insomnia, poor appetite or anorexia, diarrhea,

and constipation. All of these adverse effects disappear spontaneously upon cessation of treatment.<sup>68,69</sup>

### Dosage

Two capsules (380 mg each) orally, twice a day for 6 weeks continuously, is usually recommended. However, a multicenter, randomized, controlled, open-label trial found that doubling the dose for the first week of treatment can significantly enhance symptom relief. Therefore, in some cases, recommended dosage is four capsules twice daily during week 1, three capsules twice daily during week 2, and two capsules twice daily during weeks 3–6.<sup>72</sup>

## Sinisan

### Composition

“Zhishi” (*Citrus aurantium* fructus) 6 g, chaihū (bupleuri radix) 6 g, shaoyao (*Paeonia radix*) 9 g, “zhigancao” (*Glycyrrhiza radix* preparation) 6 g.

### Chemical constituents

Sinisan (SNS) contains hundreds of constituents. These include gallic acid, oxypaeoniflorin, albiflorin, paeoniflorin, liquiritin, benzoic acid, narirutin, naringin, hesperidin, neohesperidin, meranzin hydrate, liquiritigenin, quercetin, benzoylpaeoniflorin, isoliquiritigenin, formononetin, quercetin-3-*O*-rhamnoside, isoliquiritin,<sup>39</sup> quercetin-3-*O*-glucoside, naringenin, licorice saponin A<sub>3</sub> and G<sub>2</sub>, glycyrrhizic acid, saikosaponin A and D, glycyrrhetic acid,<sup>73</sup> paeoniflorin sulfonate, liquiritin apioside, uralsaponin A and B, ononin, hesperetin, nobiletin, licochalcone, 5-methoxyflavone,<sup>74</sup> synephrine, catechin, tangeretin, and β-sitosterol.<sup>75</sup>

### Pharmacology and bioactivity

In rats subjected to chronic restraint stress, SNS reverses impairments in spatial learning and memory, reduces aggressive behavior, and increases growth rate.<sup>76</sup> However, SNS has a relatively long lag. After 4 weeks' treatment, SNS alone was less effective than fluoxetine alone or in combination with SNS in reducing depression-like behavior in rats after CMS, although the combination was more effective than fluoxetine alone. However, after 8 weeks' treatment, SNS alone was more effective in reducing depression-like behavior than fluoxetine alone, and markedly increased central 5-HT and reduced peripheral 5-HT in model rats.<sup>77</sup>

The main active ingredients of SNS are saikosaponins, paeoniflorin, naringin, and glycyrrhizic acid. SNS exerts its antidepressant effects via modulation of cerebral monoamine-neurotransmitter expression, hippocampal neuroprotection, inhibition of HPA-axis hyperfunction, and immune and

second-messenger regulation.<sup>78</sup> A single dose of SNS (1.3 g/kg) significantly decreased immobility time in the mouse TST, but not FST, comparably to a fluoxetine group. In addition, pretreatment with *p*-chlorophenylalanine methyl ester (an inhibitor of 5-HT synthesis) or α-methyl-*p*-tyrosine (an inhibitor of tyrosine hydroxylase) prevented the anti-immobility effect of SNS in mice exposed to the TST. Moreover, acute SNS decreased serum corticosterone levels and elevated 5-HT, NE, and dopamine levels without affecting BDNF levels in the whole brain after the TST.<sup>79</sup> A study using the auxiliary mechanism-elucidation system for Chinese medicine and network pharmacology methods found that 263 chemical constituents in SNS directly or indirectly affected 19 targets for the treatment of depression, such as the β<sub>2</sub>-adrenergic receptor, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and the dopamine D<sub>2</sub> receptor. It also revealed that SNS exerted its antidepressant effects via a multitarget and multipathway mechanism, involving G-protein coupled-receptor signaling, the cAMP pathway, neurological systems, neurotransmitter secretion, and the inflammatory response, among others.<sup>80</sup>

### Indications and usage

SNS expels pathogens and resolves depression, soothes the liver, and regulates the spleen. It treats the syndrome of yang stagnation (manifesting as cold limbs, abdominal pain, diarrhea, or tenesmus), or the syndrome of liver–spleen disharmony (manifesting as distending pain in the hypochondrium and a wiry pulse).

### Dosage

Decocted in water for oral use, or taken in its powder form, twice a day.

## Wuling capsules

### Composition

Made from the mycelia of *Xylaria nigripes* (Kl.) Sacc. in People's Republic of China.

### Chemical constituents

Nucleosides (adenosine, uridine, and guanosine),<sup>81</sup> 5-methylmellein, 5-hydroxymellein, 5-carboxymellein, and genistein,<sup>82,83</sup> and 15 amino acids (aspartic acid, glutamic acid, serine, histidine, glycine, arginine, proline, alanine, γ-aminobutyric acid, threonine, methionine, valine, phenylalanine, isoleucine, leucine).<sup>84</sup>

### Pharmacology and bioactivity

A total of 16 RCTs for poststroke depression involving 1,378 patients were identified for the meta-analysis. Wuling

capsules showed some antidepressant effects compared to the no-treatment control. Combined with conventional antidepressants (mefloquine, fluoxetine, sertraline, paroxetine, or citalopram), the capsules improved treatment effects and reduced the incidence of adverse effects as an alternative choice in the treatment of poststroke depression.<sup>85</sup> They also relieved depression and anxiety in female climacteric patients.<sup>86</sup> A multicenter randomized double-blind placebo-controlled study started with 104 patients and finished with 81. The study showed that wuling capsules (three tablets, three times daily for 12 weeks) alleviated depressive symptoms in patients with epilepsy, and enhanced some aspects of quality of life without increasing the risk of exacerbating epileptic seizures.<sup>87</sup>

Wuling capsules improved hippocampal neurogenesis in rats exposed to CMS via a mechanism involving an increase in the expression of connexin 43 mRNA and protein, but not involving BDNF.<sup>88</sup> Another study also found that the mechanism by which wuling capsules improve impairments in learning and memory in rat models of poststroke depression is not mediated by BDNF.<sup>89</sup> The antidepressant effect of wuling capsules might involve facilitation of the 18 kDa TSPO-mediated mitophagy pathway. In a learned helplessness to inescapable electric shock model of depression in mice, wuling capsules showed antidepressant effects across multiple behavioral tests, including the shuttle-box test, novelty-suppressed feeding, and the FST. It also altered the expression of multiple proteins related to the TSPO-mediated mitophagy pathway in the mouse mesencephalon: it significantly upregulated the expression of TSPO, voltage-dependent anion channel 1, and PTEN-induced putative kinase 1, and downregulated parkin expression. Wuling capsules also exerted neuroprotective effects by increasing the expression of Beclin 1 and kinesin family member C2 in the mesencephalon, and increased the relative integrated optical density of synaptogyrin 3-positive nerve fibers in the ventral striatum.<sup>90</sup> Furthermore, wuling capsules exerted an antidepressant effect in rats exposed to CMS, via the l-arginine–nitric oxide–cyclic guanosine monophosphate pathway. After 4 weeks of administration, wuling capsules (at 1 and 2 g/kg) increased sucrose preference, open-field activity, and food consumption in rats exposed to CMS. Furthermore, these antidepressant effects were suppressed by pretreatment with l-arginine and sildenafil, and enhanced by pretreatment with 7-nitroindazole and methylene blue.<sup>91</sup>

### Indications and usage

Wuling capsules tonify the kidney and brain, nourish the heart, and tranquilize the mind. According to the

syndrome-differentiation theory of TCM, they treat heart–kidney disharmony or heart–spleen deficiency, which present with various symptoms, such as insomnia, dreaminess, amnesia, palpitations, listlessness, soreness and weakness of waist and knees, dizziness, tinnitus, thin and white tongue fur, and deep, weak, and wiry pulse.<sup>92</sup> According to modern diagnostic criteria, wuling is suitable for neurasthenia and fatigue syndrome, and it can enhance immunity function and ameliorate the fatigue caused by chemotherapy or blood loss. It is used to treat such conditions as hemorrhagic anemia, irregular menstruation, climacteric syndrome, and benign prostatic hyperplasia.<sup>93</sup>

### Precautions and side effects

Cigarettes, alcohol, and spicy or greasy food should be avoided while taking this formula. Wuling capsules are a safe drug with mild side effects, including diarrhea, dry mouth, dizziness, fatigue, abdominal discomfort, elevated liver enzymes, constipation, increased saliva, anterior thoracic discomfort, skin rash, and sneezing.<sup>87,94</sup>

### Dosage

Three capsules (0.33 g each) taken orally, three times daily for 20 continuous days. The dosage may be doubled if necessary.

## Xiaoyaosan

### Composition

Chaihu (bupleuri radix) 9 g, “danggui” (*Angelica sinensis* radix) 9 g, “baishao” (*Paeonia lactiflora* radix) 9 g, fuling (*Poria*) 9 g, baizhu (*Atractylodes macrocephala* rhizome) 9 g, bohe (*Mentha haplocalyx*) 3 g, shengjiang (*Zingiber officinale* rhizome) 6 g, zhigancao (*Glycyrrhiza* radix preparation) 4.5 g.

### Chemical constituents

Gallic acid, catechin, albiflorin, paeoniflorin, liquiritin apioside, liquiritin, ferulic acid,<sup>95</sup> volatile components (Z-ligustilide, palmitic acid, atractylenolide I, atractylenolide II),<sup>96</sup> isorhamnetin.<sup>97</sup>

### Pharmacology and bioactivity

Anxiolytic and antidepressant components of “xiaoyaosan” (XYS) can be isolated using a room-temperature superextraction system.<sup>98</sup> YYS treated in this way (300 µg/mL) reduces the reserpine-induced death rate of glial cells more than either untreated YYS (300 µg/mL) or fluoxetine (30 µM) at 24 hours after application.<sup>98</sup>

A systematic review of 26 randomized trials (1,837 patients) showed that YYS combined with antidepressants was more effective than antidepressants alone in



decreasing HAM-D and self-rating depression-scale scores, with no adverse effects.<sup>99</sup> Petroleum ether extracts of XYS were the most effective when compared to 30%, 60%, and 95% ethanol extracts and anhydrous ethanol residue extracts, suggesting that the lipophilic constituents of the formula contribute most to its antidepressant effects.<sup>100</sup> XYS exerts an antidepressant effect via  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-related synaptic plasticity of the hippocampus. XYS ameliorates behavioral changes and ultrastructural damage to the hippocampal CA1 region, and also reverses chronic decreases in GluR2 mRNA and increases in GluR1 mRNA in the CA1 after immobilization stress.<sup>101</sup> It may also act via cerebral 5-HT<sub>1A</sub>-receptor activation<sup>98</sup> and the inhibition of locus coeruleus NE neuron activity. XYS decreases serum NE concentrations and protein levels of tyrosine hydroxylase, dopamine- $\beta$ -hydroxylase, and corticotrophin-releasing factor in the locus coeruleus of rat models of depression.<sup>102</sup> Furthermore, XYS ameliorates HPA hyperactivation by downregulating corticosterone and urocortin 2. It reduces the level of serine/threonine-protein phosphatase 2A regulatory subunit B and increases  $\beta$ -arrestin 2, BDNF, mTOR, and tyrosine receptor kinase B.<sup>97</sup> Another study found that the CNP–NPR2 pathway is upregulated in the rectum of rat models of depression; XYS partially antagonizes this pathway by inhibiting rectal tissue expression of CNP and NPR2.<sup>103</sup>

Changes in endogenous metabolites in depressed patients have been measured before and after treatment with XYS using dynamic urinalysis and plasma metabolomics based on <sup>1</sup>H nuclear magnetic resonance. After XYS treatment, urinary and plasma measures revealed metabolic changes in energy, tryptophan, taurine, and gut microbes.<sup>104,105</sup> Quantitative urinary metabolomics using gas chromatography–mass spectrometry provided further support that the antidepressant action of XYS involves the regulation of neurotransmitter and amino acid metabolism and promotion of energy production in depressed patients.<sup>106</sup>

### Indications and usage

XYS soothes the liver and strengthens the spleen, nourishes the blood, and regulates menstruation. It is used to treat the syndrome of liver stagnation with blood deficiency, as well as spleen weakness (manifesting as pain, headache, dizziness, dry mouth and throat, spiritlessness, anorexia, irregular menstruation, breast-distending pain, and wiry and weak pulse).<sup>92</sup>

### Side effects

Modified XYS can cause headache, dizziness, fatigue, and mild diarrhea.<sup>99</sup>

### Dosage

Decocted in water for oral use, or taken in its powder form, twice daily. The decoction shows better effects than the capsule at the same dosage, whereas the capsule is more effective than the pill at the same dosage.<sup>107</sup>

### Yueju

#### Composition

“Cangzhu” (*Atractylodes* rhizome) 6 g, xiangfu (*Cyperus* rhizome) 6 g, chuanxiong (*Ligusticum chuanxiong* rhizome) 6 g, “shenqu” (medicated leaven) 6 g, “zhizi” (*Gardenia fructus*) 6 g.

#### Chemical constituents

Gardenoside,<sup>108</sup> ligustilide,  $\alpha$ -cyperone, atractylodin.<sup>109</sup>

#### Pharmacology and bioactivity

A randomized double-blind, fluoxetine-adjunct, placebo-controlled, pilot clinical study in patients with MDD indicated that the “yueju” pill contributes to fast-onset antidepressant effects. Patients taking yueju (23 g/day) + fluoxetine (20 mg/day; ten patients) showed a significant decrease in HAM-D score compared with baseline or patients taking placebo + fluoxetine (20 mg/day; eight patients) on days 3–7 of treatment, while placebo + fluoxetine had no significant changes in HAM-D score over the first 7 days of treatment.<sup>18</sup>

Yueju ethanol extract (YJ-E) decreases the duration of immobility in the TST and FST in mouse models of depression, whereas the water extract has no notable effects.<sup>110</sup> The petroleum ether fraction and *n*-butanol fraction also appear to be active fractions of YJ-E.<sup>111</sup> YJ-XCC1Z3 (a type of YJ-E) shows potent antidepressant effects by improving depression-like behavior in mice and decreasing 5-HT metabolism.<sup>112</sup> In imprinting control region (ICR) mice, acute administration of YJ-E rapidly alleviates depression-like behavior in the TST, and this effect is maintained for at least 24 hours. Additionally, YJ-E rapidly increases the expression of BDNF in the hippocampus, comparably to ketamine, although mRNA expression remains unchanged. YJ-E quickly increases BDNF synthesis by decreasing phosphorylation levels of *EEF2*. Yueju sustains both BDNF expression and *eEF2* phosphorylation for 24 hours after administration, which was longer than ketamine.<sup>113</sup> The NMDAR subunit NR<sub>1</sub> and the Akt–mTOR pathway are important therapeutic targets of yueju for depression. An improvement in the sucrose-preference test was observed as early as 2 hours after administration of yueju and ketamine, but lasted for 6 days only with yueju and 2 days with ketamine. In Kunming mice exposed

to CMS, both yueju and ketamine increased phosphorylation of the mTOR effectors 4E-BP1 and p70S6K, their upstream regulators ERK and Akt, and downstream targets, including synaptic protein GluR1, 2 days after drug administration, but only p-Akt remained upregulated with yueju 6 days after drug administration. Both yueju and ketamine decreased NR<sub>1</sub> expression 2 days after administration, but by day 6 this effect was maintained only by yueju.<sup>114</sup>

Another study in Kunming mice showed that both yueju and ketamine decreased immobility time in the FST and hippocampal NR<sub>1</sub> expression from 30 minutes to 5 days after a single administration (2.7 g/kg). Both also reduced hippocampal NR<sub>2B</sub> protein expression at 30 minutes, which returned to baseline levels within 24 hours, whereas NR<sub>2A</sub> expression was decreased only by ketamine at 30 minutes. Yueju relieved depression-like symptoms in a learned-helplessness model in mice for at least 3 days after administration, and decreased NR<sub>1</sub> expression in mouse models of depression at 1 or 3 days after administration. Antidepressant effects were not influenced by blockade of the AMPA receptor, indicating that the mechanism of action of yueju is different from that of ketamine.<sup>115</sup> Furthermore, prolonged increases in hippocampal BDNF may account for the enduring and strain-dependent antidepressant responses to yueju and ketamine, but only yueju was mediated via the PKA–CREB pathway. Yueju and ketamine upregulated hippocampal expression of total and phosphorylated CREB, as well as the CREB-signaling activator PKA 1 day after administration in Kunming but not ICR mice. Yueju and ketamine increased *BDNF* gene expression at 3 hours in both strains, but this was sustained for only 1 day in Kunming mice only. However, blockade of the PKA–CREB pathway reversed the increase in *BDNF* gene expression and the antidepressant effects of yueju but not ketamine. Conversely, the mTOR inhibitor rapamycin reversed the antidepressant effects of ketamine but not yueju.<sup>116</sup>

### Indications and usage

Yueju regulates chi, relieves depression, regulates the function of the middle jiao, and resolves chi stagnation. It is used to treat the syndrome of six stagnations (chi, dampness, fire, phlegm, blood, and food), manifesting as fullness and stuffiness in the chest and abdomen, dietetic stagnation, belching, and acid regurgitation.<sup>92</sup>

### Side effects

Gastrointestinal symptoms, such as diarrhea and constipation.<sup>18</sup>

### Dosage

All herbs can be crushed into a fine powder, sieved, mixed, then made into pills with water; 6–9 g of the pills should be taken twice daily. Alternatively, the herbs can be decocted in water for oral administration.<sup>92</sup>

### Discussion

A literature search identified nine CHF formulas with evidence-based antidepressant effects: BHD, CSS, GMDZD, KXS, shuganjieyu capsules, SNS, wuling capsules, XYS, and yueju. The present study is the first to describe these formulas in terms of source, TCM syndromes and effects, composition, chemical constituents, clinical trials, antidepressant mechanisms, indications, and side effects. This information will help to guide treatment of depression, and will be of value to neurologists, neuroscientists, and those interested in CHF.

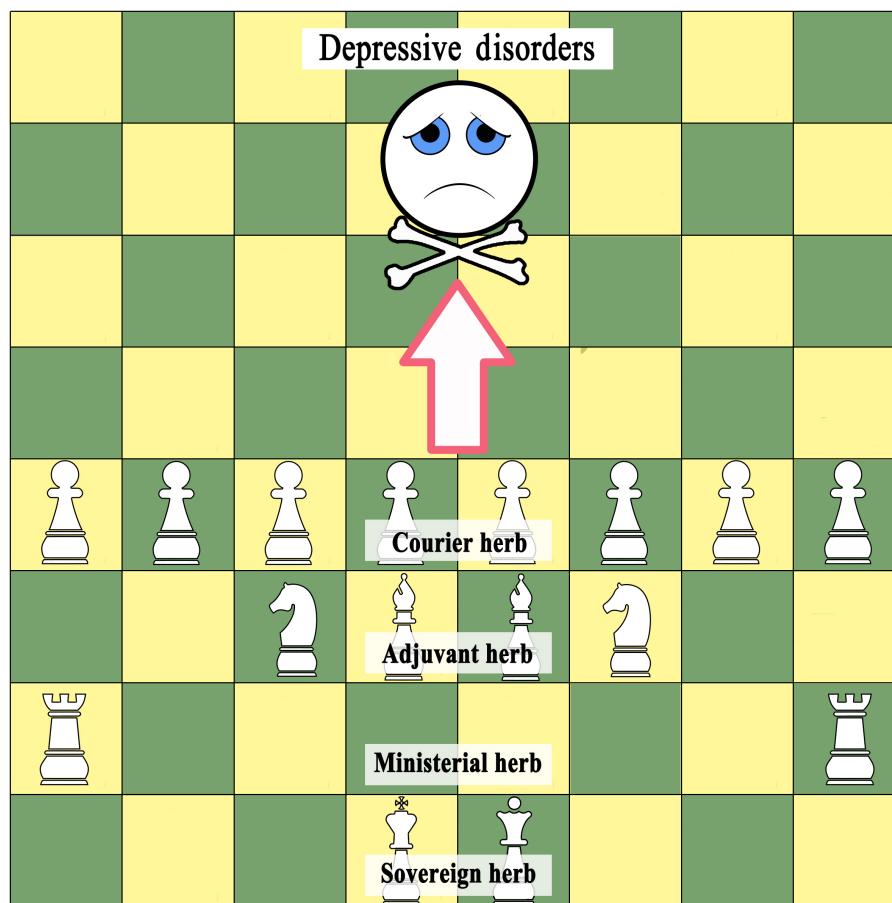
Depression is a serious affective disorder characterized by persistent low mood with frequent residual depressive symptoms and relapse.<sup>117</sup> Furthermore, there is a significant association between depression and excess mortality.<sup>118</sup> Despite considerable research efforts, antidepressant treatments remain unsatisfactory. Existing Western medicines for MDD have a delayed onset of therapeutic action, severe side effects, withdrawal symptoms, and even treatment-related suicidal behavior.<sup>24</sup> The NMDAR antagonist ketamine, recently indicated as an antidepressant, has consistently shown antidepressant effects within a few hours after administration (intranasal or intramuscular).<sup>119</sup> However, many obstacles remain before it can gain widespread clinical approval.<sup>120</sup> Ketamine is an anesthetic with neurotoxic and hallucinogenic side effects, such as visual or auditory hallucinations, out-of-body experiences, or abnormal sensations.<sup>121</sup> Its long-term use is associated with cardiotoxicity<sup>122</sup> and impairments in neurocognitive function and psychological well-being.<sup>123</sup> Abuse potential and addictive properties are significant barriers to its widespread use.<sup>120</sup> There is an increasing need to develop a practical and effective antidepressant, due to the growing prevalence of depression worldwide. A search on the Web of Science shows that the number of reports on antidepressant CHF formulas is growing every year, revealing that the subject is drawing increasing attention, likely due to treatment efficacy and minimal side effects.

A characteristic of Chinese herbal medicines is their use as formulas rather than single herbs. Thousands of years ago, TCM practitioners generally used a single herb for disease treatment, but this was increased to two or more herbs, constituting a formula, to achieve additive or synergistic actions

and reduce adverse effects.<sup>124,125</sup> As clinical experience in Chinese herbal medicine accumulates, practitioners modify their CHF's based on the holistic philosophy and syndrome differentiation of TCM, while carefully following the rules of herb synergism and compatibility.<sup>126</sup> Each single herb has its own flavor and channel tropism, whereas typical CHF's are mostly built on the "sovereign, minister, assistant, courier" rule.<sup>127</sup> According to the seven methods ("emotions") in prescription compatibility, mutual promotion and mutual enhancement can synergistically enhance curative effects, and mutual restraint and mutual detoxification can alleviate toxicity and adverse effects.<sup>128,129</sup> An increasing number of studies have demonstrated the advantages of formula completeness and herb compatibility, such as comprehensive disease intervention,<sup>130</sup> favorable pharmacokinetics,<sup>131,132</sup> alleviation of drastic effects, and fewer adverse effects than single herbs.<sup>133</sup> Owing to the "sovereign, minister, assistant,

courier" rule and the seven methods in prescription compatibility, CHF's are more commonly used than single herbs for disease treatment, and have become the predominant application of TCM.<sup>131,134</sup> As illustrated in Figure 2, the relationship between CHF's and MDD's can be likened to playing chess. A single herb represents a chess piece, which cannot win the game single-handedly; however, when different herbs are combined to create a formula, their effectiveness in the treatment of depression becomes apparent.

Most CHF's have liver-soothing and depression-relieving effects. A systematic review revealed that the most common TCM-syndrome pattern of depression was liver-chi depression, followed by liver depression, spleen deficiency, and dual deficiency of the heart and spleen. In addition, YYS was the most commonly used prescription for liver-chi stagnation and liver stagnation with spleen deficiency, whereas CSS was usually used for liver-chi stagnation.<sup>25</sup> An analysis based on



**Figure 2** The relationship between Chinese herbal formulas and depressive disorders. The relationship can be likened to a game of chess.

**Notes:** Sovereign herbs play the most significant role in the treatment of the principal syndrome, like the king and queen in chess. Ministerial herbs assist the sovereign herbs with the principal syndrome or the main accompanying syndrome, like the rook. Adjuvant herbs cooperate with sovereign and ministerial herbs to treat accompanying syndromes, and can be represented by the bishop and the knight; they may also inhibit the toxicity of sovereign and ministerial herbs. Courier herbs guide drugs to illness stations like the pawn, or coordinate the drug actions in a prescription. In the same way that all the chess pieces must be coordinated for the game to be won, all the herbs in antidepressant formulas act synergistically to treat depression.

the TCM inheritance support platform software V2.0 compiled 358 TCM prescriptions for depression from modern literature databases. The main effects of these prescriptions were soothing the liver and relieving depression, strengthening the spleen and resolving phlegm, activating and enriching blood, clearing and purging heat, and tranquilizing and sedating the mind; these follow the principle of “regulating chi, relieving depression, and empathy”.<sup>26</sup>

Multicomponent CHF<sub>s</sub> exert their effects via multitarget and multipathway mechanisms.<sup>80,135,136</sup> Antidepressant CHF<sub>s</sub> comprise a series of active compounds, including terpenoids, flavonoids, xanthenes, phenylpropanoids, and phenols, providing a shortcut to finding novel antidepressant agents.<sup>137</sup> *In vitro* and *in vivo* pharmacology and bioactivity studies of CHF<sub>s</sub> in combination with conventional antidepressants have indicated that CHF<sub>s</sub> not only enhance the antidepressant response and speed of onset<sup>18,48</sup> but also reduce adverse effects of traditional psychotherapeutic drugs in patients with severe depression.<sup>27,138</sup> CHF<sub>s</sub> have a multitude of biological actions, including effects on reuptake and receptor binding of various monoamines (eg, NE, 5-HT) and endocrine and neuropsychological modulation.<sup>139</sup> CHF<sub>s</sub> regulate dysfunctions of the hypothalamic–pituitary–adrenal, –thyroid, and –gonadal axes and locus coeruleus NE system, as well as improving impairments in endogenous metabolic processes. Constructing a disease-related compound–target pathway network can help elucidate the antidepressant mechanism of CHF<sub>s</sub>.<sup>140</sup> Future studies should no longer focus on single pathways, but include multiple pathways and networks.

There is an urgent need for more and higher-quality phytochemical and pharmacological studies of these nine CHF<sub>s</sub>. Many chemical constituents have been detected and reported for most of the CHF<sub>s</sub>, but reports relating to shuganjiayu and wuling capsules have been published in Chinese only, which cannot be understood worldwide. Furthermore, to date, few chemical constituents have been identified in BHD, GMDZD, or yueju. Various bioactive chemical constituents are expected to be identified by chromatography, mass spectrometry, and nuclear magnetic resonance. Studies of the pharmacological mechanisms of these constituents are also needed. Today’s high-throughput screening technology enables us to explore bioactivity and mechanisms rapidly, resulting in a high discovery rate of candidate drugs.

There is evidence to support the effective and safe use of these nine CHF<sub>s</sub> in the treatment of depression, with demonstrations of better efficacy than placebo and synergistically increased effects of conventional therapy. However, some evidence should be interpreted with caution. First, whereas

BHD, KXS, and yueju have been investigated in RCTs, and CSS, GMDZD, shuganjiayu and wuling capsules, and XYS have been the subject of meta-analyses or systematic reviews, SNS has not been included in any such systematic studies, because of its variations in formula. Second, most clinical trials of these formulas have been published in Chinese, and the randomization and blinding methods were not clearly reported. Third, only four trials have registered online at <https://ClinicalTrials.gov> (for wuling capsules, XYS, and two for shuganjiayu capsules), and only two multicenter RCTs were identified (for shuganjiayu and wuling capsules).<sup>72,87</sup> No large-scale RCTs have been performed. Moreover, there was considerable variation between the formulas used in the trials: only a few used the traditional formulas, whereas most used a modification of the original formula, adding or subtracting several herbs based on patients’ symptoms. Although this does not change the “sovereign, minister, assistant, courier” structure of the traditional formulas, experimental evidence is needed to support the use of added or subtracted herbs. In addition, a systematic review and meta-analysis of 13 RCTs concluded that a previous meta-analysis of GMDZD for depression<sup>48</sup> did not use a comprehensive search strategy. This latter review, with a high risk of bias, found no evidence that GMDZD showed a significant antidepressant effect in MDD, postsurgical depression, or geriatric depression; it was only deemed to have an effect in poststroke depression.<sup>141</sup> Therefore, more large-scale and rigorous RCTs comparing the efficacy of each formula with placebo and established pharmacotherapy need to be registered and conducted to obtain robust evidence on the antidepressant effects of these formulas.

## Conclusion

In the present study, we reviewed important data regarding the use of CHF<sub>s</sub> in the treatment of depression. In summary, diverse CHF<sub>s</sub> have been used for various types of depression for many years, with experimentally and clinically demonstrable effects. This review highlights the possibility of CHF<sub>s</sub> as evidence-based treatment options for depression, and could help modern TCM doctors prescribe appropriate CHF<sub>s</sub> for depressed patients. We have provided a comprehensive list of the constituents, clinical effects, putative mechanisms, TCM patterns, and use for each CHF. This research will benefit patients, practitioners, and researchers in the field of TCM. Further well-designed, well-reported, placebo-controlled randomized trials and psychopharmacological studies should be carried out to substantiate clinical claims of the antidepressant actions of CHF<sub>s</sub> and contribute to the building of a compound–target pathway network.



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## Disclosure

The authors report no conflicts of interest in this work.

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