Research Progress of the Liver–Brain Cotreatment of Depression with Supplemented Danzhi Xiaoyao Powder

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Abstract

Traditional Chinese medicine (TCM) has unique advantages in preventing and treating depression based on holistic concepts and syndrome differentiation and treatment. Liver depression and spleen deficiency are the main syndrome of depression. Danzhi Xiaoyao powder has the efficacy of soothing the liver and relieving depression, nourishing blood, and strengthening spleen. Present studies have proven that it has antidepressant efficacy for the syndrome of liver depression and spleen deficiency. The basic research on pharmacodynamic substances has found that the main active ingredients of Danzhi Xiaoyao powder in the treatment of depression include bupleurum saponin, paeonol, gardenoside, angelica polysaccharide, sulfate polysaccharide, paoniflorin, albiflorin, atractylone, etc. In clinical practice, Danzhi Xiaoyao powder is often modified to make it more suitable according to the characteristics of pathogenesis and changes in the disease condition. Our research group has found that “brain and spirit failure and liver failing to disperse” are the main pathogenesis of depression. Based on the theory of “liver–brain cotreatment,” the treatment principle of “dispersing the liver and relieving depression, strengthening brain and benefiting intelligence” was put forward. On the basis of Danzhi Xiaoyao powder, Shichangpu (Acori Tatarinowii Rhizoma) was added to enlighten the mind and Yuanzhi (Polygalae Radix) to calm the mind and benefit intelligence. The modified Danzhi Xiaoyao powder was formulated, and its clinical effects on depression were remarkable. Animal experiments also confirmed that modified Danzhi Xiaoyao powder can significantly improve the depression-like behavior of depression model rats and the mechanism may be related to the regulation of the hypothalamic–pituitary–adrenal axis, the increase of the content of 5-hydroxytryptamine, and norepinephrine, which provides a reference for the further promotion of the clinical application of modified Danzhi Xiaoyao powder in the treatment of depression.

Keywords

► depression
► Supplemented Danzhi Xiaoyao powder
► liver–brain cotreatment
► Shichangpu (Acori Tatarinowii Rhizoma)
► Yuanzhi (Polygalae Radix)
Depression is a mental disorder characterized by persistent depression, which may be accompanied by symptoms such as thinking disorders, volitional activity, and cognitive impairment. It has high prevalence rate, high disability rate, high suicide rate, and high recurrence rate. Comorbidities with other diseases gets easily formed. At present, the prevalence rate of depression in China is 6.8%, an increase by 30.99% compared with 10 years ago, and the overall prevention and treatment situation are very severe. Nowadays, the commonly used antidepressant chemicals, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, have disadvantages of slow effect, easy recurrence, many adverse reactions, and narrow antidepressant spectrum. The etiology of depression is complex, and its pathogenesis is not clear yet. The above antidepressant chemicals are ineffective in at least 1/3 of patients with severe depression.

Chinese herbs, based on the holistic concept and syndrome differentiation and treatment, can effectively improve the clinical symptoms and quality of life of patients with depression. It has unique advantages in the prevention and treatment of depression, such as stable curative effect, low recurrence rate, few side effects, and good patient compliance.

Liver Depression and Spleen Deficiency is the Main Pathogenesis of Depression

The records of depression in traditional Chinese medicine (TCM) are seen in depression syndrome, lily disease, globus hystericus, hysteria (Zangzao), etc., and most of the disease locations are believed to be in the liver. According to Danger Zone of Medicine (Yi Bian), depression is often associated with dysfunction of the liver. The liver is rigid and has a strong nature. The liver qi has the properties of stretching of wood, and it ascends actively. In nature, the growth trend of all trees is to stretch their branches smoothly and extend their nature without suppression. Liver governs dispersing, and all kinds of depression can inhibit liver qi and make it fail to disperse.

In the Basic State of Spirit of the Spiritual Pivot (Benshen of Ling Shu), it recorded that “Excessive sorrow and grief in the liver will harm the internal organs and damage the ethereal soul. Damage of the ethereal soul will cause mania, amnesia, unintelligent actions,” and “deficiency of liver qi causes fear while excess of liver qi causes anger.” If the seven emotions of the human body are depressed, the liver fails to act freely and is malnourished, which can further make the liver qi depressed and sick. In clinical treatment, the concept of “depressed liver should be dispersed” is also widely accepted, and the representative prescriptions of soothing the liver and relieving depression include Chaihu Shugan powder and Xiaoyao powder which have been widely used in clinical practice.

At the same time, due to the learning and memory disorders in depression, it is closely related to the qi and blood nutrition around the human body. In the Medical Rules and Regulations (Yi Lin Sheng Mo), it recorded that “the spirit depends on blood and qi of the body. Qi and blood flow in a parallel way and circulate endlessly to generate energy and vitality of life... so the disorder of blood will lead to spirit disorder.” Blood is an important material basis for mental activity and an important carrier for cognition, learning, and memory. Sufficient blood in blood vessels and proper blood circulation are the material basis of intelligent memory. Depressed mood caused by qi stagnation is another important pathogenesis of depression. The spleen is located in the middle energizer of the body, which is the pivot of ascending and descending qi movement of the whole body. The spleen governs thinking, and overthinking leads to qi stagnation. In addition, the spleen and stomach are the acquired foundation, the source of qi and blood, and the material basis of all human activities. Therefore, it is said that “all diseases arise from the failure of the spleen and stomach.” Moreover, most patients with depression may have symptoms of spleen dysfunction such as loss of appetite, emaciation, and fatigue. Therefore, the treatment of depression is often based on the spleen. The syndrome patterns of first-episode depression in the International Chinese Medicine Guidelines for Clinical Practice are liver depression and qi stagnation syndrome, liver depression and spleen deficiency syndrome, heart and spleen deficiency syndrome, kidney deficiency and liver depression syndrome, and liver and gallbladder damp-heat syndrome. Literature studies show that liver depression and spleen deficiency are the main syndrome of depression, accounting for 34.19% of all depression syndromes.

Correlated Studies of Danzhi Xiaoyao Powder in the Treatment of Depression

Danzhi Xiaoyao powder is derived from Xue Ji’s Summary of Internal Medicine (Nei Ke Zhai Yao) in the Ming Dynasty. It is composed of Danpi (Moutan Cortex) and Zhizi (Gardeniae Fructus) on the basis of Xiaoyao powder with the effects of soothing the liver and clearing heat, relieving depression, strengthening the spleen, and nourishing blood. The whole prescription is composed of Chaihu (Bupleuri Radix), Danpi (Moutan Cortex), Zhizi (Gardeniae Fructus), Danggui (Angelicae Sinensis Radix), Baishao (Paeoniae Radix Alba), Baizhu (Atractylodis Macrocephalae Rhizoma), Fuling (Poria), Shengjiang (Zingiberis Rhizoma Recens), Bohe (Menthae Herba), and processed Gancao (Glycyrrhizae Radix et Rhizoma Praeparata cum Melle), which is a classic prescription for regulating abnormal emotions in TCM. The monarch herb Chaihu (Bupleuri Radix) has the effects of soothing the liver and relieving depression; the minister herb Danggui (Angelicae Sinensis Radix) is for nourishing blood and promoting blood circulation, nourishing yin and moistening dryness, and Baishao (Paeoniae Radix Alba) for softening the liver; the assistant herb Baizhu (Atractylodis Macrocephalae Rhizoma), processed Gancao (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle), and Fuling (Poria) are used to strengthen the spleen to prevent liver depression, subjugating the spleen. When the disease caused by liver disfunction appears, the disease caused by spleen disfunction may be soon involved, so it is necessary to strengthen the spleen first; Bohe (Menthae Herba), as a clear and light herb in
nature, can disperse depression and assist Chaihu (Bupleuri Radix) to disperse liver depression. Simmered Shengjiang (Zingiberis Rhizoma Recens) is used to warm the stomach and neutralize; all herbs together have the efficacy of soothing the liver, relieving depression, nourishing blood, and strengthening the spleen.

In clinical practice, some scholars treated poststroke depression with Danzhi Xiaoayao powder combined with acupuncture. It was found that the degree of depression was significantly reduced after treatment, and the contents of serum brain-derived neurotrophic factor (BDNF) and 5-Hydroxytryptamine (5-HT) were significantly increased.\(^20,21\) Ma\(^22\) found that the total effective rate of Danzhi Xiaoayao powder was up to 92.5% in patients with depression and insomnia after 4 weeks of administration, and there was no recurrence of symptoms after drug discontinuance. Luo et al\(^23\) used Danzhi Xiaoayao powder to treat patients with depression. They found that the depression and anxiety scores of patients were significantly reduced after treatment, and their antidepressant efficacy was comparable to that of Maiprotline, but the adverse reactions were significantly less than that of Maiprotline.

In animal experiments, Liu et al\(^24\) found that Danzhi Xiaoayao powder could significantly relieve the depressive behavior of mice with chronic psychological stress. Wang et al\(^25\) found that Danzhi Xiaoayao powder could improve the symptoms of diabetic depression rats by regulating the hypothalamic–pituitary–adrenal axis (HPA). Li et al\(^26\) found that Danzhi Xiaoayao powder could achieve antidepressant effect by regulating the content of hypothalamic monoamine neurotransmitters in chronic stress-depression rats.

**Pharmacodynamic Material Basis of Danzhi Xiaoayao powder in the Treatment of Depression**

In the Danzhi Xiaoayao powder, Chaihu (Bupleuri Radix), Danpi (Moutan Cortex), Zhizi (Gardeniae Fructus), Danggui (Angelicae Sinensis Radix), Baizhu (Atractylodis Macrocephalae Rhizoma), Fuling (Poria), Gancao (Radix et Rhizoma Glycyrrhizae), and Bohe (Menthae Herba) all have been reported on antidepressant efficacy, which is summarized as follows.

Chaihu (Bupleuri Radix): It is the monarch medicine in Danzhi Xiaoayao powder for soothing the liver and relieving depression. Saponins compounds are the most important active ingredients of Chaihu (Bupleuri Radix), mainly including saponins a, saponins b, saponins c, and saponins d. Among them, saponins a has a higher content, and saponins d has the highest biological activity.\(^27\) It was found that Bupleurum saponins can effectively improve the behavioral performance indicators of rats with chronic stress combined with orphan depression.\(^28\) Bupleurum saponin a can reduce the degree of depression in rats by regulating the imbalance of TH17/Treg cells and the secretion of inflammatory cytokines in depressed rats.\(^29\)

Danpi (Moutan Cortex): Paeonol is the main active ingredient in Danpi (Moutan Cortex). It has been found that Paeonol can reduce the loss of synapses and dendrites in different brain regions induced by chronic unpredictable mild stress (CUMS) through multiple signaling pathways such as GTPase-cofilin1 and GSK3B/calcinerin and improve depressive behavior.\(^30\) Another study showed that paeonol reduces the expression of p65, inhibitor of nuclear factor-xB-α (IKBα), IκB kinase (IKKβ), NOD-like receptor protein 3 (NLRP3) by inhibiting the activation of toll like receptor 4 (TLR4) and nuclear factor-xB (NF-xB) signaling pathways, thereby inhibiting the expression of pro-inflammatory factor tumor necrosis factor-α (TN-αF), interleukin-1β (IL-1β), and interleukin-6 (IL-6), so as to promote the production of anti-inflammatory factor IL-10 and improves depression-like symptoms.\(^31\)

Zhizi (Gardeniae Fructus): Gardenoside can relieve depression-like behavior in chronic mild stress (CMS) rats and reverse the low expression of prefrontal mammalian rapamycin target protein (mTOR), S6K, and brain failure response regulator protein 2 (CRMP2) caused by CMS.\(^32\) The iridoid components in the extracts of Zhizi (Gardeniae Fructus) can significantly improve depression-like symptoms in mice, significantly increase the activity of Akt and mTOR, increase the levels of NR1 and GluRI in the hippocampus, normalize the proportion of AMP-dependent protein kinase receptors and N-methyl-D-aspartic acid receptor (NMDA) receptors, and improve synaptic plasticity.\(^33\) Gardenia total iridoid can relieve depression-like behavior in LPS depression model mice, and its mechanism may be related to the regulation of γ-aminobutyric acid (GABA), glutamic acid (Glu), acetylcholine, 5-HT, and dopamine (DA) levels.\(^34\)

Danggui (Angelicae Sinensis Radix): Angelica polysaccharide can upregulate the mRNA expression of tryptophan hydroxylase 1 (TPH1), increase 5-HT synthesis, increase DA content, increase GABA/GLU ratio, and regulate neurotransmitters to correct the excitatory and inhibitory dysfunction of mice, and improve the depressive behavior of mice in the chronic stress model.\(^35\) Ferulic acid and turpentine ferulate are organic acids and also one of the main effective components in Danggui (Angelicae Sinensis Radix). Their amounts in Danggui (Angelicae Sinensis Radix) are 0.06 and 1.2%, respectively.\(^36,37\) It has been found that ferulic acid can significantly shorten the immobility time of forced swimming test and tail suspension test in CUMS model mice, and the mechanism may be related to the influence of 5-HT energy nervous system and the regulation of the antioxidant system.\(^38,39\) Zhang et al\(^40\) found that ferulic acid could improve the pain and depression induced by reserpine and also reverse the changes of SOD, NO, and monoamine transmitters in the hippocampus and frontal cortex of mice induced by reserpine. Liao et al\(^41\) found that the cell-free filtrate of sodium ferulate-induced PC12 cell lysate had an obvious antidepressant effect, and its antidepressant effect was related to the upregulation of nerve growth factor and BDNF and the enhancement of neurogenesis.

Fuling (Poria): Poria cocos polysaccharide sulfate has an antidepressant effect, and its mechanism may be related to the upregulation of hippocampal phosphorylation cAMP response element binding protein (p-CREB) and BDNF.
functions. 

Baishao (Paeoniae Radix Alba): Paeoniflorin and albiflorin have obvious antidepressant effects, and the mechanism may be related to the down-regulation of NO/cyclic guanosine monophosphate (cGMP) pathway in the cerebral cortex and hippocampus and the regulation of glutamate and its receptor expression in hippocampus. Paeoniflorin can promote the recovery of neurological function and improve the depressive state in rats with poststroke depression, and the mechanism may be related to the increase of BDNF and pCREB protein expression in hippocampal neurons.

Baizhu (Atractylodis Macrocephalae Rhizoma): Atractylonolide III has significant antidepressant effects on rat lipopolysaccharide (LPS) depression model and CUMS depression model, and its mechanism may be related to its inhibition of the expression of inflammatory factors TNF-α, IL-6, and IL-1β in the hippocampus. Li found that atractylone, atractylolide I, and atractylonolide II were chemical components which were closely related to the antidepressant activity of Xiaoayao powder in the despair model of mice and rats CUMS model. Gong et al. found that atractylonolide I and atractylonolide III could significantly shorten the immobility time of forced swimming and tail suspension experiments in mice and had significant antidepressant effects.

Gancao (Glycyrrhizae Radix et Rhiza): Liquiritin and its drug-containing serum have protective effects on microglia BVZ glutamate damage. Animal experiments showed that liquiritin could significantly increase the sugar preference rate of CMS model rats and relieve the central symptoms of depression. The possible mechanism of depression may be related to the inhibition of 5-HT and norepinephrine (NE) reuptake by neurons in the synaptic space. In addition, liquiritin can inhibit the expression of apoptosis-promoting factor Bax in the prefrontal cortex of rats with poststroke depression and promote the expression of antiapoptotic factors Bcl-2 and BDNF. Studies showed that the glycyrhiza flavonoids could significantly improve the stress-depression behavior of CUS rats, increase the expression of Bcl-xl protein in the hippocampus and reduce the expression of caspase-3 protein, significantly increase the expression of synaptophysin (SYP) mRNA and protein in the hippocampus, reduce the expression of post-synaptic density-95 (PSD-95) mRNA and protein, and improve synaptic plasticity. In addition, studies have shown that the extraction areas of glycyrhiza flavonoids have obvious antidepressant activity in mice, and its mechanism may be related to the enhancement of central 5-HT functional and neurological functions.

Bohe (Mentha Herba): L-menthone has antidepressant effects, and its antidepressant mechanism may be related to the inhibition of the overactivation of HPA axis and the promotion of BDNF expression in the cerebral cortex.

**Research Status of Danzhi Xiaoyao Powder**

TCM therapies are characterized by embodying the concept of holism and syndrome differentiation and treatment through the combination or compatibility of prescriptions. In clinical practice, Danzhi Xiaoyao powder is often modified to be more suitable for the pathogenesis and changes of the disease condition. Tian and Li added seven kinds of herbs on the basis of Danzhi Xiaoyao Powder, namely, Yujin (Curcumae Radix), fried Suanzaoren (Ziziphi Spinosae Semen), Baiziren (Platycladi Semen), Yejaoteng (Caulis Polygoni Multiflori), Hehuang (Albiziae Cortex) and Yejiaoteng (Caulis Polygoni Multiflori) to disperse the liver and strengthen the spleen. Liu et al. found that atractylone, atractylonolide I and atractylonolide III could activate blood and qi, resolve phlegm and induce resuscitation. The prescription was based on Danzhi Xiaoayao decoction to disperse the liver and strengthen the spleen. Fied Suanzaoren (Ziziphi Spinosae Semen), Baiziren (Platycladi Semen), Yejaoteng (Caulis Polygoni Multiflori), Yuanzhi (Polygalae Radix) and Shichangpu (Acori Tatarinowii Rhizoma) can nourish the heart and calm the mind, and Longgu (Dracoris Os) and Mulii (Ostreae Concha) can suppress yang and calm the heart and mind. The whole prescription was used to relieve liver qi stagnation, nourish the heart, and calm the mind. Chen added Shichangpu (Acori Tatarinowii Rhizoma), Yujin (Curcumae Radix), and Yuanzhi (Polygalae Radix) on the basis of Danzhi Xiaoayao powder. He believed that Shichangpu (Acori Tatarinowii Rhizoma) and Yujin (Curcumae Radix) could relieve depression and regulate the mind, Yuanzhi (Polygalae Radix) could calm the heart and mind and open the orifices, and the whole prescription could relieve the liver depression and induce resuscitation. On the basis of Danzhi Xiaoayao Powder, added Hehuang (Albiziae Cortex) and Yejiaoteng (Caulis Polygoni Multiflori) to nourish blood and calm the mind, aiming at harmonizing the viscera, regulating qi, and promoting blood circulation so as to calm the mind.

**Exploring the Efficacy and Mechanism of Supplemented Danzhi Xiaoayao Powder in the Treatment of Depression Based on the Theory of “Liver–Brain Cotreatment”**

We believe that depression, as an emotional disease, affects the liver, hampering the function of conveyance and dispersion as
the basic pathogenesis. As the residence of the primordial spirit, the brain also plays a key role in regulating human’s spirit and thinking. It can be seen that depression is most related to liver and brain. The brain is the pivotal part of life, which dominates the life activities of the human body. As it is said in the Cun Shou Jiu Gong Tai Yi Zi Fang Jue, “the brain is the spiritual clan of the whole body, the life of all spirit.” The brain is in charge of the mental activities of the human body, including thinking, consciousness, and emotional activities. These are the results of objective things reflected in the material-based brain. According to Categorized Patterns with Clear-Cut Treatments (Lei Zheng Zhi Cai), it says: “The brain is the residence of the primordial spirit, the sea of essence, and the basis of memory.” In Corrections of Errors of Medical Works (Yi Lin Gai Cuo), it also recognizes that “spiritual memory is not in the heart but in the brain.” Liver governs dredging, regulates qi movement, and stores blood. Harmonious qi and blood promote clear mind and spirit; abnormal dispersion, liver-q depression, or hyperactivity will lead to mental or emotional disorder. In the long-term clinical practice, our research group put forward the theory of “liver–brain cotreatment” for depression. It is believed that the disease location of depression is in the liver and brain, and the main pathogenesis is “brain and spirit failure and liver failing to disperse”; it emphasizes that the liver is the source of the disease, and the brain is the transmission place of the disease. The primordial spirit disorder aggravates the failed dispersion of the liver, which are evil to each other and lead to the onset of emotional disorders. And thus “clearing the liver and relieving depression, strengthening the brain and benefiting intelligence” is its important therapeutic principle.64,65

Under the guidance of the theory of “liver–brain co-treatment,” the research group added Shichangpu (Acori Tatarinowii Rhizoma) on the basis of Danzhi Xiaoyao powder to open the orifices and Yuanzhi (Polygalae Radix) to tranquilize the mind and benefit intelligence. The combined prescription of supplemented Danzhi Xiaoyao powder has been prepared as an in-hospital preparation of the First Affiliated Hospital of Henan University of Chinese Medicine. In the long-term clinical application, 60 patients with depression were treated with supplemented Danzhi Xiaoyao powder and Fluoxetine. The efficacy showed that the total effective rate of supplemented Danzhi Xiaoyao powder was 90%, while the effective rate of Fluoxetine was 76.67%, with a statistical difference.66 After 8 weeks of administration, the total effective rate of supplemented Danzhi Xiaoyao powder combined with umbilical cord mesenchymal stem cells in the treatment of poststroke depression was significantly higher in the supplemented Danzhi Xiaoyao powder group than that in the control group.67 Besides, the previous animal experiments of this research group found that supplemented Danzhi Xiaoyao powder could increase the content of 5-HT and NE in the hypothalamus of depression rats, reduce the level of CORT and ACTH in plasma, and regulate the protein expression of glucocorticoid receptors and mineralocorticoid receptors in the hippocampus. Ultrastructural results showed that chronic stress could cause mitochondrial swelling and vacuolar degeneration to hippocampal cells, while supplemented Danzhi Xiaoyao powder could reduce hippocampal neuronal damage caused by stress.68–71

Conclusion
Depression, as a seriously harmful mental disease, has become a global public health problem. Antidepressants commonly used in clinical practice are ineffective in more than 1/3 of patients with severe depression, and they often have many side effects. Chinese herbs have unique advantages in the prevention and treatment of depression based on the characteristics of holistic concept and syndrome differentiation and treatment. Liver depression and spleen deficiency syndrome is the main syndrome pattern of depression. Danzhi Xiaoyao powder has the efficacy of soothing the liver and relieving depression, nourishing blood, and strengthening the spleen, which is exactly suitable for the syndrome of liver depression and spleen deficiency. Previous basic and clinical studies have confirmed the antidepressant effect of Danzhi Xiaoyao powder. The research studies on the pharmacodynamic material basis found that the main active ingredients of Danzhi Xiaoyao powder in the treatment of depression include bupleurum saponin, paenol, gardenoside, gardenia total iridoid, angelica polysaccharide, ferulic acid, turpentine ferulate, tuckahoe sulfate polysaccharide, paenoflorin, alibiflorin, atractylenolide (I, II, III), liquiritin, glycyrrhiza flavonoids, L-menthol, etc. In the long-term clinical practice, our research group found that “brain and spirit failure and liver failing to disperse” were the main pathogenesis of depression. We put forward the theory of “liver–brain cotreatment” for depression, emphasizing that the liver was the source of the disease and the brain was the transmission place of the disease. Based on the theory of “liver–brain cotreatment,” the treatment principle of “relieving liver depression, strengthening brain, and benefiting intelligence” was further put forward. On the basis of Danzhi Xiaoyao powder, Shichangpu (Acori Tatarinowii Rhizoma) was added to enlighten the mind and Yuanzhi (Polygalae Radix) to calm the mind and benefit intelligence, and thus this combined prescription was the supplemented Danzhi Xiaoyao Powder. The clinical application of supplemented Danzhi Xiaoyao powder in the treatment of depression has been 16 years, and the clinical effect is significant. Animal experiments also confirmed that supplemented Danzhi Xiaoyao powder can significantly improve the depression-like behavior of depression model rats. It is preliminarily found that its mechanism may be related to the regulation of HPA axis and the increase of 5-HT and NE content. To sum up, the theory and experimental study on the “liver–brain cotreatment” of depression with supplemented Danzhi Xiaoyao powder performed by our research group not only help to innovate and develop the theory of TCM but also broaden the thoughts for the clinical treatment of depression.

CRediT Authorship Contribution Statement
Yajing Li: Writing—original draft, and investigation. Baoying Wang: Data curation, Formal analysis, and investigation. Yucheng Li: Methodology, Supervision, and...
writing-review & editing. Ming Bai: Project administration, and supervision. Erping Xu: Conceptualization, funding acquisition, and supervision.

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Conflict of Interest
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