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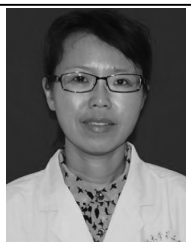
Herbal Medicine for Anxiety, Depression and Insomnia

Lei Liu[a,b], Changhong Liu[a,b], Yicun Wang[a,b], Pu Wang[b], Yuxin Li[b] and Bingjin Li[a,b,*]

[a]*Jilin Provincial Key Laboratory on Molecular and Chemical Genetic, Second Hospital of Jilin University, Changchun 130024, China;* [b]*Life Sciences Institute, Northeast Normal University, Changchun, China 130024*



B. Li

Abstract: The prevalence and comorbidity of psychiatric disorders such as depression, anxiety and insomnia are very common. These well-known forms of psychiatric disorders have been affecting many people from all around the world. Herb alone, as well as herbal formula, is commonly prescribed for the therapies of mental illnesses. Since various adverse events of western medication exist, the number of people who use herbs to benefit their health is increasing. Over the past decades, the exploration in the area of herbal psychopharmacology has received much attention. Literatures showed a variety of herbal mechanisms of action used for the therapy of depression, anxiety and insomnia, involving re-uptake of monoamines, affecting neuroreceptor binding and channel transporter activity, modulating neuronal communication or hypothalamic-pituitary adrenal axis (HPA) *etc*. Nonetheless, a systematic review on herbal pharmacology in depression, anxiety and insomnia is still lacking. This review has been performed to further identify modes of action of different herbal medicine, and thus provides useful information for the application of herbal medicine.

Keywords: Depression, herbal medicine, insomnia, mechanism, psychopharmacology.

1. INTRODUCTION

In modern society, people suffer from various psychiatric disorders, especially depression, anxiety and insomnia. As one of the most prevalent forms of mental illness, depressive disorders have a huge influence on individuals and society. According to the World Health Organization (WHO), major depressive disorders (MDD) will account for the second major illness in the world by the year 2020 [1]. In the Global Burden of Disease Study 2010, MDD was considered to be the major contributer to the incidence of suicide and ischemic heart disease and it was ranked the second leading cause of disability worldwide [2]. From the 1960s onwards, depression has been diagnosed as “major depression” which comprised of numerous symptoms including anxiety and insomnia according to the criteria established in the Diagnostic and Statistical Manual [3]. Anxiety is another common symptom of many psychiatric disorders in the community and other medical disorders. In fact, in humans, it is a common emotion intimately associated with proper fear and probably functions as a mechanism to adapt the environment psychologically [4]. Worldwide, one in five people meet with clinical criteria of anxiety disorder at least once in their lives [5]. The study of anxiety has developed into a key area of psychopharmacological research during this decade. It has been observed that people who suffer from anxiety often accompanied with sleep disorder. The most common sleep disorder is a subjective complaint that it has an inability to initiate or maintain sleep, or the sleep is non-restorative with poor quality and quantity [6]. Insomnia is a prevalent health concern in the general population, which could induce significant physical disorders [7]. It is estimated that about 9 ~ 15% of the people in the world suffer from insomnia which causes severe after effects in the day time [8]. Thus, depression, anxiety, and insomnia are common comorbid psychiatric conditions in the complexity of mental health disorders. The link between major depression, insomnia and anxiety disorders impairs the function of immune and cardiovascular systems [9]. These psychiatric disorders not only affect individuals' work and daily life, but also decrease their quality of life, and perceived well-being. To our knowledge about the present situation, the number of people with mental illness is rapidly increasing across the world [10]. Therefore, searching for more effective treatments should be an important consideration.

Evidence-based options for treatment of psychiatric disorders are limited. Pharmacological therapy is currently the most commonly used treatment for mood disorders. Although many drugs appear to have an important role in cases of most severe mental illness, many complaints that the drugs are not effective for all patients and incur diverse adverse events, as well as tolerance (if used for a long time). Therefore, it is desirable to seek fast acting, better-tolerated, more effective and fewer side effects antidepressants. Numerous studies have demonstrated that the use of complementary and alternative medicine (CAM) among psychiatric disorders, especially depression and anxiety is a common phenomenon [11-13]. A nationally representative investigation performed in America demonstrated that people with self–reported depression were about 53.6% and non-institutionalized adults with insomnia were 4.5% according to certain forms of CAM to treat their psychiatric disorders in the past year

*Address correspondence to this author at the Jilin Provincial Key Laboratory on Molecular and Chemical Genetic, The Second Hospital of Jilin University, 218 Ziqiang Street Changchun China 130041; Tel: 0086 431 88934741; Fax: 0086 431 88934741; E-mail: bingjinli@hotmail.com

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[14, 15]. Many literatures indicated the importance of CAM for the treatment of mental illnesses. Meanwhile, herbal medicine is the most commonly used form of complementary and alternative medicine therapies [16]. It was observed that more than 18.6 percent of the adult population in America (that is about 38 million) used herbs for the benefit of their health in 2002 as compared to the15% in 1997 [17, 18]. Recently, it also has been found that the use of herbs was particularly prevalent in those with psychiatric problems [19]. Comprehensive descriptions on herbs used to treat depression, anxiety or insomnia have been documented in the recent years [20-24]. However, to the author's knowledge, these reviews either focused on an individual psychiatric disorder, a specific herbal medicine or a single pattern. Given the weak points of previous studies, we performed a review to investigate: (1) herbal antidepressant, anxiolytic as well as hypnotic activities and (2) the most popular and effective single herbs and herb formulas for the treatment of these three psychiatric disorders.

2. HERBAL PSYCHOPHARMACOLOGY

In view of the complexity of psychiatric disorders, it is possible that regulating one single target does not exert the antipsychotic effect as effectively as targeting multiple systems. Herbal medicine is commonly employed to cure mental disorders by various mechanisms of action in different systems. Keeping that in view that mental disorders such as depression, anxiety, and insomnia are frequently found together in a single patient and they share some neurological basis, the mechanisms of curing drugs for these diseases might be interwtined with each other, when some factors act on one target, an activity in another field may appear. Of course, this might influence the therapy of other related mental disorders.

2.1. Herbal Antidepressants and Depression

Depression is a common mental illness with severe consequences to human fitness. For most of the synthetic antidepressants, severe defects such as narrow spectrum of antidepressants, adverse reactions, high drug price and easy recurrence exist. Many people are gradually turning towards herbal medicine in order to find out the multi-target antidepressants with a low level of toxicity. The pathogenesis of depression is intricate, and it has been found that many different kinds of mental disorders share some biological alterations [25]. In the past several decades , much emphasis has been placed on the pathophysiology underlying depression on the damage of monoamine transmission systems, such as decreased concentrations of 5-hydroxytryptamine (5-HT), norepinephrine (NE) and dopamine (DA) [26, 27]. The hypothesis resulted in the discovery of various antidepressant drugs including herbal medicine up-regulating these neurotransmitters *via* specifically suppressing the reuptake of these neurotransmitters in the brain, which is a shared mechanism between many drugs [28, 29]. Meanwhile, some herbal medicines play antidepressant role *via* sensitization of serotonin receptors or inhibiting monoamine oxidases. As a herb, ginseng has been frequently used for centuries in traditional Chinese medicine to improve mood and keep healthy in the western world. For example, the compound 20(S)-protopanaxadiol isolated from ginseng, exhibited good antidepressant activities in rodent paradigms *via* increasing the levels of NE and 5-HT in the brain of OB rats, and it possibly functions through inhibiting the reuptake of monoamine to a small extent [30]. Peony, the processed root portion of Paeonia lactiflora Pall (Ranunculaceae) is an important ingredient of various Chinese medicinal formulas used to treat depressive disorders [31, 32]. Previous studies have identified the antidepressant activity of the ethanol extract and total glycoside fraction of peony (TGP) in rodents under normal physiological condition [33, 34]. Beyond that, further studies demonstrated that TGP ameliorates depressive symptoms caused by chronic unpredictable stress, and antidepressant-like activity of TGP is probably mediated by inhibition of monoamine oxidases and the attenuation of oxidative stress in mouse brain [35]. 5-HT1A receptors underlie the pathogenesis of anxiety and depression and the effects of anxiolytic and antidepressant drugs, at least in part [36]. Albizia julibrissin, also called mimosa or silk tree, is extensively widespread throughout Asia, and Ji-Hyun Kim [37] found that acute treatment with the methylene chloride fraction of Albizia julibrissin (MCAJ), at a dose of 200 mg/kg remarkably decreased the immobility time in the forced swimming tests showing an antidepressant activity. Meanwhile, the effect could be attenuated by administration of WAY-100635 (one antagonist of 5-HT1A receptor) or pindolol (an antagonist of 5-HT1A/1B receptor). Nonetheless, these results suggests that the antidepressant-like effect of MCAJ was exerted through blocking 5-HT1A receptor. As we know the hypothalamic-pituitary-adrenal (HPA) axis is activated in response to stress (acute or chronic) processed by the brain. Neurons in the paraventricular nucleus (PVN) of the hypothalamus generate and release corticotropin-releasing factor (CRF), which promotes the secretion of adrenocorticotropin (ACTH) from the anterior pituitary, and then ACTH boosts the production and secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex [38]. Current hypotheses showed that over-activation of the HPA axis makes a contribution to the depressive symptoms mainly through increased cortisol levels in blood and enhanced CRF transmission in the brain regions [39]. A research shows that icariin, a principal flavonoid existing in Epimedium (a kind of herb) remarkably suppresses the elevation of corticosterone concentration caused by social defeat stress, suggesting that icariin exerts its antidepressant activity in part through restoring the normal expression and function of GR [40]. Ginseng total saponin and Rc was demonstrated to attenuate the rise in the concentration of corticosterone in plasma induced by restrictive stress through suppressing the activity of ACTH in adrenal gland. This indicates that ginseng might be a potential therapy for mental disorders associated with stress [41].

Recent studies suggest that neurotropic factors play an important role in the pathogenesis of depression as well as the therapies for depression [42, 43]. Among one of the most widely-spread neurotrophic factors in the brains of adults, brain-derived neurotrophic factor (BDNF) is overexpressed in hippocampus as well as cortex [44]. In response to stress, acute or chronic, the expression levels of BDNF decrease in

the dentate gyrus and the pyramidal cell layer of the hippocampus in rats and mice [45]. BDNF could stimulate the survival and differentiation of neurons and could maintain their functions and neuroplasticity [46], indicating that BDNF plays an important role in the pathophysiology of depression [47]. Animal studies indicated that rats injected with exogenous BDNF into brains exhibited antidepressant behaviors [48]. Clinical and pharmacological studies showed that BDNF concentrations in serum decline in depressive patients. Antidepressant treatment could induce BDNF expression [49]. In the recent years, BDNF has been considered to be a valuable antidepressant in therapies. The traditional Chinese herb Perilla frutescens, has been employed for hundreds of years to cure diverse psychiatric disorders such as depression. Present researches found that essential oil of Perillafrutescens (EOPF) reduces the depressive-like symptoms in rodent models [50]. EOPF reduces the increase of immobility time induced by chronic unpredictable mild stress (CUMS) in the forced swimming test, without significant changes to other assessment parameters such as gain of body weight and locomotor activity. At the same time, 3~4 weeks causes a decrease in expression levels of both mRNA and protein of BDNF in the hippocampus, which could be improved by EOPF for 4-weeks. In view of the results, they suggest that the expression of BDNF is relying on the length of CUMS stimulation and administrated concentration of EOPF [50]. "Yueju" (with the meaning of overcoming depression) pill, conceived 800 years ago in Song Dynasty by a famous traditional Chinese doctor Zhu Danxi, has been frequently prescribed to cure depression, anxiety, and irritability. Xiang Fu, Chuan Xiong, Zhi Zi, Cang Zu, and Shen Queach herb in the same amount, constitute the formula of Yueju [51]. Previous researches on animal paradigms showed that Yueju possesses antidepressant activity [52, 53]. Xue *et al*. [51] pointed out that Yueju, rapidly increased the expression of hippocampal BDNF, without altering the expression of BDNF mRNA and it can also quickly decrease the phosphorylation level of eukaryotic elongation factor 2 (eEF2) resulting in initiation of BDNF synthesis, which is followed by an increase of BDNF expression and eEF2 phosphorylation in 24 hours after the treatment of Yueju.

Recently, increasing attention has also focused on the mechanisms of actions in molecular level of the commonly used antidepressants. Transcription of some genes regulated by signaling pathways involving cAMP has been implicated in the therapeutic effects of chronic, other than acute administration of diverse antidepressants of chemically different classes. To the author's knowledge, researches till date have not shown similar results *in vivo*. Up-regulation of CREB is a shared characteristic after the treatment of antidepressant that may result in modulation of specific target genes, for example BDNF and trkB and the durative influence of these treatments upon brain function [54, 55]. Fuzi (Radix Aconiti Lateralis Preparata) or its constituents have been used as treatment of depression for many years in practice. Our previous work demonstrated that total alkaloid from Fuzi increased the phosphorylation level of CREB (cAMP response element-binding protein) and the expression of BDNF in the frontal cortex and hippocampus of mice that were ovariectomized rather than normal mice, indicating that in ovariectomized mice the generation of antidepressant-like results by total alkaloids of Fuzi may involve the CREB-BDNF pathway [56].

However, molecular mechanism was also not the sole cause of depressive diseases, current understanding includes the role of neuroendocrinological abnormalities as well as stress, alterations in the transmission of GABAergic and/or glutamatergic transmitters, impaired endogenous opioid function, changes of cytokine and steroids and dysregulation of circadian rhythm [57-59]. The perennial plant Rhodiola rosea extract (one member of crassulaceae integripetal Rhodiola genus), contains 96 species worldwide with 73 in China [60]. Rhodiola rosea contains more than 40 kinds of chemical compounds and it could be used to ameliorate symptoms such as stress, anoxia and fatigue, to improve immune function, and to protect central nervous system as well as cardiovascular system [60, 61]. In the year 2009, Q.G. Chen [61] proved that Rhodiola rosea extracts could elevate the 5-HT level in the hippocampus in depressive rodent models, and that Rhodiola rosea could promote the proliferation of neural stem cell in the hippocampus, and repair the damaged neurons in the hippocampus. Rhodioloside and extracts of S. chinensis and R. rosea were meanwhile demonstrated that they, with highest activity, could inhibit the p-SAPK/p-JNK signaling pathways induced by stress, and the suppressing activity of R. rosea and S. chinensis on p-SAPK/p-JNK may be related to their anti-depressant activity and their beneficial influence on mental status under stress [62]. As a traditional herbal medicine that has been already prescribed across East Asian countries, Radix Polygalae is composed of the dried root of Polygala tenuifolia. The extract of Radix Polygalae showed depression-alleviating activities in the forced swimming paradigm of rats and the tail suspension test. Further study showed that RP extract shows fast-acting antidepressant activity *via* regulating the AMPA receptor in the hippocampus [63]. The traditional herbal medicine Saffron (stigmates of Crocus sativus L.) has been employed for medicinal purposes for millenaries. Safranal and crocin are two main constituents of Saffron. In mice forced swimming test safranal and crocin exhibited antidepressant-like activity. Crocin may play that role through inhibiting the re-uptake of dopamine and norepinephrine, while safranal through inhibiting the re-uptake of serotonin [64, 65]. *In vitro*, crocin was found to ameliorate the depressive symptoms induced by ethanol through NMDA-receptor [66]. Matthias Lechtenberg [67] also indicated that Saffron extracts, along with crocetin, showed good affinity to the PCP binding site of the NMDA receptor.

2.2. Herbal Anxiolytics and Anxiety

Anxiety (including generalized anxiety, panic, posttraumatic stress, obsessive-compulsive, and phobic disorders) is one of the principal symptoms of diverse mental disorders. The mechanism of action of anxiety disorders remains unclear. Current evidences suggest that the neurobiological mechanism of anxiety was related to dysregulation of serotonergic, noradrenergic, glutamatergic and GABA-ergic transmission [68]. In view of these pathways, a number of drugs are considered beneficial to

combat anxiety disorders, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenalin reuptake inhibitors (SNRIs), and benzodiazepines for example [69]. Nonetheless, long-term use of these drugs causes multiple inevitable side effects or tolerance. There has been considerable popular interest in using natural extracts and plant preparations to treat anxiety disorder. Consisting of 10 herbs including Gardeniae fructus, the Kampo formula Kamishoyosan could be prescribed for remedying menopausal psychotic syndromes. A research showed that extracts of Gardeniae fructus-extract or the major component (geniposide) taken orally elevated the social interaction duration in a dose dependent pattern, which indicates that Gardeniae Fructus and geniposide in Kamishoyosan exert the anxiolytic effects, at least partly [70].

Serotonin (5-hydroxytryptamine, 5-HT) has been considered to be involved in the aetiologies of many disease states, such as depression, anxiety, and panic disorders. Selective 5-HT re-uptake inhibitors (SSRIs) are frequently prescribed the therapy for generalized anxiety disorder in Humans. Generally, 5-HT exerts its effects *via* the transmembrane receptors which have many splice variants and RNA edited isoforms and are coupled with the G proteins in the cytoplasmic side. Up-regulation of 5-HT2C receptors in the hippocampus of pilocarpine could induce epileptic rats antagonism by Bacopa monnieri [71]. Some of the most notable findings involving psychiatric research have also pointed to a role for CRF and noradrenergic system dysregulation in particular, anxiety disorders. The CRF system is an important regulator of behavioral responses to anxiety and stress. Dysregulation of CRF system is hypothesized to underlie many disorders including anxiety. Recent researches have indicated the interactions between monoaminergic and CRF systems in anxiety-related behavior in the mouse models [72, 73]. The extract of G. biloba leaves (EGb) is famous for alleviating psychiatric symptoms. EGb, at high concentrations, inhibits the uptake of tritiated neurotransmitters (such as NE, DA, and 5-HT) into synaptosome-enriched regions in the brain of rats [74]. EGb 761 has anti-dementia effects and could also alleviate the anxiety symptoms in people inflicted with mental diseases. However, the exact anti-anxiety mechanism of EGb 761 is still unclear. Numerous evidences indicated that elevated corticotropin releasing hormone (CRH) and hyper-activity of the HPA axis mainly lead the depressive and anxious symptoms in humans [75-77]. Therefore, suppression of CRH secretion looks to be a practicable strategy. CRF produces anxiogenic effects, whereas the transmitter neuropeptide Y (NPY), which consisted of 36 amino acids, shows anxiolytic activity. This widespread peptide in the brain pertains to the pancreatic polypeptide family. NPY has been demonstrated to modulate numerous physiological processes. Preclinical and clinical studies suggest that NPY modulates numerous physiological processes, especially depression and anxiety. We could see a general down-regulation of NPY in various animal models of depression and anxiety even in depressed human patients [78, 79]. In addition to these neurotransmitters, cholecystokinin (CCK) also involves in the onset of anxiety disorders induced by stress, while cholecystokinin-tetrapeptide (CCK-4) is one well-tested paradigm to produce subjective panic anxiety. In the recent years, results obtained from many regions of inquiry have frequently suggested that manipulating glutamatergic transmission is another method for the improvement of anxiolytic medicines. Direct blocking of ionotropic glutamate receptors may become a possibly practicable strategy for developing new antianxiety therapies. As pointed out in literature, extracts from Centalla asiatica (totukola) and Valeriana officinalis (valerian) could activate glutamic acid decarboxylase (GAD) at a concentration of 1 mg/ml and Matricaria recutita (German chamomile) and Humulus lupulus (hops) inhibited the enzymatic activity of GAD in a concentration range from 0.11 to 0.65 mg/ml [80]. Gamma-aminobutyric acid (GABA, the main inhibitory neurotransmitter in the mammalian central nervous system) also plays an important role in anxiety. Low central GABA level is known to lead to hyperactivity and is linked to disorders such as anxiety, depression, epilepsy, Parkinson's disease and many other motor diseases [81]. Various herbal agents have been enlisted to have anxiolytic effects through elevating levels of central GABA. Aqueous extract of Melissa officinalis (lemon balm) was found to have the largest inhibitory activity of GABA-T (IC_{50} =0.35 mg/ml) [80]. Meanwhile, hydrophilic constituents of Morinda citrifolia (a folk medicine for a wide range of health purposes such as anti-inflammatory, antioxidant, detoxifier, and cell-rejuvenator property) fruit have GABAA receptor agonistic effect [82]. Valerian and its primary active component valerenic acid produce anxiolytic and sedative effects mainly *via* GABA-ergic mechanisms, similar to the benzodiazepine drugs [83, 84]. Zizyphi Spinosi Semen (ZSS), which is the dried seed of Zizyphus jujuba Millvar. spinosa (Rhamnaceae), has been applied for anxiety and insomnia treatment in Asia [85]. The anxiolytic-like effects of Sanjoinine A (a principal alkaloid compounds in ZSS) is suggested to be mediated by activating Cl-Channel and GABA-benzodiazepine receptor. Furthermore, Sanjoinine A exerts its anxiolytic effect through synthesizing more GABA by activating GAD65/67 or by overexpressing receptors for benzodiazepine/ GABA *via* influencing the composing subunits of GABA receptor [86]. To sum up, sanjoinine A could be a good drug candidate for combating anxiety. Except those mechanisms of action, there is increasing evidence in animals which clearly demonstrated that cytokines mediate illness-associated behavioral changes, which indicate that cytokines may represent a novel target for herbal anxiolytics research.

In addition to the herbal anxiolytics above, sunginseng (heat-processed ginseng at higher temperature), Coumarins from Angelica archangelica Linn., root bark extract from Rauwolfia vomitoria, lavender oil, Stachys tibetica Vatke and Magnolia officinalis, all are responsible for the anxiolytic activity [87-91].

2.3. Herbal Hypnotics and Insomnia

Insomnia, the most common sleep disorder, is often neglected. It is evaluated that almost one-third of the whole population suffer from a long-term derangement of sleep and wakefulness [92]. Multiple medicinal herbs and complex

formulas are commonly used for insomnia. The mechanism of sleep disorders are generally caused by abnormalities in various pathways, such as GABA receptor, cortisol level, cytokines, circadian rhythm (melatonin secretion, adenosine receptors) and excitatory amino acid (glutamate and aspartate) [93, 94].

Changes in the expressing level of GABA receptor expression are considered to be related to the perturbations in GABAergic function, which are not only involved in the mechanism of depression and anxious behavior but also contribute to the sleep disorder, and such alterations in the GABA receptor subunits are related to the sedative-hypnotic effects of some drugs. As perhaps the most frequently prescribed herbal medicine to cure sleep disorders, Semen Ziziphi Spinosae (SZS) is widely used in China, Japan, Korea and other oriental countries [95, 96]. SZS and its major active compound (Jujuboside A (JuA)) are described as improving sleep quality, prolonging sleep time and remarkably increasing non-rapid eye movement sleep [97], which appears to be a safe sedative/hypnotic choice in patients. In the recent years, JuA has been proved to change GABAA 1, 5, 2 subunit genes expressions as a section of the molecular mechanism underlying its sedative-hypnotic activities [98]. A large number of prescription drugs are also employed to cure insomnia. Extracts of valerian (Valeriana officinalis L., Valerianaceae) and valerenic acid are applied to treat insomnia as well as restlessness as 5-HT5a receptor activators [84]. On the other hand, Valerian has an activity like adenosine and promotes falling into sleep. The regulation of the sleep-wake rhythm triggers sleep when the time-related interaction functions properly, which is intimately associated with the endogenous secretion of melatonin [99]. Lactuca sativa (garden lettuce), a member of the Compositae family, is a commonly used herb for salad in Egypt, which has already been applied for centuries as a folk herb to aid in sleeping and to ameliorate pains as well as inflammation [100]. The oil from the seed of L. sativa could ameliorate the symptoms of sleeping and disorders of patients, in particular those who are old [101]. The generally used saffron, which is the stigma of Crocus sativus L (a stemless perennial herb belonging to the Iridaceae family) has demonstrated various effects upon the central nervous system. A study focused on the neuropharmacological activities of water extracts of saffron and its components in mice demonstrated that safranal possesses neuropharmacological activities [102]. The literature search revealed that several other herbal medicines, such as Passifloraincanata (passionflower), Eschscholzia californica (California poppy), P. methysticum, and Scutellaria lateriflora (scullcap) also showed to be potentially beneficial to insomnia.

3. THREE REPRESENTATIVE CHINESE HERBS USED FOR PSYCHIATRIC DISORDERS

In the recent years, numerous herbs in Europe and Western herbal traditions have been discussed widely, but description of the Chinese herbal medicines used for treating psychiatric disorders is still lacking. Chinese medical herbalism characterizes numerous frequently used herbs and conventional formulas for treating different psychiatric disorders. Here, we'll describe three single herbs frequently prescribed for people suffering from psychiatric disorders, while in the subsequent part, three herbal formulas will be detailed.

3.1. Chai Hu for Depressive Disorder

Chinese herbal medicines have already been employed for thousands of years in a number of Asian countries to cure various psychiatric disorders. Several single herbal medicines are commonly used in the therapy for depression, such as Hypericum perforatum, Crocus sativus and Lavandula angustifolia *et al*. Among these single herbs, Chaihu (Rx Bupleurum) was one of the most frequently used for the treatment of depression in numerous Chinese herbal medicine formulas [22].

The Bupleurum genus of the Apiaceae family consists of about 185 to 195 kinds of plants and it is initially characterized in the book ‘‘Shennong’s Herbal’’ for the treatment of psychosomatic disorders. Pharmacological studies in depression models have been performed on several species, such as Bupleurum chinense DC., Bupleurum yinchowense and Bupleurum falcatum L. [103-105]. In the last several years, a number of studies have been performed on Bupleurum chinense DC, which grows predominantly in the northern and northeast part of China [106]. Originally documented in the classic book *Treatise on Cold Induced Febrile Disease (Shang Han Lun)* as a chief component of an ancient formula Xiao Chai Hu Tang from about decades before Christ, Bei Chaihu is one of the most important components of Chaihu-Shugan-San, and reportedly has remarkable antidepressant-like pharmacological activities in animals [107].

To our knowledge, B. chinense is a harmony herb applied by Chinese capable of keeping the energy equilibrium among various organs in the body, and it is concurrently applied as a nourishing agent due to its capability to potentiate the functions of the alimentary system, enhance the function of liver and circulatory system, and ameliorate relieve hepatic tension [108, 109]. However, the present study provides evidence for the antidepressant-like effects of B. chinese at both the behavioral and molecular levels. The major discovery of the current researches was that B. chinese possesses antidepressant-like effects, and the antidepressant-like actions are regulated at least in part through up-regulation of CREB and BDNF, leading to stimulation of the PI3K/Akt/GSK-3β signaling pathway *via* the TrkB receptor [110], while aqueous extracts of this herb have affinity for 5-HT1A and dopamine D2 receptors [111]. There are many constituents, such as saikosaponin, flavonoid, fatty acid, adonitol, a-spinasterol, and other volatile oils were found in B .chinese. At present, many studies have been performed to probe the activities of saikosaponin, which not only exists in B. chinese but also in Bupleurum yinchowense. The root of Bupleurum yinchowense has the action of alleviating fieber (fiber), nourishing hepar (liver) and enhancing yang (the harmony of all the opposite elements and forces that make up existence) qi (vital energy) in organs like stomach and spleen, and was also used to relieve the clinical manifestations of mental disorders such as depression, anxiety, fear, and somatic symptoms like vertigo, menstrual

problems and pains in chest and the flank [112, 113]. The Total Saikosaponins (TSS) from Bupleurum yinchowense was improved to have antidepressant activity in depression models induced by acute and chronic unpredictable mild stress by modulating the monoamine neurotransmitter level in the prefrontal cortex [114]. The cell-protecting effect of TSS probably is among the potential mechanisms underlying the antidepressant activities. TSS could in part cure pathological alterations caused by corticosterone, and could contribute to protect neurons, for the reason that TSS may probably help to stabilize endoplasmic reticulum (as is evidenced by the decrease in activation of endoplasmic reticulum biomarkers such as XBP-1) and suppress the intrinsic apoptotic signaling through keeping the equilibrium of Ca^{2+}as well as modulating the expression of members of Bcl-2 family [115]. Regarding the clinical and animal effects, it is important to further study about TSS, which could be used as an effective potential antidepressant candidate drug.

3.2. Ginkgo Biloba for Anxiety

Several herbs have been employed to treat anxiety, such as Brahmi, California poppy, Gotu cola, Kava et.al. Ginkgo biloba, the oldest plant existing in the world for over 200 million years, is a famous Chinese herb employed frequently in the world to treat anxiety. This herb is first documented in a Chinese book about 2800BC and the herb is also considered as a component of the Ayurvedic elixir soma [116].

As we know, drugs aiming to produce or increase the serotonin have been gaining much attention as possible anxiolytic candidates in searching for drugs that could be a substitute to the benzodiazepines [117]. Extracts of Ginkgo biloba, are capable of suppressing the agglutination of thrombocyte and thus indirectly antagonizing the serotonin activity, besides their elevating effect upon the velocity of blood flow [118-120]. Extract of Ginkgo biloba leaves is widely and frequently used to ameliorate the clinical manifestations related to a series of cognitive disorders, producing removable suppressing effects on monoamine oxidase in rat brain, thus exhibiting the pharmacological activities of this natural product against mental disorders, such as anxiety [121]. A literature showed that EGb, at high concentrations, suppresses the absorption of norepinephrine (NE), dopamine (DA) and 5-HT (all labeled with tritium) by the synaptosome in rat brain [122]. The pharmacological effect of ginkgo leaf is exerted by numerous components existing within it e.g., flavonoids and terpenoids. One particular extract from Ginkgo biloba (EGb 761) has been approved in many countries such as Germany for treating dementia. Moreover, EGb761 has anti-stress and anxiolytic-like activities in a dose-dependent manner in preclinical studies and treatment with EGb 761 generates better results in secondary parameter as compared to the control, which indicate that EGb 761 may involve in regulating the function of HPA axis. Taking into account the good compatibility, the drug is of particular anxiolytic value not only for senile people, but also for younger workers, as it reduces the tendency for addiction and decrease side effects on the cognitive function [123].

3.3. Suan Zao Ren for Insomnia

It is probable that the most famous treatment for vigilance in Traditional Chinese medicine is Suan Zao Ren. With the formal name of Semen Ziziphi spinosae, the dried ripe seed of the sour jujube or spiny date has been frequently used for a long time among Chinese to treat vigilance, anxiety, hyperhidrosis and dreaming too much [124]. Recent researches demonstrate that Suan Zao Ren has various pharmacological effects, such as protecting the functions of cardiovascular systems, enhancing the function of immune system, lowering the blood lipid and counteracting anxiety [125]. Suan Zao Ren is also an indispensable component of some traditional formulas, such as Suan Zao Ren Tang and Fufang Suan Zao Ren decoction, which are frequently used to cure insomnia in clinical practice [126]. Animal studies suggest that Suan Zao Ren could reduce the sleepless symptoms in rats [127], regulate the sleeping alteration in mice caused by stress [128], and prolong the time of total sleep and that of slow wave sleep in a rabbit model [129].

Recent studies have largely investigated the chemical compounds composing Suan Zao Ren. Sufficient researches suggest that saponins like jujuboside A and B, alkaloids [130], flavonoids including swertisin and spinosin [131] and fatty oils such as oleic acid and linoleic acid [132, 133] are major components of Semen Zizhiphi Spinozae. The results also proved that jujubosides exert the hypnotic activity possibly through regulating the circadian rhythm as well as modulating the serotonergic system [134]. Meanwhile, it has also been observed that intraperitoneal administration of a high concentration of jujuboside A exerted some sedative activities but that activity did not show up at low doses [135]. Relative to the control animals, treatment with spinosin and swertisin from Semen Zizhiphi Spinozae orally extended the sleeping induced by pentobarbital [136]. While *in vitro* results indicate that these compounds have high affinity for 5HT1a and 5HT2 receptors, as well as GABA receptors [132].

4. THREE REPRESENTATIVE CHINESE HERBAL FORMULAS FOR PSYCHIATRIC DISORDERS

4.1. Xiao Yao Decoction for Depressive Disorder

Chinese traditional herbal formulas, in the center of traditional Chinese medicine theory, have gained increased attention as the therapeutic methods for depression. Among them, the most frequently used formula was xiao yao decoction [22]. Xiao Yao San (XYS) (a kind of xiaoyao decoction) was first documented in the medical book of Taiping Huimin Heji Jufang which was written in Song Dynasty (960–1127 AD). XYS decoction was suggested to exert various actions, including ameliorate the hepar (liver), strengthening the spleen, alimenting blood to reconstruct the regular menstruation, and curing the liver inflammation caused by insufficient blood, which has been frequently considered to be a secure and potent formula in treating diverse depressive disorders for hundreds of years in traditional Chinese medicine. XYS, a well-known formula dedicated to relieve depression is composed of the eight herbs: Radix Bupleuri (Bupleurum chinense DC.), Radix

Angelicae Sinensis (Angelica sinensis (Oliv.) Diel), Radix Paeoniae Alba (Paeonia lactiflora Pall.), Rhizoma Atractylodis Macrocephalae (Atractylodes macrocephala Koidz.), Poria (Poria cocos (Schw.) Wolf), Herba Menthae (Mentha haplocalyx Briq.), Rhizoma Zingiberis Recens (Zingiber officinale Rosc.) and Radix Glycyrrhizae (Glycyrrhiza uralensis Fisch.). In this formula the major ingredients are Radix Bupleuri and Radix Angelicae Sinensis, while Radix Bupleuri usually functions to be the primary agent, Radix Angelicae Sinensis and Radix Paeoniae Alba play the role of ministers in these herbs, and other drugs play the role of assistant agents. The eight herbs interact with each other and together they perform the pharmacological functions of the formula. The present work demonstrated that petroleum ether extract (a mixture of hydrophobic compounds) is the effective component of XYS [137]. Additionally, XYS demonstrated remarkable antidepressant activity through reducing the immobility time in the forced swimming tests and the tail suspension test [138]. The antidepressant activity of XYS at median concentration, which is like the effects induced by positive drugs, is better than those of both high and low concentration in CUMS model of depression. In fact, the abnormal metabolisms in amino acid, energy and glucose are involved in depressive symptoms generated by CUMS [139]. Nevertheless, the mechanism of XYS may be due to significantly increasing BDNF in the serum, hippocampus and cortical area [140] or increasing serotonin in the prefrontal cortex and the hippocampal concentration of 5-hydroxyindoleacetic acid (5-HIAA) [141-143].

4.2. Banxia Houpu Decoction for Anxiety

Houpo (Magnolia officinalis Rehd. et Wils.), is a widely prescribed herb and is included in the authoritative Chinese Pharmacopoeia [144], and this herb has been identified as an valid therapy for curing various diseases, such as neurological disorders, thrombotic stroke, typhia and muscle necrosis [145, 146]. The herbal formula Banxia houpu decoction is composed of pinellia tuber, magnolia bark, hoelen, perilla herb and ginger rhizome, and it has been employed for hundreds of years among Chinese for curing some kinds of psychiatric disorders including several subtypes of depressive disorders, anxiety as well as schizophrenia [147]. Clinical studies indicated that Banxia houpu is one secure, efficacious as well as well-tolerated anxiolytics and antidepressant prescription without notorious adverse events in the patients [148]. A recent research showed that the 90% ethonal extract of Banxia houpu decoction and some of the fractions demonstrated antidepressant-like effects in animal paradigms [149], which are possibly associated with both 5-HT system as well as DA systems [150]. However, honokiol and magnolol having multiple therapeutic effects and pharmacological activities were the main anxiolytic principals of Banxia Houpu Decoction [151]. For example, a literature suggests that among the various compounds isolated from magnolia bark, only honokiol exhibits the anxiolytic effect, while others including magnolol do not have such effect and hardly affect the anxiolytic activity of honokiol [152]. Considering the anxiolytic mechanism of honokiol, it was demonstrated that the activity of honokiol might be related to the activation of benzodiazepine receptors, which is similar to that of diazepam [153]. The anxiolytic effect induced by honokiol is regulated *via* influencing the production of GABA [154]. Nevertheless, these complex mechanisms suggest that Banxia Houpu decoction played an anxiolytic effect from well-proven folk remedies.

4.3. Gui Pi Tang for Insomnia

The standard formula Gui Pi Tang is one of the most widely employed in China [23]. The formula Gui Pi Tang, with the meaning of, as well as the function of, replenishing the qi of the spleen dates back to the Song Dynasty and has been remedied in the Ming dynasty in the book "Revised Fine Formulas for Women". It also enhances the qi, promotes the hematogenesis, and aliments the heart. In modern society, Gui Pi Tang plays an important role in the treatment of a vast number of different diseases, especially insomnia. The mechanism of action of Gui Pi Tang used for the treatment of insomnia is mainly through nourishing the heart, invigorating the spleen and tranquillizing the nephridium to regain regular sleep. Additionally, Gui Pi Tang could aliment and tonify tissues (such as heart and blood and so on) to prevent the sweating caused by insomnia.

Gui Pi Tang contains a variety of nature components, while the chief herbs (Dang Shen, Huang Qi, Bai Zhu and Zhi Gan Cao) exert their effects upon the spleen, with the concomitant effects of nourishing and enlarging qi of the spleen, as well as dispelling wetness. The auxiliary herbs, Long Yan Rou, Dang Gui, Suan Zao Ren, Fu Shen and Zhi Yuan Zhi mainly function as nourishing and soothing components. The assistant agents, Mu Xiang, tunes qi in order to overcome the greasy property of the tonic herbs. Sheng Jiang and Da Zao potentiate the effects of others and concurrently help to enhance the function of spleen [155]. However, Gui Pi Tang commonly plays the role in treatment for various diseases *via* slightly modifying its components. For example, Shu Di Huang, Wu Wei Zi, Long Gu and Mu Li are often being added for improving different symptoms.

CONCLUSIONS

A growing number of people are plaguing by different kinds of psychiatric disorders, especially depression, anxiety and insomnia. These mental illnesses not only affect people's daily life, but also cause a great economic burden for society. Over the past decades, growing investigations have focused on the psychopharmacology of herbs. A large data show that a lot of intricate psychotropic activities of herbs probably help to combat depression, anxiety as well as sleep disorders. Nonetheless, the etiology and pathogenesis of herbal medicines employed for treating mental diseases are still not clear and the acting mechanisms are often overlapping, which may possibly exert some influence upon the therapies for other comorbid psychiatric diseases. Hence, the scientists cannot fully illustrate the mechanism of the diseases until now.

Overall, this paper has provided an insight into the research that has been conducted on the different herbal mechanisms of action involving re-uptaking of monoamines,

affecting neuroreceptor binding and channel transporter activity, and modulating neuronal communication or HPA. The nervous, immune and endocrine three systems are associated with mental disorders, and the destruction of the balance between them or any of them with abnormalities can lead to psychiatric disorders. Therefore, Anyway, keeping in view of the complexity of these mental health disorders, there is it would a need for a more effective and more comprehensive treatment. In the Rrecent years, numerous herbs in Europe and Western herbal traditions such as St. John's wort are is being discussed widely, but none of them has been conventionally prescribed for combating mental disorders in Chinese herbal medicine. In this overview, we listed a few typical Chinese herbs such as Chai Hu, Ginkgo Biloba and Suan Zao Ren. Each of them has almost been most frequently examined as a single herb and often prescribed for curing patients with psychiatric diseases. They work through different herbal mechanisms of action as we described. However, they are evaluated in only a small part of the including studies, which indicated that antipsychotic single Chinese herbal medicine needs further research. Besides probing hopeful single Chinese herbs to combat mental diseases, the present study focused on the combinations of various herbs, also called Chinese herb formula. We mentioned three typical Chinese herbal formulas, namely Xiao Yao decoction, Banxia Houpu decoction and Gui Pi Tang, for psychiatric disorders. Treatment for mental diseases by using Chinese herbal formulas in general has multiple links and targets. We know that the pathogenesis of mental illness is complex and may involve dysfunctioning of multiple links or systems, which highlight the advantage and good application prospect of Chinese herb formula in the treatment of psychiatric disorders. Besides, focusing on a single herb and certain frequently prescribed formulas should be preferential for a deeper insight into the therapeutic effects and safety of Chinese herbal medicine for mental diseases. Future research with improved methodology targeted at some potentially efficacious and safe single herbs and herbal formulas will still be needed. As we know, western medicines for treatment of depression, anxiety and insomnia are widely available, they are often ineffective and commonly associated with side effects, which could be severe in some cases. Comparing with western medicine, Chinese herbal medicine is generally more effective, better-tolerated with fewer side effects. However, adverse events caused by Chinese herbs indeed exist and occur because of a variety of reasons. Hence, understanding the herbal mechanism of action plays a fundamental role in advancing pharmacological therapies in order to keep away the notorious the side effects. In current field of herbal psychopharmacology, a lot of herbs with *in vitro* activities have not yet been logically confirmed through testing in human disease models or herbs with good *in vitro* or *in vivo* pharmacodynamic activities have not been investigated in clinical trials. In the future study, herbal medicine used for the treatment of mental illnesses *in vivo* will be needed to explore further.

In conclusion, this review presents some inspiring results for the application of herbs in the therapies for mental disorders such as depression, anxiety and insomnia and clarifies the acting mechanisms of some of the antipsychotic herbs. Meanwhile, we summarize several representative Chinese single herbs and herbal formulas for depression, anxiety and insomnia, to enrich the knowledge about the field of herbal psychopharmacology.

CONFLICT OF INTEREST

The authors confirms that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

5-HT	=	Serotonin
ACTH	=	Adrenocorticotropin
BDNF	=	Brain-derived neurotrophic factor
CAM	=	Complementary and alternative medicine
CCK	=	Cholecystokinin
CREB	=	cAMP response element-binding
CRF	=	Corticotropin-releasing factor
CRH	=	Corticotropin releasing hormone
CUMS	=	Chronic unpredictable mild stress
DA	=	Dopamine
EGb	=	Extract of *G. biloba* leaves
EOPF	=	Essential oil of *Perilla frutescens*
GABA	=	Gamma-aminobutyric acid
GAD	=	Glutamic acid decarboxylase
GPCR	=	G protein-coupled receptor
HPA	=	Hypothalmic-pituitary adrenal axis
KSS	=	Kamishoyosan
MCAJ	=	Methylene chloride fraction of Albizia julibrissin
NE	=	Norepinephrine
NPY	=	Neuropeptide Y
PVN	=	Paraventricular nucleus
RP	=	Radix Polygalae
SNRIs	=	selective serotonin and noradrenalin reuptake inhibitors
SSRIs	=	Selective serotonin reuptake inhibitors
SZS	=	Semen Ziziphi Spinosae
TGP	=	Total glycoside fraction of peony
TSS	=	Total Saikosaponins

XYS = Xiaoyaosan

ZSS = Zizyphi Spinosi Semen

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