



The Efficacy of Chinese Herbal Medicine in the Treatment of Depression: a Systematic Review of Literature

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The Efficacy of Chinese Herbal Medicine in the Treatment of Depression: A Systematic
Review of Literature

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A Thesis in the Field of Biotechnology
for the Degree of Master of Liberal Arts in Extension Studies

Harvard University

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Abstract

Major depressive disorder is a common and deadly disease affecting roughly 18% of Americans. It is the leading cause of disability in the United States and its conventional treatment options are minimally effective. As a result over 50% of sufferers seek out alternative treatments. Chinese herbal medicine is one of the most commonly sought alternative treatment strategies. In this systematic review we searched PubMed and the Cochrane central register through May 2019 for randomized controlled trials evaluating the efficacy of Chinese herbal medicine in the treatment of depression in comparison to placebo or conventional antidepressants. Our goals for this review were 3 fold: (1) to summarize the existing literature that met our quality criteria of a modified Jadad score greater than or equal to 3, (2) to examine the efficacy and safety of CHM in treating depression alone or in conjunction with antidepressants, (3) to determine the most commonly used herbs and formulas used in the treatment of depression. The most commonly used single herb was Saffron, and the most commonly used formula was Xiao Yao San. Pooled analysis showed that CHM was more effective than placebo and equivalently effective to antidepressants in reducing HAMD scores (Versus placebo: Change in HAMD: -7.95, 95% CI: +/- 2.14; HAMD at endpoint: -3.12, 95% CI: +/- 1.02; Versus antidepressants: Change in HAMD: 2.05, 95% CI: +/- 2.13; HAMD at endpoint: -0.74, 95% CI +/- 0.74). Adverse events were less common in CHM users, with antidepressant users carrying 213% higher risk of experiencing an adverse event. Overall, the results of this review indicate that CHM may be an effective and safe alternative to antidepressants in treating major depressive disorder.

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Chapter I.

Introduction

The Research Problem

Major depressive disorder (MDD) is a mental health disease that affects over 18% of Americans every year and is a leading cause of disability (WHO, 2017). Currently the most common treatment for MDD is pharmacotherapy, but antidepressant drugs build dependence, have a wide variety of side effects, and are questionably effective when compared to placebo (Kirsch, 2014, Anderson, 2012). The number of individuals with MDD is on the rise (Baxter, 2014), and as it goes up there is an increasing need to identify safe, effective, and non habit forming therapies. For centuries, Chinese herbal medicine has used traditional formulas to treat depressive symptoms. In the past, clinical trials have been performed to evaluate the safety and efficacy of these formulas, but few systematic reviews have been performed to create a wider view of their therapeutic potential. Previous systematic reviews have either focused on singular herbal formulas, have failed to exclude clinical trials with low methodological quality, and many are greater than 5 years old. These limitations mean that they are not accurately representing the potential of MDD treatment with Chinese Herbal Medicine. Herein we perform a systematic review of clinical trials using Chinese herbal medicine either alone, or in conjunction with western medicine, to treat MDD. We use only clinical trials that are of high methodological quality, and include studies using a full range of formulas and herbs that are used clinically to treat depression. In this way, our systematic review provides a

more clinically translatable picture of how MDD responds to herbal therapy, and provides a comprehensive view of the formulas being used to treat it. We demonstrate that Chinese herbal medicine alone has far fewer side effects and similar effectiveness than standard pharmacological treatment, and further, that in conjunction with standard pharmacological treatment it has a greater effect than antidepressants alone.

Background of the Problem

Depression is a chronic condition affecting 322 million people worldwide, and is globally a leading cause of years lived with disability (GBD, 2018). Symptoms include reduced ability to concentrate, reduced self esteem, feelings of guilt and unworthiness, ideas or acts of self harm, poor sleep, and reduced appetite. In severe cases, the individual is unable to continue to work or participate in social activities (ICD-10, 1992). Women are nearly twice as likely as men to be affected, and it is more prevalent in affluent countries than low to middle income (Bromet, 2011). Symptoms impact nearly every aspect of an individual's life, and can be crippling. Currently, the treatment for major depressive disorder falls into three major categories: psychotherapy, pharmacotherapy, and alternative therapies. Globally, rates of MDD are rapidly increasing (Baxter, 2014), and as they rise, identifying effective treatments with minimal side effects will mitigate suffering.

Psychotherapy is limiting in that it is often expensive, time intensive, requires a skilled practitioner, and requires the patient to participate and be highly motivated - all things that are extraordinarily difficult for depression sufferers (WHO, 2017).

Pharmacotherapy is the most commonly used treatment, but recent studies indicate we should be concerned about its effectiveness and it comes with a long list of side effects. Analysis of studies provided to the FDA for approval of six new generation antidepressants showed nearly half the studies submitted were never published (Kirsch, 2014, Turner, 2008). In one study of unpublished trials, 74 FDA registered studies were compared. Of the 37 that demonstrated a positive outcome, all but one had been published. Of the 37 that conveyed a negative or questionable outcome, 22 were unpublished, 11 were published in a way that conveyed a positive outcome, and only three were published in a way that reflected the FDA's opinion of the results. In the published literature, it appeared 94% of the data view the drugs positively, but the FDA analysis showed only 51% (Turner, 2008). When the full data set of published and unpublished studies is taken together, only 43% of the trials show statistically significant benefit to the studied antidepressants when compared to placebo, and placebo is responsible for up to 82% of the patient's response to treatment (Kirsch, 2014). In addition to its low efficacy, antidepressant therapy is frequently used incorrectly. Only 42% of patients prescribed antidepressants take them continuously, merely 26% take them as recommended by international guidelines (Bockting, 2008). When on antidepressants, patients often experience side effects which include headache, nausea, vomiting, agitation, sedation, long term weight gain and sexual dysfunction (Anderson, 2012). These side effects can continue even after treatment has ceased, and ironically can make patients more susceptible to future depression (Andrews, 2012).

Possibly as a reaction to the low efficacy and high side effect rate of pharmacotherapy, alternative therapies are commonly used to treat major depressive disorders. A national representative survey indicated 53.6% of adults with depression use some form of CAM to treat their symptoms (Kessler, 2011). Chinese herbal medicine is one of the most common complementary therapies used, and is used very frequently for treatment of depression in China (Hsu, 2008). Over 38 million Americans are currently using Chinese herbal medicine (Tingle, 2005), and that number is growing (Eisenberg, 1998). With herbal medicine on the rise, adequate analysis is needed to determine if it is an effective treatment strategy. Previous systematic reviews have examined the efficacy of Chinese herbal medicine in the treatment of depression (Zhao, 2009, Butler, 2013, Wang, 2012, Qin, 2011, Zhang, 2012), but have focused on one particular Chinese herbal formula, or diagnosis, have often included studies of poor methodological quality, and do not contain the research published in the last 5 years. In the following systematic review, we examine the existing literature of clinical trials of the effectiveness of Chinese herbal medicine in the treatment of depression. We summarize the current findings, with special attention paid to clinical trials of greater methodological quality, then examine the effectiveness and safety of CHM in treating depression, either alone or in conjunction with other therapies. Finally, we identify the most commonly used CHM formulas and herbs with their individual success rates.

Western Biomedical Perspective on Depression

Conventional thinking is that depression is caused by a chemical imbalance in the brain, however that thinking is simplistic, short sighted and not inclusive of all available literature. The truth of depression is more complicated, and the true biological basis is still being discovered. Research suggests it is far more than a simple chemical imbalance, and encompasses errors in mood regulation in the brain, genetic susceptibility, stressful life events, medications, and other medical problems.

Mood Regulation

Current research suggests the brain regions most important to mood regulation are the amygdala, thalamus, and hippocampus (Zhu, 2019; Martin, 2016). The thalamus receives sensory information from the world, and directs that information in order for you to perform high level tasks such as speaking, thinking, moving, and learning. The amygdala processes emotionally charged memories, particularly fear and sadness. The hippocampus processes long term memory and recollection, and works closely with the amygdala to create fear conditioning as in the expression, “once bitten, twice shy.”

Patients who suffer from depression demonstrate unique changes in their mood regulation centers when compared to healthy individuals. Neuroimaging studies show heightened activity in the amygdala of depressed patients when they are experiencing symptoms, and this heightened activity reduces, but still persists above healthy controls, when depressive symptoms lessen (Fu, 2004). Furthermore, the hippocampus is smaller

in the brains of depressed women than in healthy controls. The greater the duration and severity of the depression, the greater the reduction in hippocampal volume (Sheline, 1999).

Stressful Life Events

A prevailing theory for why these changes in brain activation and hippocampal volume occur is tied to glucocorticoid neurotoxicity, which may occur when the body responds to intensely stressful stimuli (Sapolsky, 1986; McEwen, 1992).

The “fight or flight” response to stress is regulated by the body’s hypothalamic - pituitary - adrenal system, also called the “HPA axis.” In response to stress, the hypothalamus secretes corticotropin releasing hormone (CRH), which signals to the pituitary gland to secrete adrenocorticotrophic hormone (ACTH) into the bloodstream. In the bloodstream, ACTH travels to the adrenal glands and triggers the release of cortisol, Cortisol then begins a cascade of events that make up the “fight or flight” response including increase in heart rate and blood pressure, more rapid breathing, vasodilation, sharpening of the senses, and release of glucose into the bloodstream. These changes are beneficial from a survival stress, such as being chased by a tiger, but are problematic when they are triggered by non-survival stress, such as a stressful job, and when they do not “turn off” completely or persist for a long period of time. Prolonged cortisol levels that either rise too high, or fail to fall, called HPA axis dysregulation, can have wide ranging effects on the body. Common symptoms are high blood pressure, immune suppression, and even asthma, but less obvious is the effect that chronic stress can take

on the brain.

Prolonged exposure to glucocorticoids, such as cortisol, has been linked to reduced neurogenesis in the hippocampus, potentially resulting in the decrease in hippocampal volume we see in the brains of depressed patients (Sapolsky, 2000; Czech, Lucassen, 2007). CRH additionally plays a role in coordinating thoughts, behaviors, and involuntary responses in the amygdala, which can influence neurotransmitter expression and concentration, potentially being further linked as a cause of depressive symptoms (Hanley, Van de Kar, 2003).

Regulation of the HPA axis can be effected by acutely stressful or traumatic events throughout life. Children who undergo sexual or physical abuse have more acute and extreme reactions to stress in adulthood when comparable adults who did not suffer from abuse (Heim et al, 2000; Mello et al, 2009). They show higher levels of ACTH and cortisol, and have faster and more extreme reactions to stressful situations such as exercise or speaking in front of an audience. This effect was particularly robust if they were currently experiencing depression or anxiety symptoms. Furthermore, children who were mistreated or who grew up in poverty have more extreme reactivity to negative emotional stressors in their amygdala than their more affluent peers (Ochsner 2016).

Brain Chemistry

You're probably familiar with the commercial for the popular antidepressant Zoloft. A sad blob sits under a gray cloud, moving lethargically through life. A voice tells him the problem lies in an imbalance of serotonin in his brain. He takes Zoloft, the

serotonin levels increase, and suddenly he is happy and bouncing through a sunshine-y life again. We now know there are differences in the brains of depressed patients, but the problem does not rest entirely on the “feel good” neurotransmitter serotonin.

Selective serotonin reuptake inhibitors, called SSRIs are thought to work by increasing the levels of serotonin in the brain. Serotonin influences feelings of wellbeing and happiness, but also has far reaching systemic effects that range from constricting smooth muscle and regulating appetite, to playing a role in cognition and overall coordination of the nervous system (Frazer, Hensler, 1999). These wide reaching side effects are one of the reasons SSRIs also have such a wide range of side effects.

When a patients take an SSRI, serotonin levels increase very quickly in the brain, but it takes 4-6 weeks for the patient to begin to feel improvement in their mood. This timeline suggests that serotonin concentration alone is not the true culprit of depressed mood, and increasing its concentration is not the sole source of symptom improvement. Rather, research in animal models suggests that the value of SSRIs is in allowing improvement in neurogenesis and increased nerve density in the hippocampus, which takes weeks to occur (Song, 2017). Depressive symptoms may improve as a result of improving nerve connections and improving the exchange of information through nerve circuits, and not necessarily as a result of the neurotransmitters themselves.

Beyond serotonin, patients with depression show altered levels of cortisol. Cortisol levels typically fluctuate throughout the day, with the highest levels occurring 30 minutes after waking, then falling to less than half that value by noon. The lowest levels should occur at night, where they stay low throughout the sleeping hours. Plotting

cortisol levels against time of day produces a curve called the Cortisol Awakening Response (CAR). Depressed patients exhibit a “flattened” CAR, meaning they exhibit less variability in cortisol throughout the day, and overall have elevated cortisol levels. Following treatment with an SSRI, the cortisol level of depressed patients improves to more closely match their peers who do not have major depressive disorder (Manthey et al, 2011).

Underlying Medical Conditions

The brain is not always the source of depressive symptoms. Many other medical conditions can have depression as a symptom, and in these cases appropriate diagnosis is important for treatment. Hypothyroidism, or when the thyroid produces too little hormone, can have depression as a chief symptom. Thyroid hormones affect metabolism and how efficiently nutrition from food can be converted to energy, and through this process indirectly affect nearly every tissue in the body. When the thyroid is not functioning optimally, many organ systems will subsequently slow down, and result in symptoms including depressed mood, fatigue, weight gain, reduced sexual desire, and trouble concentrating. Correcting the imbalance with synthetic thyroid hormones typically resolves all symptoms, including depression (Hage, Azar, 2012).

Heart disease is linked with depression with up to 30-40 percent of patients hospitalized for a cardiac event simultaneously experiencing a depressive episode, and between 15 and 20 percent of outpatient heart disease patients experiencing depression (Mittag et al, 2016). The exact reason for this link is not clear, but hypotheses include

linking both diagnoses to chronic inflammation and a persistent stress response which can worsen both diseases (Fioranelli, 2018). An increase in “stickiness” of depressed patients’ platelets has been hypothesized as a potential source of heart disease (Williams, 2012), but a mechanism for this is not yet known.

Degenerative neurological conditions such as MS, Parkinsons, Alzheimers, and Huntington’s disease are often associated with depression. As previously discussed, brains of depressed patients show characteristic neurodegeneration, so it’s possible the root cause of these diseases may be intertwined (Sheline, 2003), and antidepressants have been demonstrated to act by helping with neurogenesis (Santarelli, 2003). Similarly, depression is the most common long term consequence of brain injury following a stroke (Lokk, 2010).

Traditional Chinese Medical Perspective on Depression

Much as different parts of the brain are responsible for processing and integrating different forms of thought and consciousness, from the Traditional Chinese Medicine perspective, consciousness can be broken into different components of the spirit. The “5 spirits” in Chinese medicine are called the Shen, Po, Yi, Zhi, and Hun each of which metaphorically resides in and is primarily affected by the Heart, Lung, Spleen, Kidneys, and Liver, respectively (Hammer, 6). The Shen is the “emperor” of the spirits, and facilitates communication between the other spirits and organs to create balance and harmony in the body. The Po is the corporeal soul which deals with immediate needs and wants, and is affected by grief and sadness. The Yi is the intellect, and deals in

intellectual pursuits of learning, decisiveness, and manifests as intelligence and understanding. Zhi is willpower and the motivating force that drives us through life. Finally, the Hun is the ethereal soul. It creates consciousness and can be strongly injured by undue stress. Traditional Chinese medicine views depression as a lack of movement in the Hun (Maciocia). This lack of movement can be caused by many different patterns of disharmony, but all of them will fall into two broad categories: energy that is not moving because it is stuck or stagnant, and energy that is not moving because it is deficient, and therefore is not abundant enough to move (Maciocia).

Stagnant Patterns

Energy can become stagnant through emotional or physical means. The primary emotions that cause energy to stagnate are stress and anxiety (Holman, 22-23). Energy of the liver is particularly susceptible to stagnation, and when it does, it manifests as irritability, headaches, neck and back tension, high blood pressure, constipation, irregular menstruation in women, and depression (Maciocia, 503-505). As discussed above, the Hun is housed in the liver, so stagnation of this energy immediately and drastically effects the mental emotional state. Small amounts of day to day stress can be rectified relatively easily, but when stress is extreme or persists for very long periods of time, it becomes harder and harder for the body to recover. The effects of trauma or habitual high stress can build up in the body and result in more extreme presentation of stagnation such as depression, anxiety, and other mood disorders (Holman, 23-25).

Physical causes of stagnant energy are predominantly “dampness” or “phlegm accumulation.” In the Traditional Chinese concept of digestion, food is digested by the Spleen and Stomach. When food is well tolerated by the body and nutritious it breaks down into energy used to fuel the body’s processes, and waste products excreted in the urine and stool. When food is not well tolerated by the body or is very difficult to process a third product appears and accumulates in the body as “dampness” (Maciocia, 151-153). When dampness accumulates in large amounts or for long periods of time it congeals as phlegm. Signs of dampness include feeling sluggish, swollen, bloated or groggy, and show up physically as water retention, phlegm in the throat, runny nose or sinus congestion, and weight gain. Foods that contribute to dampness are foods we consider in the west to be inflammatory: processed foods, fried/greasy foods, sugar, wheat products, and dairy, among others. Dampness obstructs the flow of energy in the body by physically blocking the passage of energy through the channels. Energy that is stagnant due to dampness and phlegm accumulation often manifests as depression with physical and emotional heaviness, cloudy thinking, lethargy, exhaustion, and pain that is widespread such as in fibromyalgia (Maciocia, 692-696).

Deficiency Patterns

When energy is deficient in the body, it can stagnate because there is not enough to move. This happens most often when a person’s body has been heavily taxed for long periods of time, and their overall constitution is depleted. The most common culprit here is a constitutional predisposition or excessive physical or mental work, coupled with

inadequate sleep, recovery, or nutrition. The systems most commonly effected by a Qi deficiency are the Heart and Spleen (Maciocia, 343-344). From a Traditional Chinese perspective the Heart is responsible for the “fire” of motive energy that moves us through the day and directs the flow of emotion (Maciocia 108-110). The Spleen is the motive force behind digestion and pulling nutrition from food, as well as commanding mental work and the intellect via the Yi as discussed above (Maciocia 145-150). Symptoms of Heart deficiency include insomnia, exhaustion, dizziness, mental restlessness, palpitations, low libido, thirst, and cold hands (Maciocia, 465-466). Symptoms of Spleen Qi deficiency include bloating, loose stools, fatigue, weak muscles, and a propensity to depression and worry (Maciocia 568-570). The Heart is taxed most by inadequate nutrition and prolonged emotional strain while the Spleen is particularly taxed by diets that are difficult to digest and mental overwork. Recall that the Spleen is the organ responsible for helping the body to pull nourishment from food, and that when it is unable to do it’s job effectively the Heart is weakened and dampness will accumulate. You can see how the two organs’ functions are intimately intertwined, and that their weaknesses often presents as a dual imbalance. We call this imbalance a Heart and Spleen Disharmony (Maciocia, 181-182). A primary symptom of this disharmony is the depression or anxiety that results from an inability of energy to move smoothly through the body, and most notably through the Hun.

East Meets West

On the surface, the highly technical view of the body from the Western perspective and the highly metaphorical view of the body from the Eastern perspective may seem disparate. In truth, they are simply describing two sides of the same coin. We can distill what we know about the root cause of depression from a Western perspective to a few key factors: (1) glucocorticoid neurotoxicity or neurodegeneration in response to intensely stressful stimuli, chronic inflammation, or genetic factors (2) dysregulation of the HPA axis as a response to acute stress or trauma, (3) underlying health conditions such as hypothyroidism or cardiac disease. From a Traditional Chinese medical perspective, we can distill the key factors underlying the root cause of depression to: (1) the body's response to chronic stress, (2) the body's response to extreme stress and trauma (3) a constitutional (genetic) pre-disposition to a weakened heart (as in heart disease), or weak motive force in the body (as in hypothyroidism), (4) the body's response to unhealthy and inflammatory foods. The sole difference between these two explanations lies in the importance Chinese medicine places upon excellent digestion and nutrition. A nutritional link is not yet fully established from a Western perspective, however the link between a healthy microbiome and health in nearly all other aspects of the body is being strengthened every day. A review published in the October 2019 issue of the Journal of Neuroscience Research demonstrated an emerging link between gut microbiome health and mental health (Peirce, 2019), but time and more studies are needed to firmly elucidate a causal role.

Chapter II.

Materials and Methods

Purpose and Aims

The specific aims of the proposed systematic review are threefold:

1. Summarize the existing literature on clinical trials in the treatment of depression with CHM, with special attention paid to clinical trials of greater methodological quality.
2. Examine the efficacy and safety of CHM in treating depression, either alone or in conjunction with other therapies.
3. Determine the most commonly used CHM formulas used in the treatment of depression.

Aim 1

Summarize the existing literature on clinical trials in the treatment of depression with CHM, with special attention paid to clinical trials of greater methodological quality.

Study Search

The databases of PubMed and the Cochrane central register of controlled trials were searched for clinical trials containing the grouped keywords show in Table 1.

Keywords were chosen based on diagnosis, Chinese herbal medicine variations, and known common formulas to treat depression. Upon creation of the initial list of studies, we further searched their listed references for potential additional clinical trials.

Study Inclusion Criteria

Studies were included only if they met the following requirements:

1. Randomized controlled trial
2. Include a comparison of CHM treatment to placebo or conventional therapy, OR a comparison of CHM treatment in conjunction with conventional therapy vs conventional therapy alone.
3. Depressive scores are either reported by clinicians or self reported by patients, and are applied against a standardized scale.

The herbs and formulas included as search terms were chosen because they are traditionally known to treat the Chinese Medicine patterns of disharmony discussed in Chapter 4. Specifically, Xiao Yao San and Chai Hu Shu Gan San move stagnation of Liver energy, Yu Ju Wan releases all types of energy stagnation, Ban Xiao Huo Po Tang and Wen Dan Tang reduce “dampness” and “phlegm,” and Gan Mai Da Zao Tang and Gui Pi Tang strengthen the Spleen, nourish the Heart, and calm the spirit (Bensky, 2009).

Evaluation of methodological quality

Methodological quality was assessed using a Jadad Scale (Jadad, 1996, White, 1999) and the Cochrane risk of bias assessment (Higgins, 2011). The Jadad Scale is out of 5 potential points. 1 point was awarded if the study is randomized, 1 point was awarded if it had an appropriate randomization method, 1 point was awarded if it was subject blind, 1 point was awarded if it was evaluator blind, and 1 point was awarded if it contained a description of withdrawals and dropouts. Only studies with a Jadad score greater than or equal to 3 were included in this systematic review. To minimize bias, all studies were scored by two researchers independently.

Table 1. Search Terms

Term 1	Term 2
Depression	Chinese Herb
Depressive	Herbal Medicine
Mood Disorder	Traditional Chinese Medicine
Dysthymia	TCM
Major Depressive Disorder	Xiao Yao
MDD	Ban Xiao Huo Pu
Affective Disorder	Chai Hu Shu Gan
	Gan Mai Da Zao
	Wen Dan Tang
	Gui Pi
	Yue Ju

Description of search terms used in study search

Aim 2

Examine the efficacy and safety of CHM in treating depression, either alone or in conjunction with other therapies.

Data Extraction

For each study, the following data was extracted: study design, sample size, recruitment procedure, diagnostic patterns, inclusion and exclusion criteria, participant characteristics (age, gender, duration of depression), treatment regimen, treatment outcomes.

Only clinical trials with a Jadad score greater than or equal to 3 were used in this systematic review. Of those studies, a meta analysis was performed if studies had similar clinical outcomes. Otherwise, data was summarized using a risk ratio with 95% confidence intervals for a singular outcome, or the standardized mean difference in studies that measured the same outcome but on different scales. Any adverse effects were summarized using a rate ratio.

Aim 3

Determine the most commonly used CHM formulas used in the treatment of depression.

Methods

Using the extracted data mentioned in aim 2, we compiled a list of the CHM formulas used throughout the systematic review ranked from most common to least. In addition to this ranking, I included their efficacy scores as determined in part 2.

Chapter III.

Results

Paper Selection & Description of Included Studies

The initial search performed using the terms listed in Table 1 yielded a total of 274 papers. Of those papers, 87 were duplicates, and 139 were removed because their published language was not English. The remaining 48 were evaluated for suitability, and 28 were excluded for various reasons (detailed in Figure 1), leaving 20 studies to be included in this review.

The 20 studies included were subsequently evaluated for methodological quality. Quality was assessed using a Jadad Score (Jadad, 1996, White, 1999), and then those with a Jadad score greater than or equal to 3 were subsequently evaluated according to the Cochrane risk of bias assessment (Higgins, 2011). Two evaluators worked independently to score each study, and the results of the quality assessment are summarized in Table 2.

For the purposes of this review we divided the included studies into 3 categories: CHM vs Placebo, CHM vs antidepressants, and CHM plus antidepressants vs antidepressants or placebo alone. The patient characteristics and format of each study are summarized in Figure 2, Figure 3, and Figure 4.

A total of 16 studies met our quality standards and were used in this systematic review. Across those 16 studies, 1,350 participants were recruited. Twelve studies were 2-arm, three were 3-arm, and one study was two parallel 2-arm studies performed

simultaneously. For the purposes of this review we treated each arm of the former study as separate studies, as all patients and datasets within that study are fully independent from one another. The inclusion criteria used in 10 studies was a diagnosis of Major Depressive Disorder as defined by the DSM-IV, 3 studies included patients with depression as a component of bipolar disorder, one study included depression in menopausal women, one included depression in patients post hemorrhagic stroke, one included depression in epileptic patients, and one included patients diagnosed with clinical anxiety by DSM-IV. All but two studies used the the Hamilton Depression Scale (HAMD) to rate the severity of depression. The HAMD scale runs from 0 to 54 with high scores indicating greater severity of symptoms. Inclusion criteria often required participants to demonstrate a minimum HAMD score of 10-20. One study used the Korean Beck Depression Inventory (K-BDI) to assess severity of depression. The K-BDI runs on a scale of 0 - 63, with higher scores indicating greater severity of depression. One study used the Montgomery Asberg Depression Rating Scale (MADRS), which runs from 0-60 with higher scores indicating greater severity of symptoms.

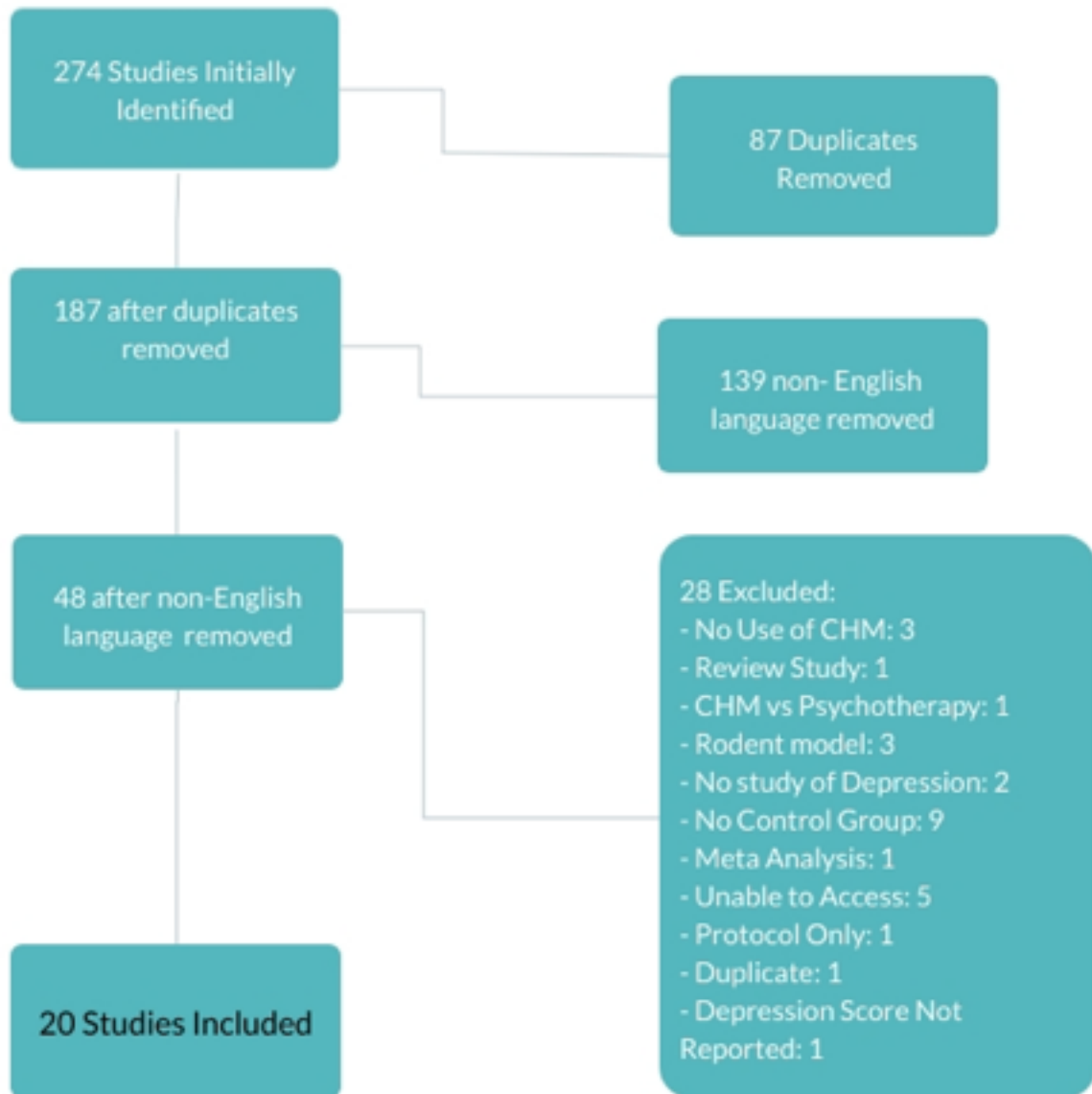


Figure 1. Flowchart of Study Selection

Out of 274 studies initially identified, 20 were ultimately included in this systematic review

Table 2. Summary of Jadad scores and Cochrane Risk of Bias assessment

Study #	First Author	Publication Year	Jadad Score	Cochrane Risk of Bias
1	Akhondzadeh	2004	5	L, L, L, L, L, L, L
2	Akhondzadeh	2005	5	L, L, L, L, L, L, L
3	Basti	2007	5	L, L, L, L, L, L, L
4	Li	2008	5	L, U, L, L, L, L, L
5	Mao	2015	5	L, L, U, H, L, L, L
6	Moshiri	2006	5	L, L, L, L, L, L, L
7	Noorbala	2004	5	L, L, L, L, L, L, L
8	Peng	2015	5	L, U, U, L, L, L, L
9	Rui	2019	5	L, L, L, U, L, L, L
10	Weng	2007	5	L, U, L, L, L, L, L
11	Wu	2015	5	L, L, L, L, L, L, L
12	Park	2014	4	L, L, L, H, L, L, L
13	Zhang	2005	4	U, U, L, L, L, L, L
14	Zhang	2007	4	U, U, U, L, L, L, L
15	Fan	2009	3	L, U, L, L, U, U, L
16	Wang	2015	3	U, U, L, L, U, U, L
17	Youtian	2006	2	n/a
18	Guangji	2004	1	n/a
19	Kudoh	2015	1	n/a
20	Liu	2015	0	n/a

Table 2 details Jadad scores of each study as well as the Cochrane Risk of Bias assessments

Author, Year	Alhondradah, 2005	Moshiri, 2006	Park, 2014	Peng, 2015	Wang, 2015	Zhang, 2007	Li, 2008	Mao, 2015
Design	2 Parallel Arms	2 Parallel Arms	3 Parallel Arms	2 Parallel Arms	2 Parallel Arms	2 Parallel studies of 2 Parallel arms	3 Parallel Arms	3 Parallel Arms
Diagnostic Criteria	DSM IV MDD + baseline HAM-D score 18+	DSM IV MDD + Baseline HAM-D score 18+	DSM IV GAD	DSM IV Epilepsy + Baseline HAM-D score 17+	DSM IV Depression	DSM IV Unipolar Depression + HAM-D 18+	HAMD >20 within 6 weeks of hemorrhagic stroke	DSM IV MDD + baseline HAM-D score 10+
Study Duration	6 Weeks	6 Weeks	8 Weeks	12 Weeks	12 Weeks	12 Weeks	8 Weeks	6 Weeks
Sample Size (CHM / Control)	40 (20 / 20)	40 (20 / 20)	147 (49 / 49 / 49)	100 (51 / 49)	80 (40 / 40)	87 (49 / 38)	150 (60 / 60 / 30)	57 (20 / 19 / 18)
Intervention 1	Saffron (20mg/day)	Saffron (20mg/day)	Gamciyoyn San Multi Individual Extract Mixture (GSSS-I) 23.01 g/day TID	Wu Ling Shen (0.39g TID)	Radix Bupleuri (1g/ day)	Free and Easy Wanderer 26 g/day	FEWP (Gao Yao San 16g BID)	Phospha (340mg) with dose escalation after 2 weeks in pts with <50% reduction in HAM-D
Intervention 2			Gamciyoyn San Multi Compound Extract (GSSS-M) 23.01g/ day TID				Fluoxetine (20-40mg daily based on pt response and tolerability + placebo for 2x daily)	Setraline (50mg)
Control	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Outcome Measure	Change in HAM-D	Change in HAM-D	Change in K-SDI	Change in HAM-D	Change in MADRS	Change in HAM-D	Change in HAM-D	Change in HAM-D
Conclusion	CHM > Placebo	CHM > Placebo	CHM > Placebo	CHM > Placebo	CHM > Placebo	CHM > Placebo	Herbs = AD > Placebo	AD > Herbs > Placebo

Figure 2. CHM vs Placebo

Figure 2 describes the key characteristics of studies included in this systematic review that compared Chinese herbal medicine with placebo

Author, Year	Akhondzadeh, 2004	Bastil, 2007	Fan, 2009	Noorbala, 2004	Rui, 2015	Weng, 2007	Li, 2008	Mao, 2015
Design	2 Parallel Arms	2 Parallel Arms	2 Parallel Arms	2 Parallel Arms	2 Parallel Arms	2 Parallel Arms	3 Parallel Arms	3 Parallel Arms
Diagnostic Criteria	DSM IV MDD + baseline HAMD score 18+	DSM IV MDD + baseline HAMD score 18+	6+ months amoxiclothea + HAMD 20+	DSM IV MDD + baseline HAMD score 18+	DSM IV MDD + baseline HAMD score 20 < 35	DSM IV Bipolar Depressive Episode + HAMD 18+	HAMD >20 within 8 weeks of hemorrhagic stroke	DSM IV MDD + baseline HAMD score 10+
Study Duration	6 Weeks	6 Weeks	12 Weeks	6 Weeks	8 Weeks	6 Weeks	8 Weeks	6 Weeks
Sample Size (CHM / Control)	30 (15 / 15)	40 (20 / 20)	47 (21 / 26)	40 (20 / 20)	210 (105 / 105)	76 (37 / 39)	150 (60 / 60 / 30)	97 (20 / 19 / 18)
Intervention 1	Saffron (30mg/day)	Saffron (30mg/day)	Geng Nian Le 200ml	Saffron 30mg/day (BD)	Jia Wei Xiao Yao San 10g BID	Siberian Ginseng 250mg (TID) + Lithium 250mg (BID)	FEWP (Kao Yao San 18g BID)	Rhodiola (340mg) with dose escalation after 2 weeks in pda with <50% reduction in HAMD
Control	Imipramine (100mg/day)	Fluoxetine (10mg BID)	Tibolone 2.5mg/day	Fluoxetine 20mg/day	Sertraline 50mg/day	Fluoxetine 20mg (TID) + Lithium 250mg (BID)	Fluoxetine (20-40mg daily based on pt response and tolerability + placebo for 2x daily)	Sertraline (50mg)
Outcome Measure	Change in HAMD	Change in HAMD	Change in HAMD	Change in HAMD	Change in HAMD	Change in HAMD	Change in HAMD	Change in HAMD
Conclusion	CHM = AD	CHM = AD	CHM = AD	CHM = AD	CHM = AD	CHM = AD	Herbs = AD > Placebo	AD > Herbs > Placebo

Figure 3. CHM vs AD

Figure 3 describes the key characteristics of studies included in this systematic review that compared Chinese herbal medicine with antidepressants

Author, Year	Wu, 2015	Zhang, 2005
Design	2 Parallel Arms	3 Parallel Arms
Diagnostic Criteria	DSM IV MDD + baseline HAMD score 20+	DSM IV Bipolar Disorder Depressive Episode + HAMD 18+
Study Duration	7 Days	12 Weeks
Sample Size (CHM / Control)	20 (10 / 10)	124 (50 / 49 / 25)
Intervention 1	YueJu 23g/day + fluoxetine 20mg/ day	Free and Easy Wanderer 36g/day + CPZ
Intervention 2		Carbamazepine 300mg/day monotherapy
Control	Fluoxetine 20mg/ day + placebo	Placebo
Outcome Measure	Change in HAMD	Change in HAMD
Conclusion	Herbs & AD > AD	Herbs+AD > AD alone > Placebo

Figure 4. CHM & AD vs Placebo or AD

Figure 4 describes the key characteristics of studies included in this systematic review that compared Chinese herbal medicine in conjunction with antidepressants with placebo or antidepressants alone

Efficacy

CHM vs Placebo

Nine studies compared the efficacy of Chinese Herbal Medicine vs Placebo. Their data was reported as change in HAMD, HAMD at the study's end point, MADRS at end point, or K-BDI at endpoint. Three Studies evaluated the Chinese Herbal Formula "Free and Easy Wanderer" (also called Xiao Yao San) against placebo, two studies at a dose of 26g/day and one at a dose of 36g/day (each arm of Zhang, 2007 and Li, 2008 respectively). One study used a modified version of this formula, Jia Wei Xiao Yao San, formulated in two different ways and both at a dose of 23.01g/day (Park, 2014). Two studies used Saffron at a dose of 30mg/day (Akhondzadeh, 2005 and Moshiri, 2006). Other herbal medicines used in the studies were Wu Ling Shen at 0.99g TID (Peng, 2015), Rhodiola at 340mg (Mao, 2015), and Bupleurum Root at 1g/day (Wang, 2015). Pooled analysis showed that CHM was more effective than placebo in reducing HAMD score (SMD: -7.95, 95% CI: -10.09 to -5.81) and at endpoint HAMD (SMD: -3.12, 95% CI: -4.14 to -2.09). There were no significant difference in MADRS at study end point (SMD: -3.41, 95% CI: -7.30 to 0.48) or K-BDI scores at study end point (SMD: -0.36, 95% CI: -3.09 to 2.38). Results are summarized below in Figure 5, Figure 6, Figure 7, and Figure 8.

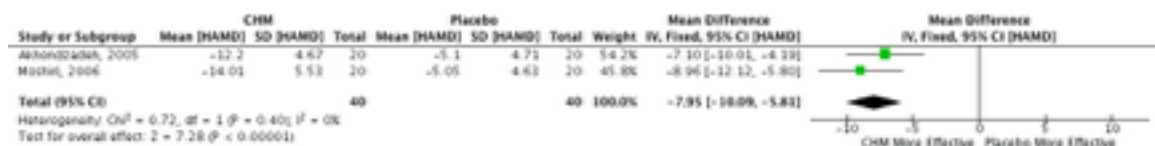


Figure 5. CHM vs Placebo change in HAMD

Pooled analysis shows patients treated with CHM had greater reduction in HAMD scores than those treated with placebo

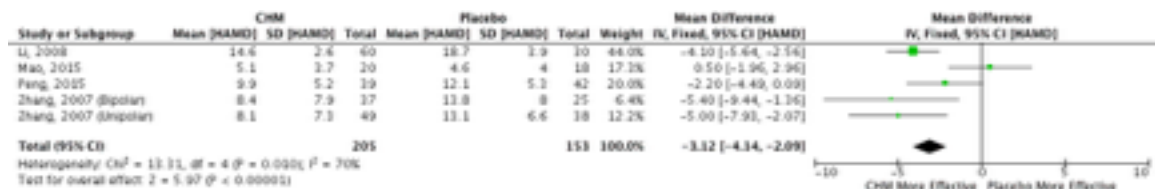


Figure 6. CHM vs Placebo HAMD at Endpoint

Pooled analysis shows patients treated with CHM demonstrated lower HAMD scores at the study endpoint than those treated with placebo

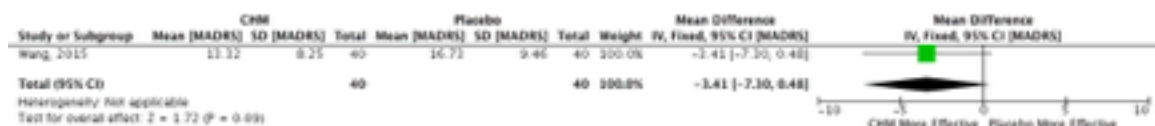


Figure 7. CHM vs Placebo MADRS at Endpoint

Pooled analysis shows no significant difference in MADRS scores at study endpoint in patients treated with CHM vs patients treated with placebo

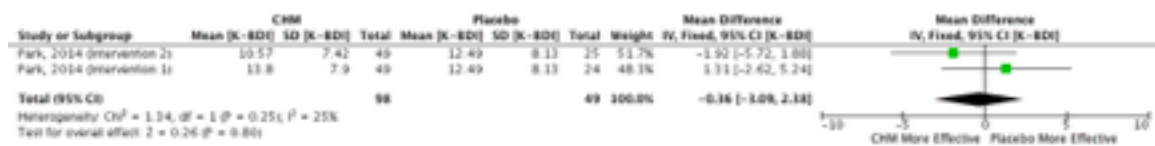


Figure 8. CHM vs Placebo K-BDI at Endpoint

Pooled analysis shows no significant difference in K-BDI scores at study endpoint in patients treated with CHM vs patients treated with placebo

CHM vs Antidepressants

Seven studies compared the efficacy of Chinese Herbal Medicine vs Antidepressants. Their data was reported as change in HAMD, or HAMD at the study's end point. The most commonly used antidepressant was Fluoxetine which was used in 4 of the 7 studies, followed by Setraline used in 2 studies (both SSRIs), and Tibolone. Tibolone is a synthetic molecule with estrogenic effects not inherently considered an antidepressant. It is known to have mood stabilizing properties, and in the context of this study was used in the treatment of menopausal depression. For this reason we categorize it as an antidepressant within this review. The most common Chinese Herbal Medicine used was Saffron at 30mg/day used in two studies (Basti, 2007 and Noorbala, 2004). Other Chinese Herbal Medicines used were Xiao Yao San at 36g/day (Li, 2008), a modification of that same formula, Jia Wei Xiao Yao San at 20g/day (Rui, 2019), Siberian Ginseng at 250mg TID (Weng, 2007), Rhodiola at 340mg (Mao, 2015), and Geng Nian Le at 200ml decocted (Fan, 2009). Pooled analysis showed no significant difference between CHM and Antidepressants in either change in HAMD score (SMD: 2.05, 95%

CI: -0.09 to 4.18) or HAMD at endpoint (SMD: -0.74, 95% CI: -1.48 to -0.00). Results are summarized below in Figure 9 and Figure 10.

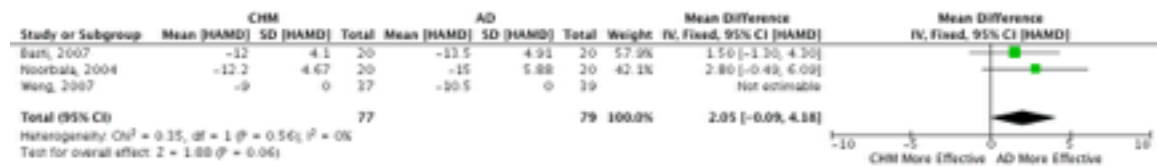


Figure 9. CHM vs Antidepressants Change in HAMD

Pooled analysis showed no significant difference in change in HAMD scores between patients treated with CHM and patients treated with antidepressants

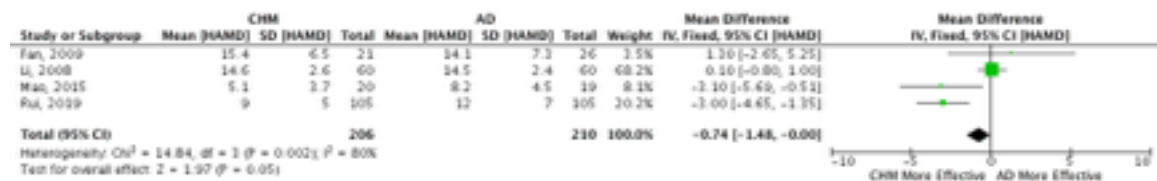


Figure 10. CHM vs Antidepressants HAMD at Endpoint

Pooled analysis showed no significant difference in HAMD scores at endpoint between patients treated with CHM and patients treated with antidepressants

CHM & Antidepressants vs Antidepressants alone

Two studies compared the efficacy of Chinese Herbal Medicine in conjunction with Antidepressants vs Antidepressants alone. One study focused on bipolar depressive episodes, and combined Xiao Yao San with Carbamazepine. Carbamazepine is not inherently an antidepressant, but is used in the treatment of bipolar disorder so is classified as such for the purposes of this review (Zhang, 2005). Data was reported as change in HAMD, and no significant difference was found between treatment with CHM and CHM in conjunction with Carbamazepine (SMD: -2.50, 95% CI: -5.60 to 0.60). The other study used Yue Jue Wan at 23g/day in conjunction with Fluoxetine (Wu, 2015). Results were reported as HAMD at end point and showed treatment with Yue Jue Wan to be significantly more effective than treatment with Fluoxetine alone (SMD: -7.00, 95% CI: -9.63 to -4.37). Resulting data is summarized in Figure 11 and Figure 12.

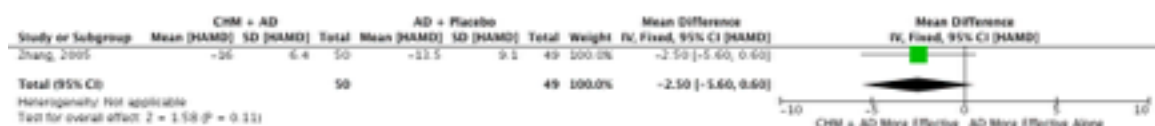


Figure 11. CHM & Antidepressants vs Antidepressants alone Change in HAMD

Analysis showed no significant difference between patients treated with CHM and antidepressants together versus patients treated with antidepressants alone

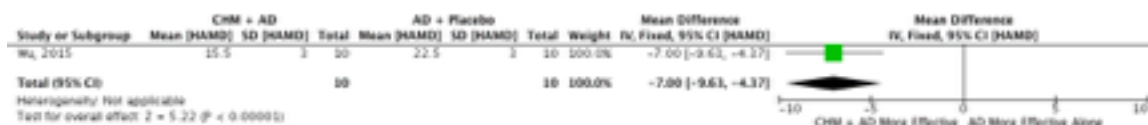


Figure 12. CHM & Antidepressants vs Antidepressants alone HAMD at Endpoint

Analysis showed patients treated with CHM and Antidepressants together had lower HAMD scores at study endpoint than those treated with antidepressants alone

Safety

Adverse events were reported in 13 out of 16 studies and details are reported in Table 3, Table 4, and Table 5. Pooled analysis revealed that participants receiving CHM were statistically significantly less likely to report adverse events than those taking antidepressants (pooled RR = 0.47, 95% CI: 0.38, 0.58). When compared to placebo, there was no significant difference in the rate of reported adverse events in participants taking CHM (pooled RR= 0.89, 95% CI: 0.71, 1.12). Participants receiving both CHM and antidepressants, showed no significant difference in adverse events reported when compared to those taking antidepressants alone (pooled RR= 0.79, 95% CI: 0.56, 1.12).

Table 3. Adverse Events Reported in Studies of CHM vs AD

	CHM (occurrence/ total)	AD (occurrence/total)	RR	95% CI
Headache	22/160	19/160	1.16	0.65, 2.05
Nausea	15/277	33/173	0.28	0.16, 0.51
Sweating	13/145	19/145	0.68	0.35, 1.33
Anxiety	11/55	14/55	0.79	0.39, 1.58
Dry Mouth	11/140	29/139	0.38	0.20, 0.72

Decreased Appetite	9/92	12/94	0.77	0.34, 1.73
Increased Appetite	7/55	10/55	0.70	0.29, 1.71
Sexual Dysfunction	3/60	16/59	0.18	0.06, 0.60
Heart Pounding	3/40	5/39	0.58	0.15, 2.28
Insomnia	3/242	20/243	0.15	0.05, 0.50
Dizziness	3/125	2/124	1.49	0.25, 8.75
Hypomania	2/15	1/15	2.0	0.20, 19.78
Constipation	2/52	6/54	0.35	0.07, 1.64
Tremor	2/40	9/40	0.22	0.05, 0.96
Nervousness	2/20	2/19	0.19	0.01, 3.73
Sedation	1/55	6/55	0.17	0.02, 1.34
Urinary Retention	1/15	5/15	0.20	0.03, 1.51
Skin Rash	1/37	0/39	3.16	0.13, 75.16
Darrhea	1/37	0/39	3.16	0.13, 75.16
Appetite Change	0/20	4/19	0.11	0.01, 1.84
GI Disturbance	0/20	3/19	0.14	0.01, 2.47
Yawning	0/20	3/19	0.14	0.01, 2.47
Fatigue	0/20	2/19	0.19	0.01, 3.73
Low Blood Pressure	0/105	5/105	0.09	0.01, 1.62
Tinnitus	0/37	1/39	0.35	0.01, 8.35
Pooled			0.47	0.38, 0.58

Use of CHM is associated with 0.47 times the risk of experiencing an adverse event compared with antidepressants

Table 4. Adverse Events Reported in Studies of CHM vs Placebo

	CHM (occurrence/ total)	Placebo (occurrence/ total)	RR	95% CI
Nausea	22/206	15/151	1.08	0.58, 2.00

Headache	18/126	12/103	1.23	0.62, 2.43
Dizziness	12/145	23/123	0.44	0.23, 0.85
Skin Rash	12/125	15/105	0.67	0.33, 1.37
Blurred Vision	12/86	8/63	1.10	0.48, 2.53
Somnolence	10/86	12/63	0.61	0.28, 1.32
Anxiety	7/40	3/40	2.33	0.65, 8.39
Fatigue	7/145	16/123	0.37	0.16, 0.87
Decreased Appetite	6/40	4/40	1.50	0.46, 4.91
Increased Appetite	5/20	1/20	5.00	0.64, 39.06
Heart Pounding	4/40	2/38	1.90	0.37, 9.78
Stomach Pain	4/20	2/20	2.00	0.41, 9.71
Tremor	3/20	1/20	3.00	0.34, 26.45
Hypomania	2/20	1/20	2.00	0.20, 20.33
Constipation	2/39	1/42	2.15	0.20, 22.82
Sweating	2/20	1/20	2.00	0.20, 20.33
Nervousness	2/20	2/18	0.90	0.14, 5.74
Abdominal Discomfort	2/39	1/42	2.15	0.20, 22.82
Sedation	1/20	2/20	0.50	0.05, 5.08
Increased Saliva	1/39	0/42	3.23	0.14, 76.90
Sneezing	1/39	1/42	1.08	0.07, 16.63
Insomnia	0/80	2/48	0.12	0.01, 2.47
Dreaminess	0/39	1/42	0.36	0.02, 8.54
Palpitations	0/39	4/42	0.12	0.01, 2.15
Ablepsy	0/39	1/42	0.36	0.02, 8.54
Pooled			0.89	0.71, 1.12

Use of CHM shows no significant difference in risk of experiencing an adverse event when compared to placebo

Table 5. Adverse Events Reported in Studies of CHM + AD vs AD Alone

	CHM+AD (occurrence/total)	AD+Placebo (occurrence/total)	RR	95% CI
Skin Rash	10/50	9/49	1.09	0.48, 2.45
Headache	8/50	9/40	0.87	0.37, 2.07
Blurred Vision	8/50	3/49	2.61	0.74, 9.28
Dizziness	7/50	16/49	0.43	0.19, 0.95
Somnolence	6/50	3/49	1.96	0.52, 7.40
Nausea	5/50	5/49	0.50	0.16, 1.57
Constipation	4/60	8/59	0.49	0.16, 1.55
Darrhea	2/10	2/10	1.00	0.17, 5.77
Fatigue	1/50	8/49	0.12	0.02, 0.94
Pooled			0.79	0.56, 1.12

Use of CHM and antidepressants together shows no significant difference in risk of experiencing an adverse event compared to taking antidepressants alone

Common CHM Formulas and Herbs

The most commonly used herb in the selected studies was saffron, dosed at 30mg/day. It was used in a total of 5 studies (Akhondzadeh, 2004; Akhondzadeh, 2005; Basti, 2007; Moshiri, 2006; Noorbala, 2004). The most commonly used formula was Free and Easy Wanderer, also called Xiao Yao San, which was used in 4 studies (Li 2008, Zhang 2005, both arms of Zhang 2007). A derivative formula of Xiao Yao San, called Jia Wei Xiao Yao San or Augmented Free and Easy Wanderer, differs from the classical Free and Easy Wanderer by the addition of just two herbs: peony bark and gardenia fruit. The Modified Free and Easy Wanderer was used in one additional study (Rui, 2019).

Additional formulas used in only one study each were Yue Ju Wan, also called escape

restraint pill (Wu, 2015), Gamisoyo San (Park, 2014), and Gan Nian Le (Fan, 2009).

Single herbs used in only one study were Wu Ling Shen, also called *Xylaria Nigripes*

(Peng, 2015), Siberian Ginseng (Weng, 2007), *Rhodiola* (Mao, 2015), and *Radix*

Bupleuri (Wang, 2015). Table 6 details formulas and single herbs used, and summarizes

their relative efficacy according to the above analysis compared to placebo or

antidepressants.

Table 6. Efficacy of Herbs and Formulas

	# of Studies Used	CHM vs Placebo	CHM vs AD	CHM vs CHM + AD
Single Herb				
Saffron	5	CHM > Placebo	CHM = AD	
Rhodiola	1	CHM = Placebo	CHM > AD	
Wu Ling Shen	1	CHM = Placebo		
Siberian Ginseng	1		CHM = AD	
Bupleurum Root	1	CHM = Placebo		
Formulas				
Xiao Yao San	4	CHM > Placebo	CHM = AD	CHM + AD = AD
Jia Wei Xiao Yao San	1		CHM > AD	
Yue Ju Wan	1			CHM + AD > AD
Gamisoyo San	1	CHM = Placebo		
Gang Nian Le	1		CHM = AD	

Table 6 outlines the relative efficacy of common CHM formulas and herbs compared to antidepressants or placebo as calculated in our pooled analysis

Chapter IV.

Discussion

The aims of this systematic review were 3 fold: (1) To summarize the existing literature on the treatment of depression with Chinese herbal medicine, (2) to examine the efficacy and safety of Chinese herbal medicine in treating depression, and (3) to determine the most commonly used Chinese herbs and formulas in the treatment of depression. Using a systematic search we identified 274 initial studies, and narrowed that pool to 20 English language studies that met our selection criteria. Of the 20 studies included, 4 were eliminated due to low methodological quality, ultimately leaving 16 studies included in our analysis. Taken together, the data suggest Chinese herbal medicine is consistently more effective than placebo at reducing depressive symptoms, and shows no statistical difference in efficacy when compared to antidepressant treatment. However, it is important to note that due to a small number of available English language studies, and wide variability in the herbs studied, these results should be viewed as a jumping off point for further research not a conclusive assessment.

The most commonly studied herb was Saffron, which was evaluated in 5 of the papers included in our systematic review. Saffron, also called Fan Hong Hua, has been used medicinally and as flavoring in many cultures throughout the world. In Traditional Chinese Medicine it is considered to work in the Heart and Liver meridians, acting primarily to remove stagnation, invigorate the blood, clear the meridians, and remove stagnation. From the Traditional Chinese perspective depression is caused by stagnation that prevents the flow of sufficient energy movement in the Hun, or ethereal soul. This

stagnation is often rooted in imbalances in the Heart and Liver meridians, so saffron is a natural choice as a single herb candidate for the treatment of depression. The 5 studies that evaluated the efficacy of Saffron (Akhondzadeh, 2004; Akhondzadeh, 2005; Basti, 2007; Moshiri, 2006; Noorbala, 2004) compared it to both the antidepressants Imipramine and Fluoxetine, and to placebo. In studies evaluating Saffron vs placebo, Saffron was demonstrated to be more effective than placebo at reducing HAMD scores (SMD -7.10, 95% CI +/- 2.91 in Akhondzadeh 2005; SMD -8.96, 95% CI +/- 3.16 in Moshiri 2006), and in studies comparing Saffron to antidepressants, there was no statistical difference in their ability to reduce HAMD scores (SMD 1.50, 95% CI: +/- 2.8 in Basti 2007; SMD 2.8 95% CI: +/- 3.29 in Noorbala 2004). The fifth study, Akhondzadeh 2004, was limited by a lack of placebo and little raw data published in the paper, but by Fisher Test demonstrated no statistically significant difference between the efficacy of Saffron and imipramine in reducing HAMD score. Saffron was the only single herb considered in this review that demonstrated efficacy over placebo.

The most commonly studied formula was Xiao Yao san, also called Free and Easy Wanderer, which was evaluated in 4 studies (Zhang, 2005; Li, 2008; both arms of Zhang, 2007), and in its modified form in 1 additional study (Rui, 2019). In Traditional Chinese Herbal medicine, the formula Xiao Yao San addresses Liver Qi stagnation that is rooted in deficiency. It moves Liver Qi, strengthens the Spleen, nourishes the Blood, and harmonizes the Liver and Spleen in relation to how they work with one another. According to the seminal text by Bensky, which cites the classical text Formulary of the Pharmacy Service for Benefitting the People in the Taiping Era written in 1107, Xiao Yao San is traditionally composed of 6 individual herbs: bupleurum root, angelica root, white

peony root, atractylodes rhizome, poria, and honey fried licorice root. It is traditionally modified to become Jia Wei Xiao Yao San by adding peony bark, & gardenia fruit, a change which was first documented in the Summary of Internal Medicine written during the Ming Dynasty. Despite this ancient and widely accepted standard for what is included in the formula, each study had slight variations in the herbs actually used. All studies used the base herbs cited by Bensky plus mint and ginger rhizome. Beyond these modifications, Li, 2008 used lily bulb, rehmannia root, and red sage. Zhang, 2007 additionally used Chinese skullcap, gardenia fruit and peony bark making it a a misnomer to call the formula Xiao Yao San. More correctly, the study used Jia Wei Xiao Yao San plus Chinese scullcap. Rui, 2019 used classical Jia Wei Xiao Yao San with the consistent additions mentioned above. Despite small discrepancies in the specifics of the formula, Xiao Yao San and its derivatives consistently demonstrated efficacy in reducing HAMD scores when compared to placebo (SMD -4.10, 95% CI: +/- 1.54 in Li, 2008; SMD -5.40, 95% CI: +/- 4.04 in Zhang, 2007 bipolar arm; SMD -5.00, 95% CI: +/-2.93 in Zhang, 2007 unipolar arm). Only one study compared the formula to antidepressants, but in this case Jia Wei Xiao Yao San out performed setraline with SMD -3.00, 95% CI: +/- 1.65.

These issues of study to study formula variation highlight a hurdle in researching Chinese Herbal Medicine. At its core, TCM is a personalized approach. Patients are treated on a case by case basis, and in practice herbalists rarely prescribe identical formulas twice. Rather, base formulas such as Xiao Yao San are modified for the individual patient with respect to their specific symptoms. A patient exhibiting depression with changes to their sleep pattern would be prescribed something slightly different from a patient with depression exhibiting changes to their appetite. If a patient

experienced headaches or nausea once taking a formula, the formula would be further modified to reduce those adverse events. The end result is a formula created precisely for a patient's body and specific symptom set. This entirely custom formula should create zero adverse events, and be highly effective because it is so personalized. Theoretically this is a wonderful way to practice medicine, but from a research perspective it is extremely challenging to create a study that is clinically translatable, and further, to review multiple studies together in a way that is statistically powerful. Individual herbalists from different lineages may modify base formulas so, as is seen here, even studies examining the same formula name are not identical treatments. Going forward, greater standardization is needed to insure studies are clinically translatable and results can be easily interpreted and compared.

All other single herbs and formulas were examined in only one study each. Mao, 2015 used *Rhodiola*, also called *Hong Jing Tian*, which is a known adaptogen that has previously demonstrated an effect on serotonin levels and neural stem cell proliferation in rats (Chen, 2009). Peng, 2015 examined *Xylaria Nigripes*, also called *Wu Ling Shen*, which is a common Chinese herb for sleep disturbances and trauma. *Siberian Ginseng*, also called *Ci Wu Ju*, was used in Weng, 2007 and is thought to invigorate and move energy while supporting spleen and kidney energy. Finally, Wang, 2015 examined *bupleurum* root alone, also called *Chai Hu*, which is a strong mover of Liver energy and a primary ingredient in the formula *Xiao Yao San* further researched in other studies. Each study of these single herbs alone failed to demonstrate efficacy over placebo, and the single study that compared to antidepressants (*Siberian Ginseng* in Weng, 2007) demonstrated equivalent efficacy between the two.

Additional formulas that were included in this review but studied in only one paper each were Yue Jue Wan, Gamisoyo San, and Geng Nian Le. Yue Ju Wan, also called Escape Restraint Pill, regulates the flow of energy in the body and powerfully combats all types of stagnation. Wu, 2015 looked at it in combination with Fluoxetine and found this combination to be substantially more effective than Fluoxetine alone at reducing HAMD scores (SMD: -7.00, 95% CI: +/- 2.63). Gamisoyo San is a formula commonly used in Traditional Chinese Medicine for women's health conditions and anxiety, but Park, 2014 failed to demonstrate any efficacy over placebo in its ability to reduce K-BDI scores. Geng Nian Le is a formula commonly used for post menopausal depression, and Fan, 2009 demonstrated comparable efficacy between the formula and the menopausal antidepressant Tibolone (SMD 1.30, 95% CI: +/- 1.35).

Taken together, we see greater efficacy in Traditional Chinese Medicine when it is taken in the traditional way, as a formula. With the exception of Saffron, no single herb compared to placebo was more effective than it. The formula Xiao Yao San repeatedly demonstrated efficacy over placebo and comparable to antidepressants. Examined alone, its primary herb, Bupleurum, did not have a similar effect size. Although Bupleurum is the primary driver of the formula's action, it must be taken in conjunction with its traditional accompanying herbs to achieve the desired effect. Three of the four formulas covered in this review demonstrated efficacy over placebo or an effect comparable or above antidepressants.

In Chinese herbalism, great importance is put on the synergistic effect of herbs, and no traditional herbalist would prescribe a single herb in isolation. Combining herbs is

thought to enhance the individual herbs' strengths, while mitigating side effects and reducing safety concerns. A great example of the dangers of a single herb alone is the Chinese herb ephedra stem, also called Ma Huang. Ephedra has been used safely in Chinese medicine for thousands of years as the primary herb in a formula to treat allergies, flu, common colds, and nasal congestion. Traditionally, ephedra would always be taken in combination with apricot seed, ginger, gypsum, or skullcap root. In a formula, each of these would have the purpose of counteracting "side effects" that might occur taking ephedra alone. Ephedrine, the active compound derived from ephedra, was famously outlawed in the United States in 2004 (Harvard Health Publishing, 2004). The outlawing came in response to multiple deaths caused by its incorrect use in the supplement Hydroxycut which used ephedra alone with no mitigating herbs to counteract its side effects. Despite this traditional perspective, research often focuses on a reductionist approach to herbs. It frequently distills single herbs for single purposes, and further, single herbs into single active compounds. Of the top 150 prescription drugs in America 118 are active compounds derived from plants (Chen, 2016). While small and therefore not conclusive, this review raises the question of whether a reductionist research approach does a disservice to traditional medicines. It is possible side effects of these drugs could be reduced or eliminated by incorporating a traditional approach, and we could find greater efficacy in the drugs we already have from a combination approach.

The most common adverse events reported in connection to taking either Chinese herbal medicine or antidepressants were headache, nausea, sweating, and dry mouth. In each case except headache, these were more prevalent in the antidepressant group than in the group receiving herbs. Risk ratios showed that patients who took Chinese herbs

instead of antidepressants had a 1.16 times the risk of experiencing headache, but 0.28 times the risk of nausea, 0.68 times the risk of sweating, and 0.38 times the risk of experiencing dry mouth. Pooled analysis showed an overall 0.47 times the overall risk of experiencing any adverse effect when taking herbs instead of antidepressants. Taking herbs at the same time as antidepressants also seemed to reduce a patient's risk of experiencing any adverse events. Those taking the two together had 0.79 times the risk when compared to patients taking antidepressants alone. However, the risks of taking herbs simultaneously with SSRIs or other antidepressants is not yet known. A systematic review (Izzo and Ernst, 2009) suggests there may be dangers in taking herbs simultaneously with a variety of pharmaceuticals. While this is a topic to be explored further, it is also important to note that the review assessed herbs taken in isolation which is not how they would be taken in practice. Additionally, should a patient experience adverse effects while taking a personalized formula from a qualified herbalist clinically, the formula would be modified to eliminate the undesired symptoms.

Methodological quality and English language studies were a persistent problem in identifying studies for this systematic review. The majority of studies identified in our initial search were published in Chinese language journals, with no translation available. Of those translated, many lacked appropriate control groups or failed to publish raw data for reader interpretation. There was great heterogeneity in population researched, ranging from post menopausal depression, to depression as a component of bipolar disorder. In Western medicine these are often treated with the same pharmaceuticals, but Traditional Chinese Medicine views these as very different patterns.

It would benefit the overall data set to have a greater number of studies within each sub population group. Journal editors should place greater emphasis on high quality and complete studies, and there is a need for a greater number of high quality studies to elucidate clinical implications of the treatment of depression with Chinese Herbal Medicine. These persistent problems suggest an overarching standardization is needed when doing randomized controlled trials for CHM. Poor methodological quality and lack of attention to pertinent details such as a standardized formula restricts our ability to draw clear conclusions from the papers published. This undermines the industry as a whole by hindering progress toward science backed and peer reviewed clinical recommendations. This problem is discussed in great deal in a paper published in *Sleep Medicine Reviews* (Sarris, 2012) who concluded a need for improved methodological design, including blinding and appropriate placebo, validating outcomes, and greater research into toxicology and adverse effects are needed.

As a result of few high quality research studies, we have very little data on appropriate dosage and toxicology for CHM herbs and formulas. Saffron was consistently dosed at 30mg/day in each study that researched it, and other single herbs were dosed as little as 340mg daily (Rhodiola in Mao, 2015) and as much as 1g daily (Bupleurum root in Wang, 2015). Formulas were dosed as high as 36g daily (Xiao Yao San in two of the studies that featured it Li, 2008 and Zhang, 2005) and as low as 20g per day (Xiao Yao San in Rui, 2019). None of the studies included in this review assessed for a dose response relationship, and going forward greater research is needed to determine the therapeutic range. In addition, very little data exists on the toxicology of herbs and their safety for long term use as well as during pregnancy and lactation. Preliminary studies

suggest saffron may be teratogenic in pregnant mice (Moallem, 2016), and may increase cervical ripening in humans (Sadi, 2016). Administration of rhodiola to pregnant mice seems to affect the immune system of offspring (Lewicki, 2017). There is documented risk of taking herbs during pregnancy, but the body of data is not robust enough to make definitive conclusions, and the authors of this review were unable to find any research studies evaluating the safety of any of the other herbs or formulas mentioned throughout this review.

Further study is needed to evaluate the mechanism by which herbal medicines work to reduce depressive symptoms. In rats, some research has been done into Xiao Yao San's effect on the locus coeruleus-norepinephrine (LC-NE) system as a possible mechanism for reducing depressive symptoms. In a 2014 study (Ding, 2014) rats treated with Xiao Yao San showed a significant decrease in norepinephrine levels following stress compared to their control counterparts. Accompanying this reduction was reduced expression of tyrosine hydroxylase (TH), dopamine- β -hydroxylase (DBH) and corticotrophin-releasing-factor (CRF) all of which play a role in mediating the body's response to stress. It has been suggested that the mechanism for Saffron's antidepressant effect is increasing transcription and protein levels of cAMP response element binding protein (CREB), brain-derived neurotrophic factor (BDNF), and VGF which play a role in neuroplasticity also in the hippocampus of rats (Vahdati, 2014). Rats dosed with saffron demonstrated decreased immobility time during a forced swim test, and their brains showed an increase in protein expression of CREB, BDNF, and VGF in the hippocampus. Further research is needed to more clearly connect the dots between herbal

treatment of depression and amelioration of symptoms, but these initial studies provide an excellent jumping off point.

Conclusion

This review did not focus on the efficacy of antidepressants versus placebo, but as discussed earlier in this paper, the data are not compelling that antidepressants exhibit any substantial effect when viewed through a comprehensive lens of the published and unpublished literature (Turner, 2008). Clinical practice should be informed by the most efficacious and least harmful treatment strategies available. With this in mind, pooled analyses demonstrated Chinese herbal medicine to be more effective than placebo at reducing HAMD scores (Change in HAMD: -7.95, 95% CI: +/- 2.14; HAMD at endpoint: -3.12, 95% CI: +/- 1.02), and equivalently effective as antidepressants (Change in HAMD: 2.05, 95% CI: +/- 2.13; HAMD at endpoint: -0.74, 95% CI +/- 0.74). When we look at the pooled incidence of adverse events in these same studies, we see that antidepressants are associated with a 213% increased risk of suffering from one or more adverse event. We cannot draw a clear conclusion as to whether one is more effective than the other, Chinese herbal medicine or antidepressants, but we can be sure of which is safer for the patient. With a duty to safety, and comparable clinical results, this review then suggests that Chinese herbal medicine is the most ethical first line choice for the treatment of depression.

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