

Research Progress on Improving Perimenopausal Syndrome with Chinese Herbal Compounds

Tingting Wang^{1,a}, Tonghua Liu^{2,b,*}

¹*Shaanxi University of Chinese Medicine, Xiayang, 712046, Shaanxi, China*

²*Beijing University of Chinese Medicine, Beijing, 100029, China*

^a*15709104314@163.com*, ^b*thliu@vip.163.com*

**Corresponding author*

Keywords: Perimenopausal Syndrome, Chinese Herbal Compound, Classical Prescription, Empirical Prescription

Abstract: Perimenopausal syndrome is a physiological and psychological syndrome induced by declining ovarian function and fluctuations in sex hormones during the transition from the reproductive period to menopause, which severely affects women's physical health. Traditional Chinese Medicine has unique advantages in treating this condition, as it can effectively alleviate clinical symptoms, delay disease progression, and reduce side effects associated with Western medicine. Traditional Chinese Medicine adheres to the principles of holistic concept and syndrome differentiation. This paper selects classical prescriptions and empirical prescriptions from Traditional Chinese Medicine compounds. This approach reviews classical and empirical prescriptions. Their multi-target and multi-pathway mechanism of action provides a favorable option for managing this condition.

1. Introduction

Perimenopause is a critical stage in the transition from childbearing to postmenopausal women, lasting approximately 4 years. It is most prevalent and severe 1–2 years after the Final Menstrual Period. Some women's discomfort symptoms may last for more than 10 years. Its symptoms are complex and diverse, such as menstrual disorders (irregular menstruation, prolonged menstruation, increased or decreased menstrual volume), vasomotor symptoms (hot flashes, night sweats), autonomic nervous system disorders (insomnia, anxiety, depression, memory loss, etc.), and long-term symptoms including genitourinary syndrome of menopause, osteoporosis, etc.^[1].

At present, Western medical treatments mainly include hormone replacement therapy (centered on estrogen supplementation) and non-hormonal therapies (e.g. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, selective estrogen receptor modulators). Long-term use of hormone replacement therapy increases the risk of cardiovascular diseases (thrombosis, stroke) and breast cancer. Therefore, the prevention and treatment of perimenopausal syndrome have become a focus of public attention. Traditional Chinese Medicine is effective in preventing and treating perimenopausal syndrome. This paper reviews the recent research progress of Traditional Chinese Medicine compounds in treating perimenopausal syndrome^[2].

2. Understanding of Perimenopausal Syndrome in Traditional Chinese Medicine and Modern Medicine

2.1. Traditional Chinese Medicine's Understanding of Perimenopausal Syndrome

Perimenopause syndrome belongs to the category of “pre- and postmenopausal syndromes” in Traditional Chinese Medicine. *Su Wen (Plain Questions) Treatise on Ancient Innocence* states: “At the age of 14, Tian Gui (innate essence) matures, the Ren Meridian opens, the Chong Meridian flourishes, and menstruation begins”; “At the age of 49, the Ren Meridian declines, the Chong Meridian weakens, and Tian Gui is exhausted.” “Exhaustion of Tian Gui and depletion of the Chong and Ren Meridians” is the key pathological link, which may secondarily lead to disorders of other zang-fu organs: impaired liver dispersion (liver failure to regulate discharge) causes stagnation of liver qi, resulting in mental symptoms such as emotional irritability and depression; spleen dysfunction (abnormal transportation and transformation of the spleen and stomach) leads to insufficient production of qi and blood, aggravating fatigue, sallow complexion, and other manifestations. Compound compatibility takes tonifying the kidney as the core, while incorporating herbs for soothing the liver, invigorating the spleen, and regulating qi and blood, achieving “treatment of both symptoms and root causes”^[3].

2.2. Modern Medical Understanding of Perimenopausal Syndrome

During perimenopause, the physiological decline of ovarian function and reduced follicular reserve lead to a decrease in inhibin B concentration, which weakens the negative feedback inhibition on the pituitary gland, resulting in a continuous increase in follicle-stimulating hormone. Meanwhile, the sensitivity of the hypothalamic-pituitary axis to the positive and negative feedback of estrogen decreases, leading to disorders in the secretion of luteinizing hormone and estrogen. Due to the non-specificity of early hormone fluctuations, perimenopausal syndrome can be diagnosed when typical symptoms occur in women over 45 years old^[4].

3. Traditional Chinese Medicine Compounds

3.1. Classical Prescriptions

Classic TCM formulas are derived from ancient medical books, verified by thousands of years of clinical practice

3.1.1. Chaihu Shugan San

Chaihu Shugan San is composed of Bupleuri Radix, Citri Reticulatae Pericarpium, Ligustici Chuanxiong Rhizoma, etc. It exerts core effects of soothing the liver, relieving stagnation, and regulating qi and blood. It is suitable for perimenopausal syndrome with syndrome of liver qi stagnation. A large number of clinical and pharmacological studies have confirmed that it can significantly improve menstrual disorders, insomnia, and other symptoms^[5]. High-exposure components of Chaihu Shugan San were identified by LC-MS/MS as renin, isoaurin, and hesperidin. Network pharmacology and molecular docking showed that these flavonoids can directly bind to FMO3 protein. Cell thermal shift assay was used to provide in vitro validation of compounds that bind to FMO3, inhibit the FMO3 pathway, regulate steroid hormone metabolism, reduce triglycerides and cholesterol, and increase IL-10 levels^[6].

Chaihu Shugan San treatment upregulated the expression of PI3K and Akt in a rat model of perimenopausal depression. Ly294002 (a PI3K/Akt signaling pathway inhibitor) inhibited the effect

of Chaihu Shugan San, indicating that the brain-liver signaling pathway can be regulated through the PI3K-Akt signaling pathway, and the behavioral performance and liver morphology of rats can be improved^[7]. Network pharmacology analysis shows that energy metabolism and neurotransmitter metabolism are closely related to the antidepressant effect of Chaihu Shugan San. Magnetic resonance imaging shows that Chaihu Shugan San can regulate functional network connectivity between the hippocampus and other brain regions of perimenopausal depression rats, improve hippocampal tricarboxylic acid cycle metabolism, upregulate citric acid and isocitric acid concentrations, downregulate guanosine triphosphate, affect energy metabolism and neurotransmitter balance, reduce Glu, increase 5-HT, and improve anxiety and depression symptoms^[8].

3.1.2. Zuogui Pill and Yougui Pill

Zuogui pill and Yougui pill are respectively indicated for perimenopausal syndrome with kidney yin deficiency and kidney yang deficiency syndromes. In a 4-vinylcyclohexene dioxide-induced perimenopausal syndrome mouse model, it was found that the two pills alone could restore the levels of sex hormones such as anti-Müllerian hormone, estradiol, follicle-stimulating hormone, luteinizing hormone, progesterone, and testosterone, improve the estrous cycle, and reduce uterine pathological damage; by reducing the levels of Caspase-3 and Bax, and increasing the ratio of Bcl-2/Bax and the expression of Bcl-2, they inhibit apoptosis. When used in combination, the regulatory effect is significantly better than that of single drugs, providing a new combination regimen for perimenopausal syndrome treatment^[9].

3.1.3. Erxian Decoction

Erxian Decoction is composed of *Curculiginis Rhizoma* and *Epimedii Folium*. It is suitable for perimenopausal patients with depression. In the mouse model established by ovariectomy combined with chronic unpredictable mild stress, Erxian Decoction can reduce serum follicle-stimulating hormone, luteinizing hormone, and IL-6 levels, upregulate the expression of brain-derived neurotrophic factor and Bcl-2 in the hippocampus, upregulate the expression of estrogen receptor in the uterus and adrenal glands, improve the morphology of the uterus and hippocampus, alleviate estrogen deficiency-related symptoms, relieve depression-like behavior, and improve spatial memory^[10].

3.1.4. Danggui Liuhuang Tang

Danggui Liuhuang Tang was listed in the *Catalogue of Ancient Famous Prescriptions (First Batch)* in 2018, which has the advantages of good curative effect, high safety, and few side effects. Five potential effective components (berberine, coptisine, palmitin, berberine, and baicalin) were screened by LC-MS, which can upregulate progesterone and estradiol levels in perimenopausal syndrome rats. The core targets identified through network pharmacology analysis include TNF, NOS3, EGFR, ESR1, etc., mainly through regulating the cGMP-PKG, PI3K-Akt, and estrogen signaling pathways, realizing multi-component, multi-target, and multi-pathway treatment of perimenopausal syndrome by Traditional Chinese Medicine^[11].

3.1.5. Qing'e Formula

Qing'e Formula originated from *Taiping Huimin Heji Ju Fang* (Formulas of the Peaceful Benevolent Dispensary) in the Song Dynasty, which is composed of *Eucommiae Cortex*, *Psoraleae Fructus*, *Juglandis Semen*, and *Allii Sativi Bulbus*. It has the effect of tonifying the kidney and

strengthening bones. In vitro experiments, Qing'e Formula, Eucommiae Cortex, and Psoraleae Fructus mainly promote the proliferation of MCF-7 cells by upregulating pS2 gene expression and activating the ER α and ER β pathways. In vivo experiments, it can improve the uterine index and serum hormone levels of ovariectomized rats, improve lipid metabolism, increase superoxide dismutase activity to resist oxidation, improve uterine atrophy and weight loss, and antagonize the appetite loss induced by single use of Psoraleae Fructus, reflecting the compatibility mechanism of "reducing toxicity and enhancing efficacy." Among these, Qing'e Formula has the strongest estrogen-like activity^[12].

3.2. Empirical Prescriptions

Modern empirical formulas are optimized based on clinical practice, with clear trial design and high evidence level

3.2.1. Kunxinning Granules

Zhou et al. included 475 patients and divided them into an experimental group and a placebo group to conduct a multicenter, randomized, double-blind, placebo-controlled trial with a course of 12 weeks. The results indicated that Kunxinning Granules could reduce the modified Kupperman Index and maintain the efficacy after 4 weeks of drug withdrawal; the disappearance rate of 13 symptoms such as hot flashes, insomnia, irritability, and urinary system disorders was better than that of the placebo group, and the incidence of adverse reactions was no different from that of the placebo group^[13].

3.2.2. Honghua Xiaoyao Pill

Honghua Xiaoyao Pill is suitable for perimenopausal syndrome with liver depression and blood stasis syndrome. A multicenter randomized controlled trial protocol showed that 60 patients were divided into a treatment group (Honghua Xiaoyao Pill) and a control group (oryzanol). After 12 weeks of treatment, the modified Kupperman Index, Hot Flash Scale, Menopause-Specific Quality of Life scale, Hamilton Depression/Anxiety Scale, serum sex hormones (estradiol, follicle-stimulating hormone, luteinizing hormone), monoamine neurotransmitters (norepinephrine, 5-HT, dopamine), vasoactive factors (nitric oxide, endothelin-1, calcitonin gene-related peptide), and the expression of PI3K, Akt, and phosphorylated Akt were improved, with high safety and no adverse reactions. The efficacy was maintained after 4 weeks of drug withdrawal^[14].

3.2.3. Ziyin Bushen Decoction

Ziyin Bushen Decoction, which contains Rehmanniae Radix, Lycii Fructus, and Ligustri Lucidi Fructus as its core components, is suitable for severe perimenopausal syndrome with liver-kidney yin deficiency syndrome. By increasing the expression of ER α , cytochrome P450 17A1, CYP11A1, CYP19, 17 β -hydroxysteroid dehydrogenase, steroid sulfatase, and sex hormone-binding globulin, reducing the expression of gonadotropin-releasing hormone receptor, improving the synthesis, metabolism, and transport process of estrogen, reversing learning and memory impairment, improving spatial acquisition, memory retention, and cognitive dysfunction in rats, and improving the uterine index and protecting the uterine structure of perimenopausal syndrome rats, it provides a new strategy of "regulating estrogen metabolism" for perimenopausal syndrome treatment^[15].

3.2.4. Chaishen Powder

Zheng et al. conducted clinical data mining on 100 patients with perimenopausal syndrome and

found that the effective rate of Chaishen Powder in treating perimenopausal syndrome was 87.33%. Through integrated network pharmacology, microRNA analysis, and animal experiment validation, 9 chemical components and 10 core targets were screened, which can regulate SRC, PIK3CA, and PRKACA targets through the PI3K-Akt and cAMP signaling pathways, realizing multi-pathway and multi-target effects of regulating hormone levels and alleviating ovarian damage^[16].

3.2.5. Gengnian Shu

Gengnian Shu is composed of *Angelicae Sinensis Radix*, *Paeoniae Radix Alba*, *Chuanxiong Rhizoma*, etc. It has the effect of nourishing blood and tranquilizing the mind. A perimenopausal syndrome rat model was established by surgical resection of 4/5 of the ovaries. Non-targeted metabolomics analysis showed that it can regulate 17 different metabolites, involving pathways such as the tricarboxylic acid cycle and amino acid biosynthesis; it can affect ovarian cell ferroptosis by regulating endogenous substances, improve organic acid and lipid metabolism disorders, and provide new insights for the metabolic regulatory treatment of perimenopausal syndrome^[17].

3.2.6. Ganmai Dazao Decoction

Liu et al.'s systematic review of randomized controlled trials in patients with perimenopausal syndrome showed that after taking Ganmai Dazao Decoction, the Kupperman Index and Subjective Health Measurement Scale scores of perimenopausal patients were both better than those of the control group. Network pharmacology found that the key active components of Ganmai Dazao Decoction, including quercetin, kaempferol, phloretin, 7-methoxy-2-methylisoflavone, and formononetin, act on targets such as Akt1, IL6, TNF, and peroxisome proliferator-activated receptor gamma by regulating the AGE-RAGE and PI3K-Akt signaling pathways, and exert anti-inflammatory, antioxidant, and ovarian protective effects^[18].

4. Conclusions

Chinese herbal formulae modulate the estrogen signaling pathway to regulate sex hormone levels (including E₂, FSH, and LH), improve the histomorphology of the uterus and ovaries, and alleviate symptoms associated with hormonal deficiency. The PI3K–Akt pathway represents one of the core signaling pathways involved in processes such as antidepressant effects, ovarian protection, and metabolic regulation. Through their multiple bioactive components, Chinese herbal formulae exert synergistic effects on various targets (e.g., TNF, IL-6, Akt1), thereby demonstrating the holistic regulatory approach characteristic of traditional Chinese medicine (TCM). This multi-target mechanism stands in contrast to the single-target mode of action typical of Western medicine.

According to Traditional Chinese Medicine theory, the pathogenesis of perimenopausal syndrome is rooted in kidney deficiency, accompanied by liver depression and spleen deficiency. Traditional Chinese Medicine compounds, as a characteristic therapy of Traditional Chinese Medicine, can play their roles through multi-component, multi-target, and multi-pathway mechanisms. However, Traditional Chinese Medicine compounds consist of multiple Traditional Chinese Medicine herbs with varying dosages and drug ratios. The specific active components of individual herbs and their mechanisms of action are insufficiently explored.

References

[1] Santoro, N., Roeca, C., Peters, B.A. and Neal-Perry, G. (2021) *The Menopause Transition: Signs, Symptoms, and Management Options. The Journal of Clinical Endocrinology and Metabolism*, 106(1), 1–15.

- [2] Crandall, C.J., Mehta, J.M. and Manson, J.E. (2023) Management of Menopausal Symptoms: A Review. *JAMA*, 329(5), 405–420.
- [3] Wang, Y.P. and Yu, Q. (2021) The Treatment of Menopausal Symptoms by Traditional Chinese Medicine in Asian Countries. *Climacteric*, 24(1), 64–67.
- [4] Talaulikar, V. (2022) Menopause Transition: Physiology and Symptoms. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 81, 3–7.
- [5] Zhang, X., Luo, L., Wang, C., Lv, W., Duan, Y. and Kong, L. (2024) Research Progress on Chaihu Shugan San in Treating Perimenopausal Syndrome: A Review. *Medicine*, 103(52), e41044.
- [6] Lyu, H., Li, T., Chen, Y., Xue, Y., Liu, W., Yuan, Y., Chen, S., Lu, D., Ren, Y., Wang, H., Cao, F., Wu, C., Chen, B. and Chen, X. (2026) Exploring the Effective Substances and Mechanisms of Action of ChaiHu ShuGan San in Treating Perimenopausal Syndrome Based on in Vivo Exposure Profiles and Steroid Hormone Metabolic Networks. *Journal of Ethnopharmacology*, 355(Pt A), 120648.
- [7] Chen, Q., Li, C., Tao, E., Asakawa, T. and Zhang, Y. (2022) Exploration of a Brain-Liver-Communication-Related Mechanism Involved in the Experimental Perimenopausal Depression Rat Model Using Chaihu-Shugan-San. *Neurochemical Research*, 47(5), 1354–1368.
- [8] Huang, R., Gong, M., Tan, X., Shen, J., Wu, Y., Cai, X., Wang, S., Min, L., Gong, L. and Liang, W. (2024) Effects of Chaihu Shugan San on Brain Functional Network Connectivity in the Hippocampus of a Perimenopausal Depression Rat Model. *Molecular Neurobiology*, 61(3), 1655–1672.
- [9] Wang, T., Li, Z., Chen, T., Cai, R., Jiang, Y., Ofori, P.K., Zhang, H. and Wu, Y. (2023) Zuogui and Yougui Pills Improve Perimenopausal Syndrome by Regulating Apoptosis in Mice. *Journal of Traditional Chinese Medicine*, 43(3), 474–483.
- [10] Zhang, L., Li, J., Chen, Q., Di, L. and Li, N. (2021) Erxian Decoction, a Famous Chinese Medicine Formula, Ameliorates Depression-Like Behavior in Perimenopausal Mice. *Endocrine, Metabolic & Immune Disorders Drug Targets*, 21(12), 2203–2212.
- [11] Xue, B., Chen, X., Wang, X., Li, C., Liu, J., He, Q. and Liu, E. (2022) Application of Multivariate Statistical Analysis and Network Pharmacology to Explore the Mechanism of Danggui Liuhuang Tang in Treating Perimenopausal Syndrome. *Journal of Ethnopharmacology*, 284, 114543.
- [12] Xiong, J.L., Cai, X.Y., Zhang, Z.J., Li, Q., Zhou, Q. and Wang, Z.T. (2022) Elucidating the Estrogen-Like Effects and Biocompatibility of the Herbal Components in the Qing'e Formula. *Journal of Ethnopharmacology*, 283, 114735.
- [13] Zhou, G., Chen, D., Qian, L., Song, D., Zhang, Q., Yan, Y., Lin, J., Li, L., Wan, G., Li, S., Hou, L., He, Y., Qi, C. and Yuan, W. (2025) Efficacy and Safety of Kunxinling Granules in Patients with Menopausal Syndrome: A Multicenter, Randomized, Double-Blinded, and Placebo-Controlled Trial. *Frontiers in Pharmacology*, 16, 1512110.
- [14] Wu, X., Zhou, L., Dong, H., Tian, M., Liu, S. and Xu, X. (2022) Efficacy, Safety and Mechanism of Honghua Xiaoyao Pill in the Treatment of Perimenopausal Syndrome: A Study Protocol for a Randomized Controlled Trial. *Frontiers in Pharmacology*, 13, 1001228.
- [15] Tang, B.X., Meng, Q.Y., Xie, C., Zhao, S.S., Wu, K.L., Wang, F. and Du, L.Y. (2020) Ziyin Bushen Decoction Alleviates Perimenopausal Syndrome in Rats by Enhancing Estradiol Production. *Evidence-Based Complementary and Alternative Medicine*, 2020, 8895809.
- [16] Zheng, A., Zhang, L., Jiang, Y., Yu, S., Li, X. and Han, C. (2025) Chaishen Powder Treats Perimenopausal Syndrome Through the PI3K-Akt/cAMP Signaling Pathway: Integrated Clinical Analysis, Network Pharmacology, MicroRNA and Animal Experiment. *Climacteric*, 1–18.
- [17] Lv, X., Bi, A., Zhang, Z., Li, J., Wei, Y., Wan, M., Wang, J., Yan, T. and Jia, Y. (2024) Non-Targeted Metabolomics Strategy Reveals the Role of Gengnian Shu in Regulating Ferroptosis in Perimenopausal Syndrome. *Journal of Pharmaceutical and Biomedical Analysis*, 241, 115980.
- [18] Liu, G.X., Zhang, G.D. and Yan, Z.Y. (2024) Efficacy and Potential Mechanisms of Ganmai Dazao Decoction in Treating Perimenopausal Syndrome: A Network Pharmacology and Meta-Analysis. *Asian Journal of Surgery*, 47(7), 3065–3067.