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Research Progress on the Treatment of Depression with Chinese Herbal Medicine

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Abstract: Depression is a common affective disorder characterized by significant and persistent low mood. Traditional Chinese medicine (TCM) attributes depression to emotional disturbances, classifying it as a mood disorder. Chinese herbal formulas have unique advantages and higher safety profiles in treating depression, despite challenges such as complexity in herb combinations, varying efficacy, and potential side effects. Currently, Chinese patent medicines and decoctions are widely used in the clinical treatment of depression, yielding positive results. This article summarizes recent research on the pharmacological effects of Chinese herbal formulas and single herbs with antidepressant properties, analyzing them from three aspects: chemical composition, pharmacological mechanism, and adverse reactions. The aim is to provide references for the clinical application of Chinese herbal formulas in treating depression and to suggest directions for future research.

Keywords: Depression; Chinese herbal medicine treatment; Yixinshu capsule

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1. Introduction

Depression, also known as depressive disorder, is a common mental illness characterized by low mood, slowed thinking, and reduced volitional activities. The WHO has listed it as a global cause of disability. According to statistics, in 2023, approximately 340 million people worldwide suffered from depression, and about 800,000 people died by suicide every year. Modern medicine believes that depression is caused by various factors such as genetic factors, neuroendocrine dysfunction, and psychosocial factors. Its clinical manifestations include poor mood, lack of interest, anhedonia, sleep disorders, fatigue, and weakness [1]. The understanding of depression in traditional Chinese medicine began with the "Yellow Emperor's Inner Canon." It is believed that "the heart governs the mind", and emotions such as "happiness, anger, worry, contemplation, sadness, fear, and surprise" can all lead to abnormalities in human consciousness [2]. Clinically, traditional Chinese medicine considers depression

a category of emotional disorders. The etiology and pathogenesis are caused by emotional dysregulation. Prolonged illness can lead to the formation of phlegm and turbidity, qi and blood stagnation, and the development of symptoms such as abdominal masses. The disturbance of qi movement can cause liver dysfunction, affecting the spleen. Prolonged illness can also harm the kidneys, leading to kidney yang deficiency, abnormal fluid metabolism, and endogenous phlegm turbidity, resulting in symptoms of blood stagnation and depression. For patients with depression, not only is effective drug treatment needed, but also emphasis on self-emotion regulation to restore the body to a state of yin-yang balance. Traditional Chinese medicine has a long history of treating depression. Doctors of past generations have accumulated rich experience in long-term clinical practice and summarized a series of prescriptions for the treatment of depression, such as Xiaoyao powder, Si Junzi decoction, Chaihu Shugan powder, Suanzaoren decoction, Ganmai Dazao decoction, Zhuru Daotan decoction, Yueju Pill, and Longdan Xiegan pill [3]. Additionally, traditional Chinese medicine can exhibit antidepressant effects by improving patients' cognitive function, enhancing their motor abilities, reducing pain symptoms, and alleviating anxiety [4]. However, there are issues such as repeated medicinal flavors, unreasonable drug combinations, and unstable efficacy in compound prescriptions of traditional Chinese medicine [5–7]. In recent years, with the continuous improvement of scientific research, many scholars have begun to pay attention to the clinical treatment effects of traditional Chinese medicine compounds on depression and have achieved good results, but there are still some limitations. This article mainly introduces the research achievements of traditional Chinese medicine monomers and compounds in the treatment of depression in recent years, aiming to provide references for the further development of traditional Chinese medicine in the treatment of depression in the future.

2. The role of traditional Chinese medicine in depression

Depression is a disease caused by multiple etiologies, primarily manifesting as a low mood. It can be classified into unipolar depression and bipolar depression, and is often treated with medication in clinical practice [8]. Traditional Chinese medicine (TCM) is an essential component of traditional Chinese medical science. Its long history, significant efficacy, low toxicity and side effects, no drug resistance, and low dependence have made it widely used in modern medical fields [9].

According to TCM theory, depression is caused by injury from the seven emotions (happiness, anger, worry, contemplation, sadness, fear, and surprise), leading to an imbalance of qi, blood, yin, and yang in the internal organs. The disease originates in the heart and is closely related to the liver, spleen, and kidneys [10]. The main pathological characteristics of depression include "irregular qi in the early stages of the disease, improper diet, excessive labor or leisure, and external and internal aggressions" [11]. Based on different causes, depression can be classified into three syndrome types: liver qi stagnation, phlegm-heat accumulation, and blood stasis obstructing the collaterals [12]. Starting treatment from the pathogenesis can achieve better results. TCM has unique advantages in treating depression. Compared with Western medicine, TCM emphasizes holistic concepts and syndrome differentiation and treatment, emphasizing the idea of "preventing disease before it occurs." Through non-drug treatment methods such as psychological counseling, emotional regulation, and dietary adjustment for patients, it can significantly improve patients' depressive state [13]. Additionally, due to its multi-target and multi-pathway effects, traditional Chinese medicine has been increasingly studied. In recent years, many researchers have dedicated themselves to developing safe and effective antidepressant traditional Chinese medicines.

3. Antidepressant mechanisms of traditional Chinese medicine

TCM exhibits multi-target and multi-pathway characteristics, exerting antidepressant effects through mechanisms such as regulating neurotransmitter systems and antioxidant stress.

3.1. Plant extracts

Yu Xiaowen's research found that flavonoids from Schizonepeta tenuifolia could increase brain-derived neurotrophic factor (BDNF) and glutamate receptor protein levels in the hippocampus of chronically stressed rats, improving depressive-like behaviors [14]. Genistein significantly increased the expression of BDNF and CREB in rat brain tissue induced by D-galactose, promoting synapse growth [15]. Hang Huaqian et al. observed the treatment of a rat model of depression with coptisine extracts. The results showed that the treatment group had better heart rate variability and physical function recovery than the control group, indicating that coptisine extracts have good prospects in treating depression [16].

3.2. Compound preparations of traditional Chinese medicine

The Chinese Pharmacopoeia lists Chaihu Shugan powder as a commonly used formula for treating symptoms caused by liver qi stagnation, such as chest and hypochondriac discomfort, irritability, or menstrual disorders, and it has a clear antidepressant effect. Bai Limin used a self-made Chaihu Shugan powder to treat depression and found that it could effectively relieve depressive symptoms and improve patients' hemorheological indicators and dyslipidemia, indicating that this compound has good efficacy and safety in treating depression [17]. Chaihu decoction consists of four herbs: Bupleurum, *Paeoniae Radix Alba*, ginger, and jujube, and can be used to treat liver qi stagnation and spleen deficiency type depression. Li Yue et al. randomly divided Chaihu decoction combined with Xiangfu Shugan powder into two groups: Chaihu decoction and Xiangfu tablets. They compared changes in the Hamilton Depression Rating Scale (HAMD) scores, physical function, and cerebral blood flow after treatment in each group. The results showed that Chaihu decoction combined with Xiangfu tablets significantly improved HAMD scores, physical dysfunction, and reduced cerebral blood flow in a depressive state, indicating that this compound preparation of traditional Chinese medicine has an antidepressant effect [18]. Furthermore, Li Dongfang believes that Chaihu Shugan powder has the effects of improving anxiety-like behaviors, regulating glucocorticoid secretion, and improving immune function and central nervous system function [19].

3.3. Single herbs

3.3.1. Trazodone hydrochloride

Trazodone hydrochloride is a benzothiazole compound extracted from the roots of the leguminous plant *Viola yedoensis*, which exhibits high analgesic activity. It acts on the dorsal root ganglion (DRN) of the spinal cord, inhibiting the release of norepinephrine, dopamine, and 5-hydroxytryptamine, thereby achieving an antidepressant effect. Studies have found that trazodone hydrochloride has a protective effect on intestinal mucosal damage caused by trichloroacetic acid in rats, indicating its good gastric mucosal protective effect and ability to prevent intestinal damage caused by aluminum trichloride [20]. Cai Congcong studied a mouse model of chronic unpredictable mild stress induced by D-galactose and found that trazodone hydrochloride has certain antidepressant effects, as well as various pharmacological effects such as anti-inflammatory, anti-oxidative stress, and improving microcirculation [21]. Ding Meiling and others reported the protective effect of trazodone hydrochloride on a mouse model of acute poisoning induced by carbon tetrachloride, showing that the drug has good antioxidant effects [22]. In summary, trazodone hydrochloride has demonstrated beneficial effects in areas

such as anti-oxidative stress and neuroprotection.

3.3.2. Yixinshu capsule

Yixinshu capsule is a traditional Chinese medicine primarily used as an adjuvant treatment for cardiovascular diseases. However, its ingredients, such as ginseng, danshen, and schisandra, have the effects of nourishing qi and restoring pulse, promoting blood circulation and removing blood stasis, and calming the nerves. In recent years, research on its use in the treatment of depression has gradually gained attention. The ingredients of the Yixinshu capsule may improve depressive symptoms through multiple pathways. For example, studies have found that Yixinshu capsule can treat depression by regulating neurotransmitters, mainly due to ingredients like danshen and schisandra that may adjust levels of 5-HT (serotonin), DA (dopamine), and NE (norepinephrine), thereby improving neurotransmitter concentrations in the synaptic cleft [23]. Research has shown that patients with depression often suffer from chronic inflammation and oxidative stress, and components like tanshinone and ginsenoside have anti-inflammatory and free radical scavenging effects. Studies have found that Yixinshu capsule can reduce stress responses by inhibiting the excessive activation of the hypothalamic-pituitary-adrenal axis (HPA axis) [24]. Additionally, it promotes the expression of brain-derived neurotrophic factor (BDNF), protecting neuronal function [25]. Research indicates that Yixinshu capsule, when combined with conventional antidepressants (such as SSRIs), can enhance treatment efficacy, improve symptoms such as low mood and fatigue, and has fewer adverse reactions [26]. For depression patients with comorbid cardiovascular diseases (like coronary heart disease), Yixinshu capsule may exert a synergistic effect through the “simultaneous treatment of heart and brain.” Studies have shown its significant effect on symptoms associated with depression, such as insomnia, palpitations, and shortness of breath [27]. In chronic stress depression models, Yixinshu capsule can reduce depressive-like behaviors (e.g., immobility time in forced swimming tests), and its mechanism may be related to regulating gut microbiota and inhibiting the TLR4/NF-κB inflammatory pathway [28]. Through ingredient-target-pathway prediction, it has been found to potentially act on inflammatory factors like IL-6 and TNF-α, as well as pathways related to neural plasticity. Yixinshu capsule demonstrates certain potential in the treatment of depression, particularly in subtypes associated with comorbid cardiovascular diseases or inflammation, although its clinical application still requires more high-quality evidence to support it.

4. Adverse reactions

Currently, the compound Chinese medicines used clinically to treat depression are mainly Chinese patent medicines. According to statistics from the National Center for Monitoring Adverse Drug Events (cde-center.org), there have been 594 reported cases of adverse events related to Chinese patent medicines for depression since 2016. Among them, adverse events related to nervous system drugs have the highest incidence, followed by cardiovascular, digestive, psychoactive, and respiratory system drugs. This is related to the complex composition and multiple herb combinations in the compounds [29]. For example, Chaihu Shugan powder, which contains herbs such as white peony root, angelica, atractylodes, and licorice, has the effect of dispersing stagnated liver qi and relieving qi stagnation, so it is prone to cause gastrointestinal adverse reactions [30]. Mahuang Fuzi Xixin decoction contains herbs such as aconite, asarum, and ephedra, which have serious toxic and side effects. In particular, aconite can cause arrhythmia and even death [31]. Xiaoyao Powder contains angelica, poria, atractylodes, bupleurum, mint, ginger, platycodon, cape jasmine, alismatis, and licorice, which may cause liver damage,

abnormal liver function, or aggravated liver injury [32]. Additionally, some compound Chinese medicines contain aristolochic acid, which can produce reactive metabolites such as dihydroxyaristolochic acid during metabolism in the body [33]. These reactive substances can cause renal toxicity, neurotoxicity, carcinogenicity, and mutagenic effects, leading to diseases such as renal failure, neural deafness, bladder cancer, and liver cancer [34].

The adverse reactions of the aforementioned Chinese medicines are closely related to their dosage, and as the treatment course increases, the adverse drug reactions show a gradual decreasing trend. Therefore, selecting the appropriate dosage and treatment course is an important measure to reduce adverse drug reactions. In addition, most Chinese patent medicines are currently extracted and prepared manually, with a simple process that is prone to contamination. Production management is not standardized, and drug quality is difficult to ensure [35]. Moreover, most Chinese patent medicines have complex components and too many medicinal flavors, which brings difficulties to clinicians in differential treatment based on syndrome differentiation, thereby affecting patient compliance with medication [36]. Therefore, it is necessary to strengthen the standardization of Chinese medicine pharmaceutical technology to ensure the production of safe and effective Chinese medicine preparations.

5. Conclusion

This article summarizes the research progress on the treatment of depression with Chinese medicine as follows: The therapeutic mechanism of compound Chinese medicines mainly includes alleviating depressive symptoms by regulating neurotransmitters, brain-derived neurotrophic factor (BDNF), and 5-hydroxytryptamine (5-HT) levels; inhibiting monoamine neurotransmitter receptors, dopamine transporters, and acetylcholinesterase, and promoting monoamine oxidase activity; affecting the balance between excitation and inhibition of the central nervous system; and reducing the production of oxidative stress products and inflammatory cytokines.

In summary, compound Chinese medicines for the treatment of depression have advantages such as fewer side effects and low cost, but clinical research is still needed. Due to differences in age, gender, and etiology of depression patients, a single prescription or compound Chinese medicine cannot meet the needs of all patients, and combination therapy has become a new trend in antidepressant drug development at home and abroad. Therefore, individualized treatment should be adopted for the treatment of depression, and the best treatment plan should be formulated after a comprehensive analysis based on the patient's physical condition, course of disease, and past history. At the same time, when selecting appropriate medicinal materials, strict quality standards should be implemented to ensure efficacy. With the development of modern science and technology, continuous research on compound Chinese medicines will bring opportunities for the development of traditional Chinese medicine in China.

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