

Advances in clinical and experimental research on xiaoyao powder in brain disorders

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Abstract: Xiaoyao Powder is composed of Radix Bupleuri, Radix Angelicae Sinensis, Radix Paeoniae Alba, Radix Glycyrrhizae, Rhizoma Atractylodis Macrocephalae, Poria, Ginger and Mentha haplocalyx. It has the effects of soothing liver and relieving depression, nourishing blood and invigorating spleen. It is a classic prescription for harmonizing liver and spleen and is widely used in clinical practice. Modern clinical studies have confirmed that this prescription has a good therapeutic effect on post-stroke depression, dementia, headache and other brain diseases, but its components are numerous, the mechanism of action is complex, and the research results are scattered. Therefore, the author focuses on the main treatment of brain diseases. Combined with the results of modern experimental research, the mechanism of action of the active components related to single herbs in the prescription and the clinical application of the compound application of the compound induction and collation, the mechanism of action and experimental research status of the prescription were further clarified, providing valuable reference for the majority of physicians in clinical application.

Keywords: xiaoyao powder; brain diseases; mechanism of action

Xiaoyao powder is a famous formula in ancient times in China, which has the effect of relieving liver depression, nourishing blood and strengthening spleen, and is often used clinically for the evidence of liver depression, blood deficiency and spleen weakness, so it is widely used clinically, and many effective formulas have been derived from it in later times, such as Black Xiaoyao powder, Dan Gardenia Xiaoyao powder, etc. Chinese medicine pays attention to dialectical treatment, and "if there is evidence, use the formula", As a result, this formula is also commonly used in the progression of many common brain disorders and has been validated in pharmacological and clinical trials. However, due to the complex pathogenesis and the multi-target therapeutic effect of traditional Chinese medicine, the role of xiaoyao powder in the treatment of brain diseases is still unclear. Therefore, this paper is intended to provide a reference for clinical and experimental research.

1. The recognition of xiaoyao powder in traditional medicine

The origin of xiaoyao powder was first described in the Song dynasty in the "Bureau of the Pacific Huimin and Medicine Formula", and was derived from the variations of four inverse powder and Angelica Paeoniae San in the "Treatise on Typhoid Fever" [1], and its name was explained by Wang Ang in the "Collection of Medical Formulae" in the Qing dynasty: Liver deficiency leads to blood disease, Angelicae and Paeoniae nourish blood and astringent yin; wood flourishes, earth declines, Gan Cao and Bai Zhu harmonize the middle and tonify earth; Chai Hu rises Yang and dissipates heat, and combines with Paeoniae to calm the liver, so that wood gets The heart Qi is tranquilized; ginger warms the stomach and dispels phlegm, regulates the middle and relieves depression; peppermint searches the liver and diarrhea the lung, regulates blood and eliminates wind^[2]. Xiaoyao powder is a representative prescription for soothing liver and relieving depression, nourishing blood and invigorating spleen. The liver governs catharsis and hides blood, likes to reach and hates depression. If the liver qi is depressed, the qi movement is not smooth, and all diseases are caused by the disease. Bupleurum is the monarch drug in the prescription. Its Xinsan is lightly raised, straight into the liver and gallbladder meridian, soothing the liver and relieving depression, Zhishi relieving depression, purging heat and breaking knots, matching with Bupleurum, one rise and one drop, to restore the balance of qi movement, Atractylodes, Poria, Ginger, Licorice, invigorating the spleen and tonifying the middle, transforming qi

and blood, to help the liver body, Angelica, Paeoniae Radix Alba nourishing blood and yin, to help the liver, all drugs play the role of nourishing blood, invigorating the spleen and soothing the liver [3]. Xiaoyao powder is also a common formula used in gynecology to regulate menstruation. In women, the liver is the precursor, the liver collects blood and is the master of drainage. If the liver is depressed, the blood is deficient and the spleen is weak, the collection of diarrhea is out of order and the qi and blood are disordered, then menstruation cannot come on time. xiaoyao powder can make qi and blood, menstruation on time. This formula has been used for the regulation of menstruation in gynecology for many years, and many new formulas have been developed based on this formula. Such as Xuan Yu Tong Jing Tang and Ping Liver Open Depression Stopping Blood Tang.

2. Recognition of xiaoyao powder in brain system diseases

In modern society, the pace of life is accelerating, and people are facing more and more pressure of life and work, so the rate of mental and emotional factors is increasing. Being in the mood of anger or pessimistic depression for a long time makes liver qi stagnant, and qi stagnation turns into fire, which leads to liver wind and easily triggers dizziness and stroke, etc. The loss of liver drainage can also lead to the loss of spleen health, phlegm and dampness, and loss of harmony between qi and blood, which can easily lead to headache and dementia. This can lead to headache and dementia. For example, Chen Shiduo in "Dialectical Record" believes that wood depression and earth failure, phlegm and turbidity are internally generated, phlegm dreams the clear orifices, and the development of dementia, that is, "the depression of both long becomes dull", so modern doctors in the treatment of brain diseases pay attention to dredging the liver and relieving depression, regulating the qi flow, and often choose to add and reduce the use of xiaoyao powder, have achieved good therapeutic results.

3. The active ingredients and mechanism of action of each single bit of medicine

3.1 Chai Hu

The active medicinal components of Chai Hu are chemical components such as saponins, volatile oils, and coumarins, which have pharmacological effects such as anti-inflammatory, analgesic, hepatoprotective, and antidepressant^[4]. A large number of studies have now shown that cholinomimetic activates the hypothalamic-pituitary-adrenal axis (HPA axis) and elevates cortisol hormones to cause depression, while studies have confirmed that chaihu saponin xi significantly reduces the protein expression and activity of AChE and ChAT in the hippocampus of rats and inhibits apoptosis of neuronal cells in the hippocampal region. The results suggest that chaihu saponin may exert antidepressant effects by decreasing the activity of the cholinergic nervous system and elevating the level of 5-mono-HT hormone, or by regulating the cholinergic nervous system to inhibit hypothalamic-pituitary-adrenal axis activation and decrease cortisol levels, thus antagonizing depression^[5]. In addition, chaihu saponin can also inhibit the expression of spase-3 and caspase-9 thereby delaying the onset of apoptosis to alleviate depressive symptoms^[6]. In addition, chaihu saponin has strong anti-inflammatory activity, mainly by inhibiting the expression of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 and enhancing the expression of anti-inflammatory cytokines transforming growth factor TGF- β 1 and IL-10, which contribute to the recovery of brain damage areas in depressed patients after stroke^[7].

3.2 White peony

Paeonia lactiflora is the dried root of *Paeonia lactiflora* (*Paeonia lactiflora* Pall.), family Buttercup, and the main components include volatile oils, monoterpenes, triterpenes, etc, with a wide range of pharmacological effects, including antispasmodic, analgesic, anticonvulsant, immunomodulatory and vasodilator, anti-platelet agglutination^[8], and related studies have shown that the levels of inflammatory factors such as c-reactive protein, TNF- α , and IL-6 in depressed patients are significantly. and the extract of *Paeonia lactiflora* may produce antidepressant and anti-inflammatory effects by acting on the monoamine transmitter system to inhibit the targets of inflammatory factors in which they act^[9], which also provides new ideas for the study of post-stroke depression. In addition, total peony glycosides can up-regulate Bcl-2 protein expression and down-regulate Bax expression in hippocampal region and increase Bcl-2/Bax, while increasing SOD and catalase (CAT) activities, decreasing MDA content, improving hippocampal neuronal pathological changes and inhibiting its apoptosis^[10].

3.3 *Angelica sinensis*

Angelica sinensis is the dried root of *Angelicasinensis* (Oliv.) Diels, family Umbelliferae^[11], and its main chemical components include volatile oil, flavonoids, amino acids, organic acids and polysaccharides, which have anti-inflammatory, anti-tumor and immune modulating effects^[11], among which angelica polysaccharide (ASP) can significantly increase lipopolysaccharide (LPS)-induced PC12 cell survival and reduced apoptosis, while significantly decreasing the expression of TNF- α , IL-1 β , IL-6 and IL-8 mRNA and protein in LPS-induced PC12 cells; in addition, ASP activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway by down-regulating cyclooxygenase-1 (COX-1) protein expression in LPS-induced PC12 cells, resulting in a significant increase in p-PI3K and p-Akt protein expression, thus providing a good protection against neuroinflammatory diseases^[12], and in a study by ZHOU et al^[13], ASP was found to be able to block the activation of NF- κ B and JAK2/STAT3 signaling pathways by upregulating the expression of mir-10a in LPS-induced HT22 cells, attenuating LPS-induced inflammatory damage to exert antiepileptic effects. Ferulic acid is also one of the main active components of *Angelica*, which has pharmacological effects such as anti-inflammatory, anti-thrombotic and anti-platelet aggregation^[14].

3.4 *Atractylodes macrocephala*

Atractylodes macrocephala Koidz. is the dried rhizome of *Atractylodes macrocephala* Koidz. in the family Asteraceae^[15], and the main components are volatile oils, polysaccharides, endolipids, and glycosides, which have good neuroprotective effects, among which *Atractylodes* endolipid III can inhibit caspase signaling pathway and reduce caspases-3 expression activity, thus exerting anti-neuronal apoptosis effects^[16], and also improves neuronal apoptosis and mitochondrial autophagy due to excessive mitochondrial fission of neurons^[17]. In addition, *Atractylodes macrocephala* polysaccharide can participate in the Bcl-2/Bax signaling pathway, increase the expression level of anti-apoptotic proteins, and exert an inhibitory effect on neuronal hypoxic apoptosis^[18]. In a depressed mouse model, *Atractylodes macrocephala* extract reduced hippocampal 5-hydroxytryptamine and norepinephrine expression, decreased inflammatory cytokine IL-1 β production, and significantly improved depression-like behavior in mice^[19]. In the MACO rat model, *Atractylodes* reduced mRNA and protein expression of inflammatory factors (IL-1 β , TNF- α , and IL-6), inhibited the JAK2/STAT3 pathway, and decreased power-related protein 1 (Drp1) phosphorylation levels^[20], acting as an inhibitor of neuroinflammation as well as preventing cerebral ischemia^[21].

3.5 *Poria cocos*

The main chemical components of *Poria cocos* are triterpenoids and polysaccharides, which have certain neuroprotective effects. It has also been reported that *Poria* can improve the learning memory ability of mice with memory impairment caused by phenobarbital, and also has obvious sedative and hypnotic effects^[22-23]. 5-HT and BDNF play an important role in the body's emotional expression, cognition and other physiological functions, and the abnormalities of their expression can be used as an observational indicator of post-stroke depression. In a depression model, *Poria* acidic polysaccharide increased the levels of BDNF, 5-HT, 5-HIAA, DA and NE in the hippocampus of rats, and significantly reduced the levels of GLU, thus exerting an antidepressant effect to a certain extent. In addition, it can also inhibit the NLRP3 inflammatory vesicle pathway by regulating the level of NLRP3-related mRNA and protein expression, which can play a role in inhibiting the inflammatory response and alleviating cell damage^[24]. Yu^[25] et al. found that *Poria* aqueous decoction has a clear anxiolytic effect, which may be related to reducing the level of excitatory amino acid neurotransmitter GLU and enhancing GABAAR α 1 receptor expression to maintain neurotransmitter levels in the brain.

3.6 *Licorice*

Glycyrrhiza glabra belongs to the legume family, and its main chemical components are flavonoids, saponins, alkaloids, amino acids, coumarins, and polysaccharides^[26], which have anti-inflammatory, anti-tumor, anti-viral, hepatoprotective, and neuroprotective effects^[27]. Modern pharmacological studies have confirmed that glycyrrhizin can effectively inhibit the release of inflammatory factors IL-1 β and TNF- α from cells in Alzheimer's disease models^[26], and that glycyrrhizin and resveratrol glycosides have high binding power to dopamine receptor D3 (DRD3) and are thought to be potential drugs for the treatment of neurodegenerative diseases in Alzheimer's disease^[28]. In a mouse model of depression, treatment with glycyrrhizin and isoglycyrrhizin significantly reduced the ratio of

5-HIAA/5-HT in the hippocampus, hypothalamus, and cortex of mice, slowed down 5-HT metabolism, and had a significant antidepressant effect^[29], in addition to the finding that glycyrrhizin can treat chronic depression through the PI3K/Akt/mTOR-mediated BDNF/TrkB pathway, which provides more possibilities for the treatment of depression^[30].

3.7 Ginger

Ginger is a medicinal and dietary herbal medicine, and its main pharmacological components include volatile oil, curcumin, ginger essential oil, and diphenylheptane^[31], among which ginger volatile oil can inhibit apoptosis of neuronal cells in a rat model of cerebral ischemia-reperfusion by blocking the lysosomal-mitochondrial pathway, thus exerting a protective effect against brain injury^[32]. Another component, total ginger phenol, protects against focal cerebral ischemic injury in rats by improving brain tissue metabolism, scavenging free radicals, and inhibiting neuronal apoptosis, reducing the size of cerebral infarcts and improving neurological symptoms^[33], and Zhang^[34] et al. also found that ginger may reduce brain tissue edema and neurological damage symptoms by inhibiting the expression of HIF1 α protein and NHE1 protein, and play a protective effect.

3.8 Peppermint

Peppermint is classified as a wind-heat dispersant in Chinese medicine, with volatile oils, flavonoids, and terpenoids as the main chemical components, and modern pharmacological studies have confirmed antibacterial, antiviral, and antioxidant effects^[35]. One of the main components of peppermint, 1,8-eucalyptene, is an N-methyl-D-aspartate (NMDA) antagonist that could provide a new strategy for the treatment of Alzheimer's disease^[36], and another major component, L-menthol (LM), has been shown to exert antidepressant effects by mediating dopaminergic, 5-hydroxytryptaminergic, and γ -aminobutyric acidergic systems, and Liang also found that administration of pentobarbital sodium-induced sleep to After inhalation of peppermint oil, mice showed significantly shorter sleep time, suggesting a good wake-promoting effect, which may be related to increased Glu/GABA ratio expression in hypothalamus and cortex^[37].

4. Use in brain system diseases

4.1 Post-stroke depression

Post-stroke depression belongs to the combined disease of stroke and depression syndrome in traditional Chinese medicine. It is a common mental and emotional disorder secondary to stroke. At present, the pathogenesis is not clear, mainly including monoamine theory and inflammation theory^[38]. Recent studies have found that Xiaoyaosan may play an antidepressant role by regulating the inflammatory factor pathway, down-regulating the levels of iNOS and TNF- α , up-regulating the level of IL-10 to reduce neuronal apoptosis in PSD rats, and improving immune regulation and oxidative stress injury^[39]. Xiaoyaosan can also be combined with electro-nape acupuncture to reduce the level of glutamate in patients. Improve the patient's motor function and depression^[40]. The monoamine neurotransmitters NE and 5-HT are also closely related to the occurrence of post-stroke depression. The destruction of brain neurons after stroke leads to insufficient secretion of monoamine neurotransmitters, which leads to enhanced oxidative stress in the body, thus aggravating neuronal damage and causing depression^[38]. In a group of clinical experiments, it was found that compared with the control group, the level of 5-HIAA in the observation group was lower than that before treatment, and the levels of 5-HT and NE increased after treatment with Xiaoyaosan. After 7 weeks of treatment, the improvement of the observation group was more obvious. This suggests that Xiaoyao Powder may play an antidepressant role by regulating the expression of monoamine neurotransmitters^[41].

4.2 Other brain disorders

Headache is very common among brain disorders, and tension headache is the most common type, the cause of which is still unclear and may be related to autonomic dysfunction, causing the body to produce excessive 5-hydroxytryptamine and catecholamine-like substances, which cause vasoconstriction muscle spasms and persistent head and neck muscle pain^[42-43]. In the clinical observation of Xiaoyao Powder in the treatment of patients with tension headache, the total attack time and attack times of patients were significantly reduced^[44]. Alzheimer's disease is a disease

characterized by progressive cognitive decompensation and belongs to the category of "dementia" in traditional Chinese medicine, and some clinical studies have reported significant effects of Hei Xiaoyao Powder in the treatment of dementia^[45]. Lou et al. identified quercetin, β -sitosterol, and kaempferol as important components for the treatment of Alzheimer's disease, with AKT1, ALB, and MAPK3 as core targets, through a network pharmacology approach^[46]. In addition xiaoyao powder is also very effective in the treatment of dementia^[45], vertigo^[47], and schizophrenia^[48].

5. Conclusion and outlook

As a classical formula for harmonizing the liver and spleen, it is widely used in brain disorders with liver-depression and spleen disharmony as the main pathogenesis^[49]. In this paper, from the perspective of experimental research, the active ingredients and pharmacological mechanisms of its single herbs are elaborated to prove that this formula has good sedative, antidepressant and anxiolytic effects and can effectively prevent and treat cardiovascular and cerebrovascular diseases. However, the current research is limited to the pharmacological effects of the individual herbs in this formula, and there is a lack of exploration of the mechanism of action of the whole formula, which is the direction we will work on next to provide more scientific and higher quality data and theoretical support for the treatment of brain system diseases.

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