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Review

Molecular basis and mechanism of action of *Albizia julibrissin* in depression treatment and clinical application of its formulae

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ABSTRACT

Albizzia julibrissin is empirically used as an antidepressant in clinical practice. Preclinical studies have indicated that its total extracts or bioactive constituents exerted antidepressant-like responses in animal models, providing the molecular basis to reveal its underlying mechanism of action. While attempts have been made to understand the antidepressant effect of *A. julibrissin*, many fundamental questions regarding its mechanism of action remain to be addressed at the molecular and systems levels. In this review, we conclusively discussed the mechanism of action of *A. julibrissin* and *A. julibrissin* formulae by reviewing recent preclinical and clinical studies conducted by using depressive animal models and depressive patients. Several representative bioactive constituents and formulae were highlighted as examples, and their mechanisms of action were discussed. In addition, some representative *A. julibrissin* formulae that have been shown to be compatible with conventional antidepressants in clinical practice were also reviewed. Furthermore, we discussed the future research directions to reveal the underlying mechanism of *A. julibrissin* at the molecular and systems levels in depression treatment. The integrated study using both the molecular and systematic approaches is required not only for improving our understanding of its molecular basis and mechanisms of action, but also for providing a way to discover novel agents or approaches for the effective and systematic treatment of depression.

Contents

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1. Introduction

Depression is a popular and all age-related mental illness, affecting approximate 10%–15% of the population worldwide (Hasin et al., 2018; WHO, 2017). According to the latest statistics, the lifetime prevalence rate of depression in China is 6.8%, that is, there are nearly 100 million depressive patients, but only 0.5% of the patients are fully treated (Huang et al., 2019; Lu et al., 2021). Depressive patients suffer greatly with poorly function at work, study, and social activities. Severe depression can lead to disability and suicide. The social and economic burdens caused by depression are gradually increasing, and depression has become a global public health problem.

Current medications in depression treatment have many shortcomings, such as slow onset, low efficacy, serious adverse effects, and high costs, all of which limit their use in clinical practice. On the other hand, the use of herbal medicine has been greatly increased as a complementary and alternative medicine in the past decades (WHO, 2019). Herbal medicine is a core part of traditional medicine that has been developed for a long history to maintain health as well as to prevent and treat physical and mental illness. The common reasons for using herbal medicine are that it is more affordable, more personalized health care, and less adverse effects than chemically synthesized drugs (Wachtel-Galor & Benzie, 2011). It should be noted that the use of herbal medicine increased when the synthesized medications are less effective in the treatment of complex diseases, such as depression.

Traditional Chinese medicine (TCM) is an important branch of traditional medicine, and it is broadly used to treat depression in East Asia today. In TCM practice, Chinese herbal medicine is usually used to exert its medicinal effects on depression by using a combination of multiple herbs, so-called formula, in which one herb at least is employed as an antidepressant drug to directly act against the main depressive symptoms, while others serve as modulators to strengthen the antidepressant efficacy or alleviate side effects (Zhang & Cheng, 2019). According to the *Chinese Pharmacopoeia*, more than 50 single Chinese herbs have empirically been used as antidepressants in clinical practice (Chinese Pharmacopoeia Commission, 2020). During the past two decades, studies have been extensively conducted to uncover the molecular basis and mechanism of action of these herbs in the treatment of depression. These studies have remarkably improved our understanding of Chinese herbal medicine for the effective treatment of depression (Li, Huang, Cheng, & Zhang, 2020).

Albizia julibrissin Durazz., a leguminous deciduous shrub, is one of the most common herbs used for depression treatment. In TCM practice, its dried flowers or bark are generally processed for medicinal purposes. The main ingredients in *A. julibrissin* include triterpenoids, lignans, flavonoids, saponins, sterols, etc. (Li, Tian, Luo, & Li, 2022). Preclinical studies have shown that these ingredients exhibited a broad array of pharmacological activities ranging from antidepressant and anxiolytic (M. Li, 2017; R. Li, Tian, Luo, & Li, 2022; W. Li, 2017; Wang et al., 2021; Yang & Li, 2019), anti-inflammation (Yang & Li, 2019), anti-oxidation (Sobeh et al., 2017; Shi et al., 2019a), and antitumor (Qian et al., 2017; Yu, Cai, & Tian, 2016) to enhance immunological function (Sobeh et al., 2017). This narrative review aims to conclusively discuss the mechanism of action as well as the latest progress in preclinical and clinical research of *A. julibrissin* in the treatment of depression. The literatures that demonstrated *A. julibrissin* constituents and formulae to produce antidepressant responses were selected for discussion. According to the mechanism of action and structural classification, several representative constituents that have been demonstrated to specifically act on the pathological systems in depression neurobiology are given. In addition, several representative *A. julibrissin* formulae traditionally used for depression treatment were discussed. Furthermore, we also discussed some *A. julibrissin* formulae that have been demonstrated to be compatible with conventional antidepressants. Finally, we discussed the future research directions to reveal the mechanism by which *A. julibrissin* exerts antidepressant-like activity in depression treatment. The comprehensive analysis could improve our understanding of the molecular basis and mechanism of action of *A. julibrissin* in the treatment of depression, which, in turn, will provide an opportunity to scientifically evaluate its benefits and risks in clinical practice.

2. Mechanisms of antidepression

Tremendous progress in preclinical and clinical studies of depression has revealed many pathophysiological factors across divergent biological systems that are involved in the neurobiology of depression (Han & Yuan, 2021). Remarkably, many pharmacological targets in these biological systems have been employed to uncover the mechanism of action of antidepressants (Duman, Aghajanian, Sanacora, & Krystal, 2016; Gerhard & Duman, 2018). Studies showed that several total extracts or bioactive constituents of *A. julibrissin* exerted profound effects on the pathophysiological systems through multiple diverse underlying mechanisms of action. Herein, we discussed the mechanism by which *A. julibrissin* acts on the diverse pathophysiological systems and thereby possesses antidepressant activities (Fig. 1).

2.1. Monoamine neurotransmission

Impairment of monoamine neurotransmission is a major cause of depression. Most of the conventional antidepressants, such as fluoxetine and sertraline, selectively inhibit serotonin (5-HT) reuptake transporter, and subsequently enhance 5-HT transmission in the central nerve system (CNS). In addition, monoamine reuptake transporters for norepinephrine (NE) or dopamine (DA), monoamine metabolic enzymes, and postsynaptic monoamine receptors also play important roles in monoamine transmission. Therefore, these proteins are considered to be potential pharmacological targets in depression treatment (Murphy et al., 2021).

Zhang et al. reported that administration of an aqueous extract of *Albiziae Flos* alleviated chronic stress-induced growth abnormalities by regulating monoamine levels in rat brain (Zhang & Li, 2006). In addition, Kim et al. demonstrated that acute treatment with methylene chloride fraction of *A. julibrissin* (200 mg/kg, 30 min, p.o.) exerted antidepressant-like effects in mice, which could be specifically reversed by a 5-HT1A receptor antagonist, WAY-100635 (Kim, Kim, Lee, & Jang, 2007). This observation suggested that the *A. julibrissin* fraction produced antidepressant-like responses by modulating 5-HT transmission (Ji, Kim, Lee, & Jang, 2007). Furthermore, a recent report demonstrated that a 70% etha-

Fig. 1. Proposed mechanisms of action by which *A. julibrissin* exerted antidepressant responses in animal models. *A. julibrissin* has been demonstrated to produce multiple antidepressant effects on various divergent pathological systems by modulating monoaminergic neurotransmission, the HPA axis, BDNF signaling cascade, or neuroimmune system.

nol extract of *Albiziae Cortex* dramatically inhibited serotonin transporter (SERT), the principal target of the conventional antidepressant drugs (Huang et al., 2022). These studies suggested that some bioactive constituents in these *A. julibrissin* extracts specially act on monoaminergic signaling by modulating monoamine transporters or receptors in CNS, and thereby produce antidepressant-like responses in depressive animal models. However, further studies should be conducted to determine the nature of these constituents as well as the specific interactions with their target proteins.

2.2. Hypothalamic–pituitary–adrenal (HPA) axis

Hyperactivation of the HPA axis induced by stress impairs neuronal survival and neurogenesis, and thereby results in depressive symptoms. Studies have extensively been conducted to reveal pathophysiological factors in the HPA axis, and several pharmacological targets, such as corticotrophin releasing factor, corticotrophin releasing factor 1 receptor, and glucocorticoid receptors, have emerged for developing novel agents that suppress hyperactivation of the HPA axis (Ding, Wei, Yan, & Guo, 2021; Juruena, Bocharova, Agustini, & Young, 2018; Menke, 2019).

Administration (6 g/kg, 21 d, p.o.) of an aqueous extract of *A. julibrissin* has been reported to reduce hyperactivation of the HPA axis in depressive rat models induced by chronic unpredictable mild stress (CUMS) (Li, 2017). Behavioral tests showed that the aqueous extract improved spatial learning and memory in the stressed rats, which was comparable with the action of a conventional antidepressant, fluoxetine. Similarly, another study also indicated that an aqueous extract of *A. julibrissin* (3.6 g/kg, 28 d, p.o.) exerted an antidepressant-like activity by modulating the HPA axis, characterized by decreasing the release of serum corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and corticosterone (CORT) in chronic restrain-stressed rats (Cui et al., 2019). A lignan glycoside isolated from *A. julibrissin* (3.6 mg/kg, 7 d, p.o.) has been demonstrated to exhibit an antidepressant-like activity by decreasing plasma concentrations of CRF (corticotropin releasing factor), ACTH, and CORT in the repeated acute restraint-stressed rats (Liu et al., 2017). However, these studies did not address if these extracts or constituents directly act on the pharmacological targets in the HPA axis. Only by understanding the specific drug-target interaction, we are able to uncover their mechanism of action at a molecular level.

It should be notable that several pharmacological targets to suppress stress-induced hyperactivation of the HPA axis have been proposed, however, attempts to develop novel agents directed toward the HPA axis in the treatment of depression have not been successful (Li, Huang, Cheng, & Zhang, 2020). The main reason is that the HPA axis and the neuroinflammatory system bidirectionally regulate through neural, immunological, and humoral interaction. The neuroendocrine-immune network poses difficulties associated with the development of antidepressant agents directed toward these biological systems for the effective treatment of depression (Li, Huang, & Zhang, 2021). On the other hand, multidrug and multitarget nature of Chinese herbal medicine has a great potential to assist in the development of novel medications for the systematic pharmacotherapy of depression. From this point of view, we expect that *A. julibrissin* could be an excellent example for the systematic treatment of depression by simultaneously acting multiple pharmacological targets in the diverse pathological systems of depression.

2.3. Neurotrophic signaling cascades

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays a key role in maintenance of neural plasticity. Deficiency of BDNF and other neurotrophins or dysfunction of their signaling cascades contributes the pathophysiology of depression (Duman, Deyama, & Fogaca, 2019; Masi & Brovedani, 2011; Voleti & Duman, 2012). The pharmacological targets in BDNF signaling cascade include cAMP response element binding protein (CREB), BDNF, BDNF receptor, TrkB, or its postreceptor signaling cascades such as Ras-Raf-ERK, PI3K-Akt, and PLCγ (Niciu, Ionescu, Mathews, Richards, & Zarate, 2013; Zhang, Yao, & Hashimoto, 2016).

An aqueous extract of *A. julibrissin* (6 g/kg, 21 d, p.o.) have been demonstrated to produce antidepressant-like effects on cAMP-CREB signaling cascade in the stressed rat models, and subsequently to attenuate behavioral abnormalities (Wang et al., 2015). In addition, total flavonoids isolated from *Albiziae Flos* (25 mg/kg, 21 d, p.o.) have been shown to increase the expression levels of BDNF and its receptor, TrkB in the hippocampal CA1 and CA3 regions, suggesting that the flavonoids possess an antidepressant-like activity specifically through regulating BDNF signaling in the stressed rat models (Wang et al., 2012; Shi, 2014). It would be interesting to know if these herbal constituents directly act on BDNF signaling cascade and what targets they specifically interact with. Hence, more in-depth studies are required to address these questions, which are important for our understanding of their mechanistic details in order to further refine the use of these herbal antidepressants.

2.4. Inflammatory system

Studies have shown that the immune system bidirectionally communicates with the CNS at several levels through neural and immunological interactions (Jiang et al., 2019; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). Dysfunction of immune system has often been observed in many patients with depression and treatment of patients with proinflammatory cytokines can produce

depressive symptoms (Chiu, Su, Su, & Chen, 2017; Ng et al., 2018). Therefore, proinflammatory cytokines and their signaling molecules have been suggested as contributing pathophysiological factors for depression (Kim, Na, Myint, & Leonard, 2016; Su et al., 2017; Zhang, Yao, & Hashimoto, 2016). Agents that act on the inflammatory systems, such as proinflammatory cytokines and their receptors, proinflammatory signaling pathways, and inflammasomes, could be effective to treat depressive symptoms (Tonhajzerova, Sekaninova, Bona Olexova, & Visnovcova, 2020; Wohleb, Franklin, Iwata, & Duman, 2016).

Wei reported that an aqueous extract of *Albizziae Flos* (6 g/kg, 21 d, p.o.) reversed the increased levels of serum proinflammatory cytokines, such as IL-2 and IL-6, and proinflammatory signaling molecules, such as nitric oxide, induced by stress in rats, suggesting that the extract exerted an antidepressant-like activity by down-regulating inflammatory system (Wei, 2016). A earlier report to investigate the effect of an aqueous extract from *Albiziae Cortex* on immune function in mice showed that administration of the extract (0.5 g/kg, 6 d, p.o.) remarkably increased phagocytic rate of peritoneal macrophages and level of lymphocytic IL-2 in mice, suggesting the aqueous extract from *Albiziae Cortex* possesses an immune-improving property (Wang et al., 2000). While these studies demonstrated that *A. julibrissin* acted as a modulator in immune system, either by suppressing proinflammatory cytokines or improving immune function, the specific interaction between the herbal constituents and their acting targets in neuroimmune system as well as the molecular mechanism of action still remain to be addressed. It should be emphasized that agents targeting neuroimmune system alone would not be effective, and an additional medication that directly acts on the HPA axis is also required to achieve a better treatment, because of the intersystem crosstalk between the neuroimmune system and the HPA axis in the neuroendocrine system (Li, Huang, & Zhang, 2021). Hence, it is reasonable to parallelly investigate the effects of herbal bioactive constituents of *A. julibrissin* on both the pathological systems in depression treatment.

3. Bioactive constituents with antidepressant activities

As mentioned above, total extracts of *A. julibrissin* exerted antidepressant-like effects in animal models through multiple underlying mechanisms of action. These findings suggest that *A. julibrissin* must contain certain bioactive constituents that specifically act on these pharmacological targets to correct dysfunction of pathophysiological systems in neurobiology of depression. It is worth noting that depressive and anxious symptoms usually coexist in many patients and share common pathological factors and pharmacological targets for their treatment (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2016; Kaiser, Herzog, Voderholzer, & Brakemeier, 2021). Hence, several *A. julibrissin* constituents or formulae that have been shown to possess anxiolytic activity in preclinical or clinical studies are also included in our discussion. *A. julibrissin* is rich in flavonoids, lignan glucosides, and saponins, which have been demonstrated to exert pharmacological effects in animal models. Herein, we list several representative bioactive constituents that show antidepressant or anxiolytic-like effects, based on their chemically structural classification.

3.1. Flavonoids

Guo et al. reported that total flavonoids isolated from *Albizziae Flos* possessed antidepressant activities by antagonizing the hippocampal apoptosis of CA3 region in CUMS rats (Guo, Xia, Yin, & Shi, 2013; Kim, Kim, Lee, & Jang, 2007). Later, Li et al. demonstrated that the reduction in hippocampal apoptosis results from flavonoids-induced increases in 5-HT and NE levels and BDNF expression as well as a decrease in the expression of Bcl-2 associated X protein in CUMS rats (Li, Wang, & Gao, 2014). In addition, total flavonoids have also been investigated their effects on learning and memory in rat models. These studies indicated that flavonoids significantly alleviated stress-induced learning and memory impairment, probably through regulating monoamine levels in the brain (Ji-Hyun Kim, Kim, Lee, & Jang, 2007; X. Shi, Zhang, Yin, & Guo, 2013; X.L. Shi et al., 2013). Furthermore, anxiolytic effects of total flavonoids have been investigated using anxious animal models. Data showed that total flavonoids possessed an anxiolytic activity, but the molecular mechanism of action has not been fully uncovered (Liu et al., 2015).

While total flavonoids from *A. julibrissin* have been shown to exert antidepressant or anxiolytic effects in animal models, quercitrin (Fig. 2) is the only one flavonoid molecule that has been identified to be responsible for anxiolytic activity. In a study conducted by Li et al. (Li et al., 2016), administration of quercitrin (5.0 mg/kg, 7 d, p.o.) produced anxiolytic effects in animal models and its effects on animal behavior were blocked by WAY-100635 (3.0 mg/kg, i.p.), a 5-HT receptor 1A antagonist, but not a γ-aminobutyric acid (GABA) receptor A antagonist, flumazenil (0.5 mg/kg, i.p.). In addition, monoamine levels (5-HT and DA) and their metabolites in the brain were reduced after quercitrin treatment. These data suggest that the anxiolytic-like effects of quercitrin are mediated by 5-HT receptor 1A to enhance monoamine neurotransmission. However, the specific interaction between quercitrin and its molecular targets as well as the specificity for the monoamine signaling pathway still remain to be addressed in the future study.

3.2. Saponins

Julibroside C1 (julibrogenin C 3-*O*-[*β*-*D*-xylopyranosyl1-(1,2)]-*β*-*D*-fucopyranosyl-(1,6)-[*β*-*D*-glucopyranosyl-(1,2)]-*β*-*D*-glucopyranoside) is a saponin-containing compound isolated from the stem bark of *A. julibrissin* (Fig. 2). Jung et al. performed a study to investigate the anxiolytic effects of julibroside C1 using behavioral and biochemical approaches (Jung et al., 2013). Administration of julibroside C1 (0.5 and 1 mg/kg, 1 h, p.o.) has been shown to increase the time spent in open arms and numbers of entries into the open arms in an elevated plus maze test. In addition, the anxiolytic-like effects of julibroside C1 were blocked by either a 5-HT1A receptor antagonist, WAY-100635, or a $GABA_A$ receptor antagonist, bicuculline or flumazenil. Furthermore, an antagonism study was conducted by using quantitative receptor autoradiography in the brain to confirm the involvement of postsynaptic receptor systems in the anxiolytic-like effects of julibroside C1. Data showed that Julibroside C1 significantly decreased [^{3}H]-8-OH-DPAT or [^{3}H]-flunitrazepam binding, with little effect on [^{3}H]-muscimol binding. Taken together, the study suggested that the anxiolytic-like effects of julibroside C1 were mediated by 5-HT1A and $GABA_A$ receptor systems (Jung et al., 2013). It is interesting to know the selectivity of julibroside C1 for the two receptor systems as well as the specific drug-receptor interaction for revealing its mechanism of action at the molecular level.

3.3. Lignan glucosides

A study was carried out to evaluate the anxiolytic-like effects of aqueous or several organic solvent extracts of *Albiziae Cortex* by using behavioral and biochemical approaches (Xiong et al., 2018). A *n*-butanol extract, which has been demonstrated to be rich in lignan glucosides, was observed to have the strongest anxiolytic-like activity among these extracts. (-)-Syringaresnol-4-*O*-*D*-apiofurano syl-(1 → 2)-*D*-glucopyranoside (SAG) is one major bioactive con-

stituent of *A. julibrissin* (Fig. 2). Liu et al. investigated the anxiolytic effects of SAG in acute restraint-stressed rats and subsequently analyzed its potential mechanism of action (Liu et al., 2017). Behavioral tests showed that administration of SAG (3.6 mg/kg, 7 d, p.o.) produced the anxiolytic-like responses in animal models. Moreover, SAG significantly attenuated the acute stress-induced increases in the plasma levels of CRH, ACTH, and CORT, as well as in the levels of neurotransmitters (NE, 5-HT, DA) and their metabolites (5-hydroxyindoleacetic acid, dihydroxyphenylacetic acid, and homovanillic acid) in the cerebral cortex and hippocampus of the rat brain.

Our laboratory has recently isolated and identified two lignan glycosides from *A. julibrissin* with antidepressant properties, one of which was SAG (Huang et al., 2022), another was a derivative of SAG, (-)-syringaresinol-4,4′-bis-*O*-*β*-*D*-glucopyranoside (SBG). Our results showed that these two lignan glycosides inhibited SERT noncompetitively by decreasing V_{max} with little change in K_m for its substrate. The two lignan glycosides decreased the accessibility of a cysteine residue placed in the extracellular substrate permeation pathway by inducing a conformational shift toward an outward-closed state of the transport protein. These results indicated that these herbal compounds from *A. julibrissin* acted on SERT by a novel underlying mechanism of action different from that of conventional antidepressant drugs (Huang et al., 2022). To our knowledge, it is the first example for one bioactive compound isolated from *A. julibrissin* that specifically targets SERT. However, both SAG and SBG have also been shown to weakly inhibit the transporters for DA and NE. The lack of selectivity for SERT increases our concerns about their addictive side effects caused by elevating synaptic concentrations of dopamine (Poisson, Engel, & Saunders, 2021).

4. *A. julibrissin* formulae

Depression is a multigenetic and multifactorial syndrome with various underlying pathological mechanisms (Hammen, 2018). Conventional antidepressants with single targets are inadequate for the effective treatment of depression in clinical practice. Hence, agents that are simultaneously directed toward multiple pharmacological targets in the pathophysiology of depression are needed for a better treatment (Li, Huang, & Zhang, 2021). One typical TCM antidepressant formula generally contains multiple herbs, which are thought to act on diverse pathophysiological factors at the same time in the systemic treatment of depression.

There are many empirical *A. julibrissin*-containing herbal formulae, which have been broadly used for the treatment of depression with comparable efficacy to the conventional antidepressants in clinical practice (Shi et al., 2019b; Shi et al., 2019c; Shi et al., 2019d; Shi, Zhang, & Jiang, 2016). As mentioned above, *A. julibrissin* contains various bioactive constituents that produce multiple antidepressant effects in animal models through diverse underlying mechanisms of action, indicating that *A. julibrissin* possibly plays a key role in these herbal formulae.

Numerous *A. julibrissin* formulae have been studied to reveal their mechanisms of action by using both behavioral and biochemical approaches. These preclinical studies demonstrated that an herbal composite formula had a greater efficacy than single herbs, possibly due to their synergistic interactions (Ou et al., 2019). On the other hand, clinical studies are also critical to improve our understanding of the underlying mechanisms of action as well as biological responses in human body. In this section, therefore, we discuss several representative *A. julibrissin* antidepressant formulae that have been preclinically or clinically studied and others are listed in Tables 1 and 2.

4.1. Suanzaoren Hehuan Decoction

Suanzaoren Hehuan Decoction is an aqueous extract of an herbal pair comprising *Ziziphi Spinosae Semen* and *A. julibrissin.* It has been generally used for the treatment of depression or anxiety in TCM practice. Preclinical studies were conducted to reveal its mechanism of action using behavioral and neurochemical approaches (Li, Qiao, Fang, & Chen, 2019; X. Shi et al., 2019; X. Shi, Zhang, & Jiang, 2016; X.L. Shi et al., 2018; X.L. Shi, Xia, Feng, Zhang, & Jiang, 2016). From these studies, its mechanism of action was proposed to include enhancement of monoaminergic transmission, elevation of neurotrophic factor expression, dehyperactivation of the HPA axis, suppression of inflammation, and attenuation of hippocampal apoptosis. A study was also performed to investigate the synergy and compatibility of the herb pair (Ou et al., 2019). While single herbs showed a potent action in stress-induced depressive animal models, a combination of the herb pair has a greater efficacy. However, this study neither addressed the synergistic interactions between two herbs at the molecular level, nor defined the optimized herb pair ratio that produced the greatest efficacy in the animal models. It would be interesting to know the role of *A. julibrissin* playing in this herb pair.

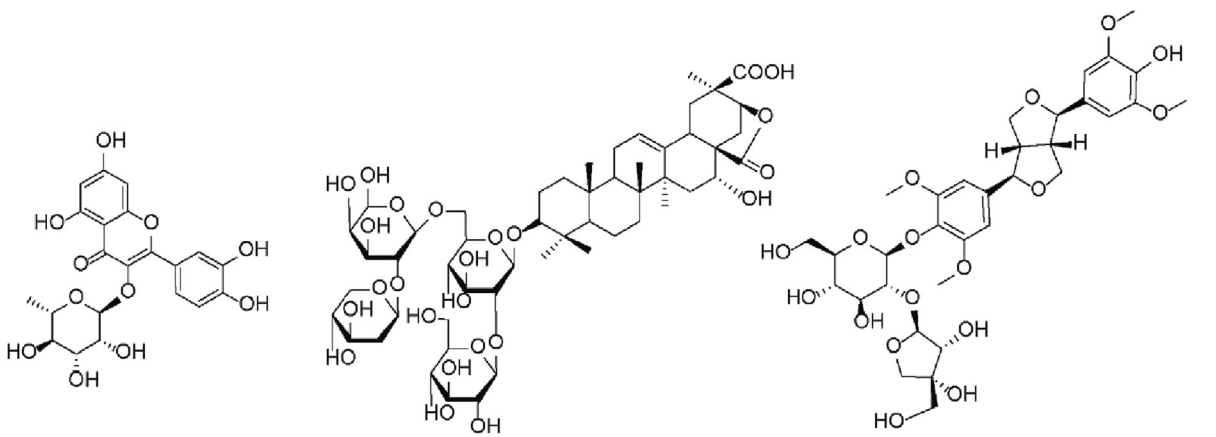

Fig. 2. Several representative bioactive compounds shown to exert antidepressant activity, specifically by modulating monoaminergic system.

Table 1
A. julibrissin formulae traditionally used for depression treatment and their efficacy in clinical practice.

Herbal formulae	Composition	Daily human doses	Types of depression	Evaluation index	Efficacy evaluation	References
Jieyu Granules	*Bupleuri Radix*, *Toosendan Fructus*, *Citri Reticulatae Pericarpium*, *Paeoniae Radix Alba*, *Acori Tatarinowii Rhizoma*, *Albiziae Cortex*, *Ziziphi Spinosae Semen*, *Ambrum*	Three times/day	Depression with chronic congestive heart failure	SDS	Relieves symptoms of depression without apparent side effects.	(Wang, Tang, Ji, Hu, & Lin, 2018)
Jieyu Granules	*Bupleuri Radix*, *Toosendan Fructus*, *Citri Reticulatae Pericarpium*, *Acori Tatarinowii Rhizoma*, *Albiziae Cortex*, *Ziziphi Spinosae Semen*	One time/day	Depression with permanent atrial fibrillation	HAMD	Alleviates symptoms of depression without adverse effects. The efficacy is better than that of Deanxit.	(Hu, Tang, Wang, & Reng, 2018)
Jieyu Granules	*Bupleuri Radix*, *Hyperici Perforati Herba*, *Albiziae Cortex*, *Coptidis Rhizoma*	Three times/day	Moderate or mild depression	HAMD SDS SAS	Relieves symptoms of depression and anxiety without apparent side effects. It is comparable with fluoxetine, but better than Xiaoyao Powder.	(Lin, Hui, Han, Li, & Rong, 2019)
Jieyu Shuxin Pills	*Bupleuri Radix*, *Angelicae Sinensis Radix*, *Rehmanniae Radix*, *Aucklandiae Radix*, *Albizziae Flos*, *Codonopsis Radix*, *Glycyrrhizae Radix et Rhizoma*	Three times/day	Postpartum depression	EPDS	Alleviates symptoms of postpartum depression without adverse effects.	(Sun & Zhang, 2016)
Hehuan Granules	*Albizziae Flos*, *Fossilia*, *Platycladi Cacumen*, *Polygalae Radix*, *Valeriana Officinalis Herba*, *Citri Exocarpium Rubrum*	Two times/day	Depression and insomnia	HAMD	Alleviates depressive symptoms and improves patients' sleep quality.	(Lei, Zhang, & Chen, 2010)
Chaihu Shugan Pills	*Bupleuri Radix*, *Curcumae Radix*, *Paeoniae Radix Alba*, *Chuanxiong Rhizoma*, *Citri Reticulatae Pericarpium*, *Cyperi Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Albiziae Cortex*, *Polygoni Multiflori Caulis*, *Coptidis Rhizoma*, *Scutellariae Radix*, *Citri Sarcodactylis Fructus*, *Citri Fructus*, *Glycyrrhizae Radix et Rhizoma*	Two times/day	Post-stroke depression	HAMD	Alleviates symptoms of post-stroke depression, and better than paroxetine in clinical efficacy.	(Ha, 2020)
Yushu Granules	*Bupleuri Radix*, *Gardeniae Fructus*, *Ziziphi Spinosae Semen*, *Albiziae Cortex*, *Fossilia*, *Ambrum*	Three times/day	Depression	HAMD	Comparable with fluoxetine without apparent adverse effects.	(Mao, Lu, & Song, 2006)

Note: HAMD, Hamilton depression scale; SDS, Self-rating depression scale; SAS, Self-rating anxiety scale; EPDS, Edinburgh postnatal depression scale; TESS, Treatment emergent symptom scale.

Clinical studies indicated that the decoction possessed a comparable efficacy with a conventional antidepressant, venlafaxine, but fewer adverse effects (Shi, Guo, Jiang, & Zhang, 2013; Shi, Zhang, & Jiang, 2016). We are encouraged by these clinical studies to explore the mechanism of action of the herb pair as an effective antidepressant in the systematic treatment of depression.

4.2. Jieyu Hehuan Decoction

Jieyu Hehuan Decoction, a combination of 13 herbs, including *Albizziae Flos*, *Curcumae Longae Rhizoma*, *Aquilariae Lignum Resinatu*, *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Platycladi Cacumen*, *Gardeniae Fructus*, *Bupleuri Radix*, *Menthae Haplocalycis Herba*, *Poria*, *Ziziphi Spinaosea Semen*, and *Citri Exocarpium Rubrum*, is an empirical formula for depression treatment (Zhang, 2018). The composition and dosage of Jieyu Hehuan decoction depend on the symptoms of individual patients and can be modified to fit specific individuals more accurately. A preclinical study showed that administration of the decoction (6.8 g/kg, 14 d, p.o.) shortened the immobility time in both the tail suspension and forced swimming tests and increased expression of hippocampal p-GSK3β in mice, suggesting its antidepressant activity is partially mediated by BDNF signaling (Jia et al., 2017). It is extremely difficult to clearly interpret a complicated herbal formula at the molecular level, the system-wide mechanism of action as well as the role of each herb including *A. julibrissin*, however, should be uncovered in future studies.

Several clinical studies have been performed to investigate the system-wide responses associated with Jieyu Hehuan decoction administration (Chen & Zhang, 2007; Jia et al., 2017; Liang, Zhang, & Hu, 2018; Tian & Zhang, 2016; D. Zhang, 2018; G. Zhang, Sun, & Wang, 2009). These studies showed that the decoction produced a better treatment efficacy than conventional antidepressants, such as fluoxetine and paroxetine, with fewer side effects. These clinical results support the idea that the holistic, multidrug, and multitarget nature of one herbal formula is more effective for the treatment of depression.

4.3. Jiawei Wendan Decoction

Jiawei Wendan Decoction, a mixture of eight herbs (*Pinellia Rhizoma*, *Citri Reticulatae Pericarpium*, *Bambusae Caulis in Taenias*, *Aurantii Fructus*, *Albizziae Flos*, *Acori Tatarinawii Rhizoma*, *Magnoliae Officinalis Cortex*, *Poria*), has been historically used for the treatment of mood disorders, loss of appetite, and sleep disturbances (Nie & Fang, 2019; Shi, Liu, Tang, & Zhang, 2007; Wu, Tang, Zhang, & Song, 2015). Zhang et al. reported that the decoction exerted both antidepressant and anxiolytic activities in rat models through enhancing 5-HT transmission (Zhang et al., 2021). In addition, studies conducted by Wu et al. (Wu, Tang, Zhang, & Song, 2015) and Wang et al. (Wang et al., 2016) showed that the antidepressant-like effects of Jiawei Wendan decoction were possibly mediated by modulating the levels of hippocampal neuropeptides, neuroendocrine hormone CRH, and Ras protein. Furthermore, studies also indicated that administration of the formula attenuated ultrastructural damage of hypothalamic neurons and gastrointestinal tissues in chronic stress-induced depressive models (Song, Zhang, Chen, & Xu, 2018; Xu, Zhang, Song, & Chen, 2019).

A clinical study demonstrated that Jiawei Wendan decoction had a comparable efficacy with fluoxetine (76.7% *vs* 80.0%), but

Table 2
A. julibrissin formulae combined with conventional antidepressants for clinical treatment of depression.

Herbal formulae	Compositions	Conventional antidepressants	Types of depression	Evaluation index	Efficacy evaluation	References
Jieyu Granules	*Codonopsis Radix*, *Albiziae Cortex*, *Trichosanthis Radix*, *Curcumae Radix*, *Chuanxiong Rhizoma*, *Cyperi Rhizoma*, *Angelicae Sinensis Radix*, *Salviae Miltiorrhizae Radix et Rhizoma*	Citalopram	Depression in elder people	HAMD	Combinative administration shows a better efficacy than citalopram alone.	(Yuan et al., 2010)
Xindanshu Capsules	*Albiziae Cortex*, *Epimedii Folium*, *Juglandis Semen*, *Euphorbiae Humifusae Herba*, *Lilii Bulbus*, *Bupleuri Radix*	Fluoxetine	Depression with lacking in self-confidence	HAMD	Combinative administration shows a better efficacy and less adverse effects than fluoxetine alone.	(Jin & Li, 2009)
Qingxin Anshen Granules	*Pinelliae Rhizoma*, *Arisaema Cum Bile*, *Citri Exocarpium Rubrum*, *Coptidis Rhizoma*, *Gardeniae Fructus*, *Bambusae Caulis in Taenias*, *Polygalae Radix*, *Curcumae Radix*, *Poria*, *Atractylodis Macrocephalae Rhizoma*, *Aurantii Fructus*, *Ziziphi Spinosae Semen*, *Albiziae Cortex*, *Fossilia*, *Glycyrrhizae Radix et Rhizoma*	Deanxit	Depression	HAMD TESS	Combinative administration shows a better efficacy than deanxit alone.	(Jiang & Zhang, 2009)
Baihe Anshen Decoction	*Bupleuri Radix*, *Lilii Bulbus*, *Curcumae Radix*, *Albizziae Flos*, *Chuanxiong Rhizoma*, *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*	Deanxit	Anxiety and depression after coronary heart disease surgery	HAMD	Combinative administration shows a better efficacy than deanxit alone.	(Xu, Ren, & Li, 2020)
Baihe Anshen Decoction	*Bupleuri Radix*, *Paeoniae Radix Alba*, *Chuanxiong Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Cyperi Rhizoma*, *Curcumae Radix*, *Albiziae Cortex*, *Ziziphi Spinosae Semen*, *Scutellariae Radix*	Deanxit	Depression with chronic heart failure	HAMD	Combinative administration shows a better efficacy than deanxit alone.	(Wang & Liang, 2016)
Baihe Anshen Decoction	*Bupleuri Radix*, *Lilii Bulbus*, *Curcumae Radix*, *Albizziae Flos*, *Chuanxiong Rhizoma*, *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*, *Triticum*, *Anemarrhenae Rhizoma*, *Sojae Semen Praeparatum*, *Gardeniae Fructus*, *Fossilia*, *Ostreae Concha*, *Glycyrrhizae Radix et Rhizoma*	Deanxit	Anxiety and depression	SAS SDS	Combinative administration shows a better efficacy than deanxit.	(Wen & Ji, 2015)
Jieyu Hehuan Decoction	*Albizziae Flos*, *Paeoniae Radix Alba*, *Angelicae Sinensis Radix*, *Cinnabaris*, *Poria*, *Platycladi Semen*, *Polygalae Radix*, *Ziziphi Spinosae Semen*, *Ambrum*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Fossilia*, *Sojae Semen Praeparatum*, *Nelumbinis Rhizomatis Nodus*, *Borneolum*, *Acori Tatarinowii Rhizoma*, *Ostreae Concha*, *Margarita*, *Ziziphi Spinosae Semen*, *Polygoni Multiflori Caulis*, *Triticum*	Deanxit	Mild depression	HAMD	Combinative administration shows a better efficacy than Deanxit or Jieyu Hehuan decoction alone.	(Li, 2015)
Jieyu Hehuan Decoction	*Moutan Cortex*, *Gardeniae Fructus*, *Angelicae Sinensis Radix*, *Cinnabaris*, *Poria*, *Polygalae Radix*, *Acori Tatarinowii Rhizoma*, *Paeoniae Radix Alba*, *Albizziae Flos*, *Ambrum*, *Polygoni* Multiflori *Caulis*, *Ziziphi Spinosae Semen*, *Triticum*, *Ostreae Concha*, *Fossilia*, *Glycyrrhizae Radix et Rhizoma*	Paroxetine	Depression	HAMD	Combinative administration shows a better efficacy than paroxetine alone.	(Gong, 2016)
Baihe Ningshen Decoction	*Lilii Bulbus*, *Polygoni* Multiflori *Caulis*, *Acori Tatarinowii Rhizoma*, *Angelicae Sinensis Radix*, *Glycyrrhizae Radix et Rhizoma*,*Curcumae Radix*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Ziziphi Spinosae Semen*, *Albizziae Flos*, *Rosae Rugosae Flos*, *Scutellariae Radix*, *Ligustri Lucidi Fructus*	Fluoxetine	Post-stroke depression	HAMD	Combinative administration shows better efficacy and fewer side effects than fluoxetine alone.	(Han, Liu, Ji, & Mi, 2010; Li, 2016)
Baihe Ningshen Decoction	*Lilii Bulbus*, *Ziziphi Spinosae Semen*, *Albizziae Flos*, *Polygoni* Multiflori *Caulis*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Angelicae Sinensis Radix*, *Glycyrrhizae Radix et Rhizoma*	Clomipramine/ Amitriptyline	Depression	HAMD	Combinative administration shows a better efficacy than clomipramine/ amitriptyline alone.	(Liu & Zhang, 2002)
Yangxin Docoction	*Platycladi Cacumen*, *Schisandrae chinensis Fructus*, *Bupleuri Radix*, *Acori Tatarinowii Rhizoma*, *Glycyrrhizae Radix et Rhizoma*, *Codonopsis Radix*, *Curcumae Radix*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Ziziphi Spinosae Semen*, *Polygalae Radix*, *Aurantii Fructus*, *Ophiopogonis Radix*, *Albiziae Cortex*, *Paeoniae Radix Alba*, *Citri Fructus*	Sertraline	Depression	HAMD	Combinative administration shows better efficacy and fewer side effects than sertraline alone.	(Gao, 2018)
Baihe Ganmai Decoction	*Lilii Bulbus*, *Anemarrhenae Rhizoma*, *Glycyrrhizae Radix et Rhizoma*, *Triticum*, *Albiziae Cortex*, *Ziziphi Spinosae Semen*	Agomelatine	First-episode depression	HAMD	Combinative administration shows a better efficacy than agomelatine alone.	(C.F. Zhang, Cheng, Feng, Zhao, & Wang, 2021; Q. Zhang et al., 2021; Y. Zhang et al., 2015)

(*continued on next page*)

Table 2 (*continued*)

Herbal formulae	Compositions	Conventional antidepressants	Types of depression	Evaluation index	Efficacy evaluation	References
Jieyu Pills	*Paeoniae Radix Alba*, *Bupleuri Radix*, *Angelicae Sinensis Radix*, *Curcumae Radix*, *Poria*, *Lilii Bulbus*, *Glycyrrhizae Radix et Rhizoma*, *Albiziae Cortex*, *Triticum*, *Ziziphi Spinosae Semen*	Duloxetine	Depression with energy deficiency	SDS BDC HAMD	Better efficacy than Jieyu pills alone.	(Li, Ge, Wang, & Pan, 2020)
		Duloxetine	Post-stroke depression	HAMD CGI	Better efficacy than duloxetine alone without increased safety concerns.	(Bai, Guo, Ma, & Wang, 2020; Zhang, Liu, Zhang, Song, & Zhang, 2020)
		Deanxit	Post-stroke depression	HAMD HAMA	Better efficacy than deanxit alone without increased safety concerns.	(Wu & Yang, 2020)
		Mirtazapine	Depression	HAMD SDSS	Better efficacy and less adverse effects than mirtazapine alone.	(Ye, Fan, Chen, Li, & Cao, 2020)
		Paroxetine	Postpartum depression	HAMD	Better efficacy and less adverse effects than paroxetine alone.	(Yang & Zhong, 2020)
		Paroxetine	Post-stroke depression	NIHSS HAMD SDS	Better efficacy than paroxetine alone.	(Tang, Han, & Chen, 2019)
		Escitalopram	Post-stroke depression	HAMD NIHSS	Better efficacy than escitalopram alone without increased safety concerns.	(Tian, Bai, You, & Yao, 2020)
Jieyu Shuxin Pills	*Bupleuri Radix*, *Angelicae Sinensis Radix*, *Rehmanniae Radix*, *Cyperi Rhizoma*, *Chuanxiong Rhizoma*, *Paeoniae Radix Alba*, *Acori Tatarinowii Rhizoma*, *Polygalae Radix*, *Polygoni Multiflori Caulis*, *Aucklandiae Radix*, *Albizziae Flos*, *Codonopsis Radix*, *Glycyrrhizae Radix et Rhizoma*	Citalopram	Postpartum depression	EPDS HAMD SDS	Better efficacy than citalopram alone without increased safety concerns.	(Fang, Du, & Zheng, 2019; Sun, Li, & Wang, 2016)
Shenshuaining Pills	*Acori Tatarinowii Rhizoma*, *Polygoni Multiflori Caulis*, *Platycladi Cacumen*, *Ziziphi Spinosae Semen*, *Albiziae Cortex*, *Schisandrae chinensis Fructus*, *Margarita*, *Cinnabaris*, *Rehmanniae Radix*, *Ecliptae Herba*, *Alpinae Oxyphyllae Fructus*	Citalopram	Depression	HAMD TESS SDS	Better efficacy, faster onset, and fewer adverse effects than citalopram alone.	(Zhang, 2013)
Xingnao Jieyu Capsules	*Acori Tatarinowii Rhizoma*, *Polygalae Radix*, *Curcumae Radix*, *Bupleuri Radix*, *Albiziae Cortex*, *Morindae Officinalis Radix*, *Salviae Miltiorrhizae Radix et Rhizoma*	Deanxit	Post-stroke depression	HAMD SDS	Better efficacy and faster onset than deanxit alone.	(Yan, Yang, & Yang, 2011)
Baicaoxiang Jieyu Anshen Capsules	*Prunellae Spica*, *Paeoniae Radix Alba*, *Albizziae Flos*, *Ziziphi Spinosae Semen*, *Bupleuri Radix*, *Cyperi Rhizoma*, *Rehmanniae Radix*, *Schisandrae chinensis Fructus*, *Polygoni Multiflori Caulis*	Paroxetine	Depression	HAMD PSQI WHOQOL-BREF	Better efficacy and sleep quality than paroxetine alone.	(Liu, Cui, Li, & Yu, 2017)
Yushu Granules	*Bupleuri Radix*, *Gardeniae Fructus*, *Ziziphi Spinosae Semen*, *Albiziae Cortex*, *Fossilia*, *Ambrum*	Fluoxetine	Post-Stroke Depression	HAMD	Better efficacy than fluoxetine alone.	(Kan, 2012)
Jiawei Xiaoyao Powder	*Bupleuri Radix*, *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*, *Albiziae Cortex*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Aurantii Fructus*, *Atractylodis Macrocephalae Rhizoma*, *Poria*, *Chuanxiong Rhizoma*, *Menthae Haplocalycis Herba*, *Glycyrrhizae Radix et Rhizoma*, *Zingiberis Rhizoma*	Fluoxetine	Post-Stroke Depression	TESS	Better efficacy and less adverse effects than fluoxetine alone.	(Yan et al., 2015; Yang & Rong, 2009)
Anshen Dingzhi Decoction	*Bupleuri Radix*, *Atractylodis Macrocephalae Rhizoma*, *Poria*, *Paeoniae Radix Alba*, *Curcumae Radix*, *Polygalae Radix*, *Lilii Bulbus*, *Acori Tatarinowii Rhizoma*, *Albiziae Cortex*, *Glycyrrhizae Radix et Rhizoma*	Duloxetine	Depression	HAMD TESS	Better efficacy, faster onset, and fewer adverse effects than duloxetine alone.	(Gou et al., 2015)

Note: CGI, clinical global impression; BDC, Burns depression checklist; HAMA, Hamilton anxiety scale; SDSS, social defect screening scale; NIHSS, National Institutes of Health stroke score; EPDS, Edinburgh postpartum depression scale; PSQI, Pittsburgh sleep quality index; WHOQOL-BREF, the world health organization quality of life-BREF.

fewer adverse effects (2.5% *vs* 5.5%), assessed by the Hamilton Depression Scale (HAMD) and Treatment Emergent Symptom Scale (TESS), respectively (Shi, Liu, Tang, & Zhang, 2007).

4.4. Jieyu Qingxin Anshen Decoction

Jieyu Qingxin Anshen Decoction is an aqueous extract from an herbal mixture composed of 12 herbs (*Bupleuri Radix*, *Aurantii Fructus*, *Curcumae Radix*, *Cyperi Rhizoma*, *Citri Reticulatae Semen*, *Citri Reticulatae Pericarpium*, *Gardeniae Fructus*, *Sojae Semen Praeparatum*, *Ziziphi Spinosae Semen*, *Polysoni Multiflori Caulis*, *Albiziae Cortex*, *Margarita*), and it has been clinically used for the treatment of depression with "vital energy" deficiency and arrhythmia symptoms (Zhang & Cao, 2013). Clinical studies showed that the herbal decoction is more effective in depression treatment than either conventional antidepressants, such as citalopram and paroxetine or one TCM antidepressant formula, Xiaoyao Powder (Gong, 2020; Gao, 2019; Sun, Gao, & Cheng, 2018; Tian, 2017). However, preclinical study to reveal the mechanism by which Jieyu Qingxin Anshen decoction produces antidepressant responses in depressive animal models has not been performed.

5. Clinical studies on combinative use of conventional antidepressants with herbal formulae

Although conventional antidepressants with single targets have been broadly used for the treatment of depression, additional agents that show synergistic activity are needed to act on diverse pathophysiological factors for a better therapeutic efficacy. An herbal formula is usually prescribed to activate blood circulation, eliminate phlegm and dampness, correct digestive and gastrointestinal dysfunction, or improve immune function, all of which are pharmacological targets in systems pharmacology in depression treatment (Wang et al., 2017). In this context, herbal formulae could serve as adjuvants to the conventional medications in the effective treatment of depression. Indeed, clinical studies indicated that treatment with a combination of a conventional antidepressant with an herbal formula showed a better therapeutic efficacy without increased safety concerns (Fu et al., 2021; Lin et al., 2021).

Several clinical attempts using a combination of an *A. julibrissin* formula with a conventional antidepressant have been conducted to treat patients with depressive symptoms. Conventional antidepressants commonly used with *A. julibrissin* formulae include fluoxetine, citalopram, paroxetine, flupentixol, clomipramine, etc., all of which exert antidepressant responses through enhancement of monoamine neurotransmission in the brain (Lv, Li, & Liu, 2018; Zhang, Zhao, & Cai, 2018; Casarotto et al., 2021; Mahmoudian et al., 2021). Clinical studies demonstrated that *A. julibrissin* formulae were compatible with these conventional antidepressants, showing a faster onset, shorter course of treatment, lower rate of relapse, and better therapeutic efficacy without increased adverse effects (Table 2). Experimental evidence for the combinative use of conventional antidepressants with herbal formulae have been obtained exclusively from clinical studies. Preclinical study using animal models is required for our understanding of the synergistic mechanism by which the combinative administration exerts a better efficacy.

6. Perspective

SERT is a well-established molecular target for the antidepressant drugs, such as selective serotonin reuptake inhibitors including fluoxetine and citalopram. The high-resolution structures of SERT in several conformational states have been resolved (Coleman et al., 2019; Coleman, Green, & Gouaux, 2016; Coleman & Gouaux, 2018; Yang & Gouaux, 2021), providing structural insight into antidepressant action on the transporter protein. In these structures, conventional antidepressant molecules occupy the central binding cavity and thus competitively inhibit the conformational conversion required for serotonin transport (Fig. 3). In addition, we previously demonstrated that a natural alkaloid, ibogaine, noncompetitively inhibited SERT by stabilizing an inward-facing conformation of the transporter (Bulling et al., 2012; Jacobs, Zhang, Campbell, & Rudnick, 2007). The cryo-electron microscopy structures of SERT-ibogaine complexes uncovered the ibogaine binding site and mechanism of ibogaine inhibition (Coleman et al., 2019). Furthermore, the recently resolved cryo-electron microscopy structures of SERT revealed an allosteric site formed by an aromatic pocket positioned in the scaffold domain in the extracellular vestibule (Yang & Gouaux, 2021). These structural analyses, thus, shifted our efforts in exploring the molecular mechanism of action toward the herbal compounds that target different conformation or the allosteric site of SERT. Experimental evidence has been recently shown that the lignan glycosides isolated from *A. julibrissin*, SAG and SBG, directly bind to SERT, presumably to the allosteric site, thus noncompetitively inhibit SERT activity (Huang et al., 2022). Taken together, these works have provided an excellent paradigm to explore the mechanism of action of the herbal compound as an antidepressant agent at the molecular level.

While several other herbal molecules isolated from *A. julibrissin* have also been demonstrated to specifically modulate one of the pathological systems in the neurobiology of depression, their targeting proteins have not been fully understood. Identification of bioactive constituents and their specific interactions with pharmacological targets is essential to reveal the molecular mechanism of action by which *A. julibrissin* exerts antidepressant-like effects. These efforts could also significantly improve our understanding of its benefits and risks at the molecular level. Several advanced identification techniques, such as DNA or RNA microarray (Panossian, Hamm, Kadioglu, Wikman, & Efferth, 2013; Panossian, Hamm, Wikman, & Efferth, 2014; Panossian, Seo, & Efferth, 2018; Panossian, Seo, Wikman, & Efferth, 2015; Woo, Lim, Myung, Kim, & Lee, 2018) and quantitative proteomics (Wang et al., 2020), have been recently used for identifying potential targeting proteins that are associated with an herb or herbal formula. We expect that these high-throughput technologies can be used for analyzing the acting targets of bioactive constituents isolated from *A. julibrissin*.

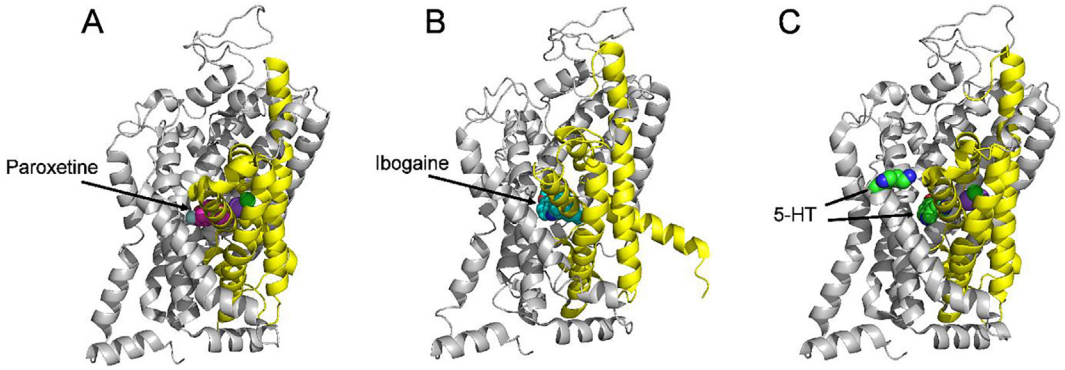

Fig. 3. High-resolution structures of SERT bound with paroxetine (PDB accession code, 5I6X, paroxetine in the central site, (A) in an outward open conformation, with ibogaine (PDB accession code, 6DZZ, ibogaine in the central site, (B) in an inward open conformation, and with two molecules of 5-HT in the central and allosteric sites (PDB accession code, 7LIA, two molecules of 5-HT in the central and allosteric sites, (C) in an outward open conformation. Cartoon views of the structures are shown from the membrane plane with the extracellular side above and the cytoplasm below the structure. The bundle domain (TMs 1, 2, 6, and 7) and other part of the protein are colored yellow and gray, respectively. The purple and green spheres in the center of the structures represent Na^+ and Cl^-, respectively. SERT structures in this figure were made by PyMOL.

Meanwhile, molecular approaches also play an important role in the identification of specific interactions of herbal molecules with their targeting proteins. The results from high-throughput screening technologies need to be validated by these molecular approaches. Three complementary molecular approaches, including biochemical analysis, genetic interaction, and computational inference, have been extensively used for identifying pharmacological targets (Schenone, Dancik, Wagner, & Clemons, 2013). Biochemical analysis is directly to detect the binding affinity of a bioactive molecule by using a binding assay (Burdine & Kodadek, 2004). Profiling the herbal molecule activity with an available panel of presumed proteins can be used to directly detect its targets. Genetic interaction is used to identify targets by genetic manipulation of putative targets in cells, by changing small molecule sensitivity (Zheng, Chan, & Zhou, 2004). Gene knockout and RNAi can be used to change the action of presumed targets, revealing the dependencies of herbal molecules on biological activity. Computational inference is to compare the responses of small molecules with those of known target molecules by pattern recognition (Daniel et al., 2008). In general, databases can be used to provide useful information about the targets of an herbal molecule by comparing the similarity to compounds with known targets. In practice, a combination of these three methods should be used for defining the pharmacological targets. Using a combinative method of high-throughput screening and molecular approaches will undoubtedly promote to reveal the molecular mechanism of action of *A. julibrissin*, which, in turn, will improve our understanding of its on-target or off-target effects in the treatment of depression.

As discussed above, *A. julibrissin* exerts antidepressant-like effects through various underlying mechanisms by acting on multiple pathological factors across divergent biological systems. It is evident that the interaction between a single herbal molecule and its target revealed by the molecular approaches cannot exactly reflect the actions of an herb or an entire herbal formula, which contains numerous bioactive constituents that are proposed to act on multiple systems or targets. Hence, it is necessary to investigate the mechanism of action at the systems level for our understanding of *A. julibrissin* formulae in the systemic treatment of depression.

It is a challenge to uncover the mechanism of action of an herb or herbal formula at the systems level because we are not clear about all bioactive constituents and their pharmacological profiles. The synergistic interactions (Chatterjee, Verma, Maurya, & Palit, 2011) and compatibility between bioactive constituents or herbs in an herbal formula are fundamental questions to be addressed in systems pharmacology. The synergistic interactions between herb pairs in several herbal formulae have been successfully studied by several laboratories (Adams, Seeram, Hardy, Carpenter, & Heber, 2006; Wang et al., 2012; Yi & Wetzstein, 2011). In addition, a study has been conducted to optimize the compatibility of herb pairs in Kaixin Powder by examining the activation of neurofilament expression in PC12 cells (Lu et al., 2015). Furthermore, Dong et al. have recently used a quantitation-based proteomics approach to identify proteins in response to Kaixin Powder administration (0.6 g/kg, 14 d) across biological systems (Dong et al., 2020). Knowledge obtained from these studies can be employed for the study of *A. julibrissin* formulae, such as Suanzaoren Hehuan decoction, a simplest herbal formula comprising only two herbs.

In summary, the identification of bioactive constituents and their interactions with pharmacological targets will offer the molecular basis for our understanding of the antidepressant effects of *A. julibrissin*. Moreover, it is vital to integrate the molecular and systematic approaches into the study of *A. julibrissin* or formulae for revealing its mechanism of action in its entirety. We expect that the comprehensive study would provide a way to discover novel agents or approaches in the effective and systematic treatment of depression.

Author's contributions

BH, YW, QT, and YZ wrote the manuscript. YW and CL prepared the figures and tables and assisted in the collection of references. YZ revised and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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