

Research Progress of Chaihu Analogous Prescriptions for Insomnia

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Keywords: Chai Hu, Xiao Chai Hu Tang, Chai Hu-like Formula, Insomnia

Abstract: The Chaihu analogous prescriptions is a class of prescriptions represented by Xiao Chai Hu Tang in the Treatise on Typhoid Fever, such as Chaihu-Guizhi-Ganjiang Decoction, Chaihuja Longgu Muli decoction, sini sanand so on. It has been widely used in the clinical treatment of nervous system diseases, and has achieved remarkable results in the treatment of insomnia. This paper summarizes the basic research and clinical application of Chaihu analogous prescriptions in insomnia, aiming to explore the mechanism of action of these prescriptions in the treatment of insomnia and to expand their clinical application, in order to provide more far-reaching ideas for diagnosis and treatment.

Insomnia refers to the subjective experience that patients are not satisfied with the time or quality of sleep and interfere with social function during the day[1]. Sedative and hypnotic drugs commonly used in modern medicine to treat insomnia have good short-term efficacy, but long-term use will have side effects, such as drug tolerance, drug addiction and withdrawal difficulties[2]. Traditional Chinese medicine has a unique advantage in the treatment of insomnia. Although the symptoms of insomnia are diverse, the pathogenesis is related to the unfavorable pivot of Shaoyang and the failure of Yang to enter Yin[3]. The formulae of the Chai-Hu class have the function of regulating the qi flow and balancing yin and yang, and are really effective in treating insomnia. The clinical application of Chai Hu class of prescriptions by later medical practitioners can effectively prevent and treat insomnia [4]. In this paper, we compile the basic and clinical research aspects of Chaihu analogous prescriptions in insomnia with the aim of providing a basis for clinical treatment of insomnia.

1. Xiao Chai Hu Tang

1.1 Basic Research

At present, some clinical depression is often accompanied by or comorbid insomnia, insomnia can further aggravate and complicate the condition. With the deepening of pharmacological research of Xiao Chaihu decoction, its clinical treatment scope has been gradually expanded. Zhang et al.[5] found that Xiao Chaihu decoction can promote hippocampal neurogenesis and reshape the

integrity of the negative feedback loop on the hypothalamus-pituitary-adrenal (HPA) axis, thus reducing the anxiety / depression-like behavior induced by chronic cortisol. Ma Jie et al[6] proved that Xiao Chaihu decoction can significantly regulate depression / anxiety-like behavior induced by chronic social isolation stress (CSIS), and its mechanism may be to activate serotonergic system to promote the expression of neurotrophins in hippocampus. Other researchers have proved that Xiao Chaihu decoction can relieve depression-like behavior during peri-menopausal period and restore 5-hydroxytryptamine (5-HT) and hormones in ovariectomized mice with chronic unpredictable mild stress (OVX-CUMS), which may be related to the functional normalization of HPA / HPO axis and increased expression of tryptophan hydroxylase 2 (TPH2) and estrogen receptor β (ER β) in prefrontal cortex and hypothalamus [7]. Therefore, the application of Xiao Chai Hu Tang not only starts from the perspective of treating insomnia, but also solves the patient's sleep problem by treating the primary disease. We follow the principle of "one evidence is seen, not all", and use it in combination with the different symptoms exhibited, if it fits one of the evidence of Xiao Chai Hu Tang.

1.2 Clinical Study

Zhu Huiyan treated 42 perimenopausal patients with insomnia of liver-depression and spleen-deficiency type with Xiao Chai Hu Tang plus reduction for 7 days as a course of treatment and two courses in total, and found that the total clinical efficiency of Xiao Chai Hu Tang for insomnia was 85.71%, and the total points of Chinese medical evidence of liver-depression and spleen-deficiency type decreased significantly after 2 weeks compared with the pre-treatment period, and it could improve spleen and stomach diseases such as emotional depression causing abdominal distension, less food and dullness, and shorten the time to fall asleep, improve early awakening and prolong the total sleep time [8]. Jin Baohui included 86 patients with Shaoyang tumor with insomnia, randomly divided into two groups of 43 cases each, the treatment group was given Xiao Chai Hu Tang with addition and subtraction, and the control group was given estradiol tablets. The treatment group was given Xiao Chai Hu Tang plus reduction and the control group was given estradiol tablets. It was found that the total efficacy of the TCM symptoms in the Xiao Chai Hu Tang group was 87.5%, compared with 70.0% in the control group, and Xiao Chai Hu Tang plus and minus had better efficacy in treating CRI with Shaoyang tumor, reducing the PSQI score, improving the TCM symptoms, and relieving the main symptoms of patients such as difficulty in falling asleep and sleepiness at night [9]. Song Jun used the general method of harmonizing the central mechanism, relieving depression and regulating the flow of Qi, and applied Xiao Chai Hu Tang with flexible addition and subtraction, as well as the flexible use of clearing heat and fire, resolving phlegm and dispersing knots, and activating blood stasis, in order to smooth the path of Wei Qi out of Yang and into Yin, and order the strength and weakness of Yin and Yang, so as to improve the Shao Yang central mechanism unfavorable type of insomnia [10].

2. Chaihu-Guizhi-Ganjiang Decoction

2.1 Basic Research

It has been demonstrated that Chaihu-Guizhi-Ganjiang Decoction can increase the levels of DA and 5-HT related substances in the hypothalamus and hippocampus, and improve the symptoms of mental restlessness, insomnia and irritability by enhancing the effects on the hypothalamus and hippocampus [11]. Part of the mechanism of action of this formula was found to substantially decrease serum vascular endothelial growth factor (VEGF) and increase 5-hydroxytryptamine (5-HT) when intervening in the treatment of migraine with anxiety in patients with liver-depression

and spleen-deficiency type [12]. Pharmacology has also demonstrated that the pharmacological basis of Chaihu-Guizhi-Ganjiang Decoction for the treatment of insomnia is the 171 active ingredients, including Chai Hu Saponin a and Chai Hu Saponin d [13], which act on various pathways including neuroactive ligand-receptor interactions with 29 targets, such as CACNA1C, to exert the effects of "sparing the liver and strengthening the spleen and harmonizing yin and yang". The network of effects.

2.2 Clinical Study

Zhu Xueqi et al ^[14] used 258 cases of insomnia patients, randomly divided into two groups, the experimental group was treated with Chaihu-Guizhi-Ganjiang Decoction combined with Sour Jujube Ren Tang plus and minus formula, and the control group was treated with placebo orally, and after 8 weeks of treatment, the conclusion showed that the PSQI total score decrease value after treatment was higher than that of the placebo control group, and this formula had significant effect in treating primary insomnia, and it could improve physical health and psychological health. Sun Mingxia ^[15] randomly divided 60 cases of insomnia with Yang energy and heat disturbance into two groups, the treatment group with Chaihu-Guizhi-Ganjiang Decoction and the control group with Shu Sleep Capsules and Sweet Dreams Capsules, and after 4 weeks of treatment, the total efficiency of the treatment group was 86.67% and that of the control group was 80.00%, and the total efficiency and improvement of symptoms of the treatment group were better than those of the control group. The overall efficiency and improvement of symptoms in the treatment group were better than those in the control group, which proved that the basic pathogenesis of Chaihu-Guizhi-Ganjiang Decoction is internal stagnation of lesser fire, deficiency of chest yang and deficiency of fluid, which is summarized as "bile heat and chest cold". Chen Bangshi used Chaihu-Guizhi-Ganjiang Decoction with additional flavor to treat insomnia with liver stagnation and phlegm condensation with good results ^[16], while the control group was given zolpidem tartrate tablets. After 2 weeks of treatment, it was found that the AIS score and TCM evidence score of the observation group were better than those of the control group. This formula can regulate the liver and spleen, regulate the pivotal mechanism of Shaoyang, and calm Yin and Yang. Among them, *Scutellaria baicalensis* with *Gardenia jasminoides* and *Tempeh*, taking the meaning of *Gardenia jasminoides* soup, can clear away heat and relieve depression, supplemented with *Dragon Bone*, *Acacia schoenantha* and *Sour Date Palm* to strengthen the calming effect of the heart and tranquilize the mind.

3. Chaihuja Longgu Muli Decoction

3.1 Basic Research

Chaihuja Longgu Muli decoction has been shown to regulate the hypothalamic-pituitary-adrenal axis (adrenocorticotrophic hormone (ACTH), corticosterone (CORT), etc.) and brain monoamine neurotransmitters (NE, DA, 5-HT, etc.) to improve insomnia symptoms ^[17]. Another study confirmed that Chaihuja Longgu Muli decoction can improve sleep by increasing serum INF- γ and IIL- 1β levels, decreasing IL-4 and IL-10 levels, and increasing the INF- γ /IL-4 ratio to shift the Th1/Th2 balance in the direction of increased Th1 activity in insomniac rats ^[18]. CHJLMD70E, the active ingredient in Chaihuja Longgu Muli decoction ^[19], is able to improve perimenopausal sleep by mediating the ER β /BDNF/TrkB/5-HT2A (estrogen receptor β /brain-derived neurotrophic factor/tyrosine protein kinase receptor B/5-hydroxytryptamine) signaling pathway, which regulates hypothalamic-pituitary-ovarian axis balance ^[20].

3.2 Clinical Study

Liu Jing ^[21] included 82 patients with perimenopausal insomnia divided into an observation group and a control group, with 41 cases in each group. The control group was given estradiol valerate, and the observation group was treated with Chaihuja Longgu Muli decoction plus reduction formula with auricular acupuncture protocol on this basis. After 1 month of treatment, it showed that the sleep quality, clinical efficacy, 5-hydroxytryptamine and dopamine were higher in the observation group compared with the control group. Chaihuja Longgu Muli decoction can tonify Yin and Yang, nourish the heart and calm the mind, and combined with Wang Bu Liu Xing seed auricular pressure point (Shen Men, kidney, subcortical, sympathetic) and other auricular points, through stimulating the points, adjust the body's autonomic nerves, promote 5-HT and DA secretion in order to reduce sleep disorders and effectively regulate neurological functions. For patients with insomnia caused by loss of drainage of the liver and unfavorable central mechanism, Professor Wang Qingguo emphasized the use of the "harmony" method in clinical treatment, i.e., harmonizing yin and yang, harmonizing Ying and Wei, and harmonizing the mind and spirit, and used Chaihuja Longgu Muli decoction to improve insomnia with remarkable efficacy ^[22]. Wang Jialin ^[23] randomly divided 100 patients with phlegm-heat internal disturbance type insomnia into two groups, the control group was given zolpidem and the experimental group was given Chaihuja Longgu Muli decoction plus and minus formula, and after 2 weeks of treatment, it was found that the clinical efficacy of the treatment group was better than that of the control group, and its total PSQI score and total TCM symptoms score were significantly lower than those of the control group, which could improve the symptoms of "easy waking, dreamy" in phlegm-heat internal disturbance. "The PSQI total score and TCM symptoms were significantly lower than those of the control group.

4. Sini San

4.1 Basic Research

Li Yuefeng [24, 25] used polysomnography (PSG) with electrical stimulation to induce insomnia in rats, and analyzed the electroencephalogram (EEG) of rats with insomnia, and found that the lyophilized powder of sini san freeze-dried prolonged SWS2 and REMS and effectively improved insomnia, and it was experimentally proved that the active substances of sini san freeze-dried lyophilized powder were the migrating components of sini san freeze-dried lyophilized powder in the serum, paeoniflorin, synephrine, chaihu saponin C and glycyrrhiza. The active substance is a mixture of paeoniflorin, cynarin, chaihu saponin C and glycyrrhizic acid. sini san freeze-dried powder increased 5-HT content in *Drosophila* brain and improved sleep by increasing the expression of 5-hydroxytryptamine 1A receptor (5-HT1A) [26]. Lili Huang [27] found that sini san freeze-dried powder solution could improve sleep through the following multiple targets: (1) excitation of 5-HT1A (independent of 5-HT2), feedback inhibition of 5-HTergic neurons in the septal nucleus, and reduction of 5-HT release from the septal nucleus; (2) increase of NO levels in the brain and enhancement of nitric oxide synthase (NOS) activity; (3) reduction of TNF- α and IL-1 β levels in whole brain exerted; (4) reduce the level of substance P (SP) exerted in the whole brain; (5) act by acting on benzodiazepine receptors and have similar sedative-hypnotic and muscle relaxation effects mediated by diazepam (DZ).

4.2 Clinical Study

Li Ting-ai used Sinisan as the basic formula, added two medicines, Hanxia and Xia Ku Cao, to balance yin and yang and induce yang into yin, added two medicines, Sour Jujube and Nightshade,

in combination to transport the heart and kidneys, and added raw oyster to nourish the heart and calm the mind, thus treating various types of insomnia based on the theory of qi-yu, with obvious efficacy [28]. Zhu Xuefei [29] divided 88 anxious insomnia patients, randomly into 2 groups, using Xini Shan combined with Baihe Dihuang Tang as the observation group, and the control group was given estradiol tablets, after 3 weeks of treatment, the efficiency of the observation group was significantly higher than that of the control group, and the SDRS, PSQI, SAS, and HAMA scores of the observation group were significantly lower than those of the control group in terms of sleep quality, alleviating anxiety, anxiety depression, insomnia, and other mental disorders. Wang Zhenxing [29] used the method of "detoxifying the liver and relieving depression, harmonizing the liver and spleen, and calming the mind and fixing the will" to treat patients with insomnia of the liver-depression and spleen-deficiency type, and found that its efficacy was better than that of the Shumian capsule, which could alleviate insomnia by improving anxiety and depression symptoms and regulating sleep mechanisms.

5. The Mechanism of Sedative-Hypnotic Effect of Unit Drugs

Numerous scientific studies have demonstrated that the levels of 5-HT, dopamine and NE in the brain of insomnia patients are reduced, and the levels of nitric oxide and GABA receptors in the hypothalamus are reduced, activating the stress response in the body, and the HPA axis function becomes more active under stressful conditions, which then regulates the invasion of cytokines into the nerve center, causing disruption of the sleep-wake system and ultimately exacerbating insomnia [31]. Regarding the sedative-hypnotic mechanism of herbal medicine, its action mechanism can be classified into five categories: the effect on the expression of monoamine neurotransmitters and their receptors, the effect on GABA and its receptors, the regulation of hormonal secretion disorder in the HPA axis, the regulation of cytokines, and the combined effect of other methods and pathways [30]. The author combined the above classification and, by reviewing the relevant literature, compiled the table 1.

Table 1: Summary of active ingredients, mechanisms of action and routes of action of single drugs

Chinese Medicine	Active ingredients	Mechanism of action	Pathway	References
Chaihu	Saikosaponins	Regulation of cytokines	Inhibition of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) IL-6 release	[31]
Shaoyao	paeoniflorin	Regulation of neurotransmitters	Improves sleep by promoting the secretion of endogenous substance 5-hydroxytryptamine in the cerebrospinal fluid	[32]
Pinellia	Fagus Sylvestris Ethanol Extract	Regulation of neurotransmitters	Effects of GABA(A) receptor antagonist flumazenil and GABA synthase blocker L-malic acid on EFRP (Rhizome Pinelliae Preparata .) Effect of hypnotic activity.	[33]
Ginseng	Saponins and glycoproteins	Regulation of neurotransmitters	Decrease the content of DA, NE and NO in the cortex and hypothalamus, affect NOS activity, inhibit 5-HTergic neurons and reduce the release of 5-HT in the brain of mice.	[34, 35]
Glycyrrhiza glabra	Photoglycyrrhizol	Regulation of GABA and its receptor expression	Promotes binding of cerebrospinal fluid GABAA-BZD (gamma-aminobutyric acid A-benzodiazepine) receptors	[36]
Scutellaria baicalensis	baicalin	Synergistic pentobarbital inhibition of nociceptors	significantly increased the concentration of NO, NOS, and inhibited the central	[37, 38]
Poria cocos	Carboxymethyl Poria polysaccharide	Synergistic pentobarbital inhibition of nociceptors	Enhanced central inhibition and reduced central excitatory effects of thiopental sodium	[39]
Longgu	Lithium-ion	Inhibition of central nervous and skeletal muscles	Lithium ions increase the reabsorption of norepinephrine (NE) at nerve endings and inhibit central nervous transmission	[40]
Oyster	Oyster enzyme	Regulation of neurotransmitters	Increase the content of inhibitory neurotransmitters 5-HT, GABA and MT and decrease the content of	[41]

			excitatory neurotransmitters DA and NE in the brain	
Jujube	Jujube Vinegar	Regulation of GABA and its receptor expression	Increase GABA content, decrease Glu glutamate (Glu) content and increase GABA/Glu ratio in mice brain tissue	[42]

6. Summary

Chinese medicine calls insomnia "sleeplessness", and the pathogenesis of insomnia is always an imbalance of yin and yang, with yang not entering yin. The formula of Chai Hu can pivot the qi mechanism, harmonize Shao Yang, draw yang into yin and improve insomnia effectively. Chai Hu and *Scutellaria baicalensis* are the key drug pairs in Chai Hu class formulas, and the combination of the two drugs plays a leading role in harmonizing Shao Yang with flexible addition and reduction, which has the effects of unblocking the three jiao, attacking the internal organs, clearing internal heat and promoting internal and external circulation. In this paper, we summarized the clinical studies and mechanisms of action of Chai Hu class formulas and unit drugs in the formulas for insomnia, and found that the pharmacological mechanisms of these formulas are regulating monoamine transmitters, regulating GABA and its receptor expression, regulating cytokines, regulating HPA axis hormone secretion and other sedative-hypnotic pathways. However, due to the complexity of insomnia, there are still some problems to be solved: for example, there are few experimental studies on Chaihu-type formulas, and some Chinese herbal medicines have not been able to reveal their intrinsic mechanisms in depth. In the future, there is a need to provide more comprehensive evidence-based medical evidence and improve the modern pharmacological mechanisms. This will provide scientific guidance for the wider clinical application of this class of prescriptions.

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