

# Current Research Progress on Pharmacological Activities and Clinical Application of Guhan Yangshengjing

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## ABSTRACT

Guhan Yangshengjing (GHYSJ) is a Chinese patent medicine mainly used for health care and health maintenance. Meanwhile, GHYSJ can help to prevent the human bodies from diseases caused by the insufficiency of kidney essence together with the deficiency of Qi and Yin, which includes a variety of tonifying Chinese herbs. Nevertheless, problems still exist, which impedes the application of GHYSJ, such as lagging research, insufficient observation of clinical efficacy and unclear pharmacodynamic substance basis and mechanism. To provide a certain reference basis for the in-depth research and secondary development of GHYSJ, this paper summarizes its pharmacological activity and clinical application, and points out the future research direction and corresponding research strategy of GHYSJ

**Abbreviations:** GHYSJ: Guhan Yangshengjing; MDA: Malondialdehyde; CA: Catecholamine; SOD: Superoxide Dismutase; RBC: Red Blood Cells; TC: Total Cholesterol; TG: Triglyceride; LDL: Low Density Lipoprotein; HMGB1: High Mobility Group Protein B1; POCD: Postoperative Cognitive Dysfunction; WBC: White Blood Cell; Hb: Hemoglobin; AMH: Anti-Müllerian Hormone

## Introduction

Guhan Yangshengjing (GHYSJ) is based on the essence of the bamboo slips "Healthcare Prescriptions" and "Endo-meridians" from the ancient tombs of the Western Han Dynasty in Mawangdui, Li Congfu, Liu Bingfan, and Ouyang Qi of the Hunan Academy of Traditional Chinese Medicine, condensed a compound recipe with their decades of clinical experience. GHYSJ, composed of a variety of Chinese herbal medicines, has the efficacy of invigorating the kidney for strengthening the spleen, tonifying qi for benefitting

essence, which is used for dizziness, palpitations, dizziness, tinnitus, forgetfulness, insomnia, impotence and spermatorrhea and fatigue and weakness caused by deficiency of qi and yin and insufficient kidney essence [1]. GHYSJ has been put into production since 1986, of which two dosage forms, oral liquid and tablets are developed with multiple specifications and models, which can meet the purchasing needs of different groups. In the process of long-term clinical application, it has been found that GHYSJ also has a good effect on many other diseases, such as atrophic gastritis,

coronary heart disease, alopecia areata, chloasma, hypotension, Meniere's syndrome, senile habitual constipation and menopausal syndrome [2].

There are still some problems in the research of GHYSJ. Firstly, the pharmacological and clinical research of GHYSJ are mostly performed in the 90s, which is hard to keep pace with the times. With the advance of research methods, its depth and breadth are difficult to fully satisfy the current application requirements of clinical drugs. Secondly, the small sample size of the clinical research of GHYSJ is hard to guarantee the clinical efficacy, so it cannot provide reliable scientific foundation for its pharmacological activity research. Finally, the effective material basis and mechanism of GHYSJ have not been clarified. In the process of clinical application, it has been found that GHYSJ has certain effects on many diseases, but the active substances are not well studied and the response mechanism between the active substance and the target proteins has not been clarified. Hence, it is necessary to carry out the secondary development of GHYSJ and the research of new direction, broaden the scope of clinical application, and further study its pharmacodynamic substances and mechanism of action. This paper summarizes the pharmacological and clinical study of GHYSJ with intent to provide research ideas and scientific basis for its further development. So that GHYSJ can better adapt to the requirements of the booming health industry and prepare for health protection for the upcoming aging society.

## Pharmacological Activity

### Antioxidant Activity

Numerous studies have shown that anti-oxidation plays an important role in preventing aging, because free radicals or oxidants can break down cells and tissues, affect metabolic functions, and cause different health problems [3-5]. GHYSJ can eliminate excessive oxidative free radicals and has anti-oxidation and anti-aging effects. Wei, et al. [6] found that GHYSJ can repair and protect red blood cells damaged by aging, exhibiting an anti-aging effect by improving the vitality of red blood cells. Zhang, et al. [7] found that GHYSJ could inhibit the content of malondialdehyde (MDA) in the heart, liver and brain mitochondria, microsomes and erythrocyte membranes of middle-aged and elderly Wistar rats and can resist lipid peroxidation. Yu [8] proved that GHYSJ could increase the content of catecholamine (CA) in the brain by increasing the activity of superoxide dismutase (SOD) in the blood of aged rats and regulate monoamine transmitters.

GHYSJ has also been found to improve the function of hypothalamus-pituitary-gonadal axis and promote the synthesis of testosterone in old male rats. Zhang, et al. [9] demonstrated that GHYSJ can improve the metabolism of free radicals in female rats, effectively increase the content of SOD in the blood, enhance the

body's ability to scavenge oxygen free radicals, and play an anti-aging effect. The proper amount of oxygen free radicals is beneficial to the body's various life activities, but the accumulation of excessive free radicals would cause damages to the body [10]. In conclusion, GHYSJ can effectively remove excessive oxygen free radicals in the body and has a good antioxidant effect.

### Regulate Immune Function

As one of the body's important defense mechanisms, the immune system plays a vital role in the treatment of infections, inflammatory diseases and cancer [11]. And GHYSJ just has a certain immune regulation effect. Zhang, et al. [12] determines the content of T cells and antibodies in the blood of rats fed by GHYSJ and researched the changes in peripheral blood red blood cell immune status in 32 cases of tumor patients, which explains that GHYSJ has the effect of enhancing humoral immunity now that it alleviates the immunosuppressive state of tumor patients and regulates the overall immune effect. As a component of natural immunity, red blood cells lay an important foundation for the body's own immune balance and stability. Wen [13] finds that GHYSJ not only improves the immune adhesion function of red blood cells inhibited by exercise stress, but also enhances the immune adhesion activity of red blood cells (RBC) and regulates the body's immunity. GHYSJ has a good regulatory effect on the immune function of the body and mainly acts on the body's first line of immune defense with the increasing number and enhancing function of immune cells, and immune active substances.

### Anti-Fatigue Effect

Fatigue, or sports fatigue, refers to the inability of the body's physiological processes to continue its function at a certain level and/or the inability to maintain a predetermined exercise intensity [14]. If fatigue is not eliminated in time, it can cause the body's endocrine dysfunction and decrease immunity, which will cause a series of physiological problems and seriously affect human health [15]. Wen, et al. [16] finds that GHYSJ can enhance the activity of SOD, reduce the content of MDA in the blood, reduce the damage of RBC membrane structure, and achieve anti-fatigue effect. Li, et al. [17] observes the influence of GHYSJ on the physical functions of competitive athletes, and the results show that: GHYSJ can not only promote protein synthesis, reduce blood urea nitrogen content, improve heart function, but also promote hematopoietic function, increase the hemoglobin concentration, improve the body's circulation and aerobic energy supply, and have the functions of anti-fatigue and delaying the appearance of fatigue.

Wen, et al. [18] and Lin, et al. [19] suggest that good results obtained for GHYSJ increase the content of liver glycogen, muscle glycogen and blood sugar in mice, increase glycogen reserves, and enhance exercise ability. Also, GHYSJ has turned out to reduce

exercise fatigue and lipid peroxidation mediated by free radical and have good anti-fatigue effects. Chen, et al. [20] finds that the anti-fatigue mechanism of GHYSJ may be related to the reduction of lactic acid production in the blood, the increase of SOD, activity and enhancement of the body's scavenging of oxygen free radicals. GHYSJ has an anti-fatigue effect by enhancing the ability of red blood cells, improving blood oxygen supply, increasing glycogen reserves, promoting the synthesis of related proteins, and scavenging oxygen free radicals. GHYSJ is such an excellent anti-fatigue drug that it can significantly alleviate the body's fatigue after exercise.

### **Hypolipidemic and Anti-Atherosclerosis**

Atherosclerosis is a chronic vascular inflammatory disease that mainly affects cerebral arteries, coronary arteries and peripheral blood vessels [21]. Abnormal lipid metabolism is the pathological basis of atherosclerosis and controlling blood lipid concentration is vital to the treatment of atherosclerosis [22]. Studies have shown that GHYSJ can significantly reduce the levels of total cholesterol (TC) and triglyceride (TG) in the blood and has a good effect on lowering blood lipids and anti-atherosclerosis. Qin, et al. [23] establishes a hyperlipidemia rat model by feeding a high-fat diet to study the lipid-lowering effect of GHYSJ and finds that GHYSJ can reduce the platelet adhesion rate, the maximum platelet aggregation rate, and the rat serum TC and TG, has anti-platelet adhesion and aggregation effect and lipid-lowering effect. Dai, et al. [24] and Liu, et al. [25] show that the GHYSJ has a super effect on lowering blood lipids and anti-atherosclerosis, which can significantly reduce the content of TC and low density lipoprotein (LDL) in the serum. It can also block plasma lipid peroxidation and LDL oxidative modification and denaturation in the arterial wall, inhibit lipid deposition on the arterial wall, increase prostaglandin I<sub>2</sub> (Prostaglandin, PGI<sub>2</sub>) levels, and adjust thromboxane A<sub>2</sub> (Thromboxane, TXA<sub>2</sub>) and PGI<sub>2</sub> balance.

### **Other Pharmacological Effects**

GHYSJ also has some other effects besides the above-mentioned pharmacological activities. Xiao's research [26] shows that GHYSJ can improve the inflammatory response in rats with kidney-yang deficiency and asthma. Its mechanism may be related to the inhibition of interleukin 6 (Interleukin, IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and high mobility group protein B1 (HMGB1) expression. Zhang [27] found that GHYSJ can regulate the gene expression of P62 protein and transforming growth factor- $\beta$  (TGF- $\beta$ 1) and inhibit airway remodeling in asthmatic rats with kidney-yang deficiency. In addition, Qin, et al. [28,29] found that GHYSJ can significantly reduce the content of aspartate aminotransferase, creatine kinase, and lactate dehydrogenase in serum through acute cerebral ischemia models and increase the content of SOD in serum and brain homogenate, at the same time increase cerebral blood flow, reduce cerebrovascular resistance, and protect brain tissue.

GHYSJ shows a good awareness of the effects of improving postoperative cognitive dysfunction (POCD), Hou [30] finds that GHYSJ can significantly reduce the levels of pro-inflammatory cytokines TNF- $\alpha$  and IL-6 in the hippocampus of aged rats after surgery and relieve the inflammatory response in the hippocampus of aged rats after surgery. Wang's research [31] shows that GHYSJ can improve postoperative cognitive dysfunction in aged rats by inhibiting the activation of astrocytes and microglia in the CA1 region of the hippocampus. Deng [32] bring to light the mechanism of GHYSJ improving postoperative cognitive dysfunction in rats may be related to the up-regulation of hippocampal synaptic protein SYN-1 and PSD-95 expression.

## **Clinical Applications**

### **Treatment of Insomnia, Senile Brain Atrophy and Vascular Dementia**

GHYSJ has the effects of replenishing qi, nourishing the kidney, and replenishing essence, which can treat neurasthenia, insomnia, forgetfulness, fatigue and weakness caused by deficiency of spleen and kidney, insufficient qi and blood, and loss of mental energy. Liu [33] compared the therapeutic effects of GHYSJ and Guilu Erxian Ointment on senile brain atrophy and detected that the total effective rate of the GHYSJ Group was 96.4%, which was 68.4% higher than that of Guilu Erxian Ointment. Yin, et al. [34] observed the therapeutic effect of GHYSJ on patients with neurasthenia and found that GHYSJ has a certain effect on neurasthenia, because the healing rate of GHYSJ (62.50%) is better than that of the control group Zishen Jiannaoye (47.22%). Yu, et al. [35] outcropped that the GHYSJ combined with oryzanol has a good effect on insomnia, with a recovery rate of 72.55% and a total effective rate of 92.16%, which is equivalent to the suldia. Yu [36] treated vascular dementia with GHYSJ supplemented by cerebral vasodilators and brain cell metabolism activators. The total effective rate was 76.1%, which was better than the 60.8% of the control group.

### **Treatment of Male and Female Infertility, Sexual Dysfunction, and Prostate Inflammation**

GHYSJ can nourish the kidney and nourish the essence, invigorate qi and nourish blood, and have a good therapeutic effect on reproductive system diseases. Xia, et al. [37] used zinc gluconate in combination with GHYSJ to treat male infertility and found that it can significantly improve sperm activity and sperm number and has a significant therapeutic effect on idiopathic oligoasthenospermia. Zhou, et al. [38] observes the clinical efficacy of the GHYSJ for sexual dysfunction, and the results show that it can improve the sexual dysfunction, it's apparent efficiency and total effective rate are significantly higher than those of the Jinkui Shenqi Pill. Zhang, et al. [39] found that GHYSJ have a good effect on prostate hyperplasia caused by spleen and kidney deficiency, and its total effective rate is

as high as 95%. The study conducted by Wu, et al. [40] showed that the total effective rate of the GHYSJ in treating prostatitis caused by insufficient kidney yang or spleen deficiency and dampness deficiency was 92%. Niu [41] find that the total effective rate of treating women's leucorrhoea with GHYSJ is 92%, which is better than that of leucorrhoea pills.

### Treatment of Leukopenia

White blood cells are an important part of the body's defense system and play an irreplaceable role in resisting the invasion of the body by pathogens. GHYSJ can resist the reduction of white blood cells due to some drugs or treatments and restore the normal functions of the human body. Lin, et al. [42] used GHYSJ to treat the leukopenia caused by clozapine because it can increase the body's immunity and enzyme activity, enhance the cell oxygen carrying capacity and the detoxification capacity, and improve the blood circulation, the oxygen carrying capacity of cells, and the vitality of SOD in the human body, and reduce the production of free radicals in the human body. Xu, et al. [43] compared the effects of GHYSJ with oral inosine, salanol, and aminopeptide on white blood cells after radiotherapy and chemotherapy in patients with intermediate and advanced tumors, pointed that GHYSJ can not only stimulate bone marrow stem cells to increase white blood cells, but also can alleviate the toxic and side effects during the chemotherapy and radiotherapy of tumor patients, and reduce the decline of white blood cells. Chen [44] revealed that the GHYSJ has a protective effect on white blood cell (WBC), RBC and hemoglobin (Hb), can reduce the bone marrow suppression caused by chemotherapy, and can enhance the patient's resistance to chemotherapy. Zhang [45] think that GHYSJ is an ideal treatment for leukopenia after tumor chemotherapy drug, because it can significantly enhance the ability of WBC, promote its recovery, and play an important role in increasing Hb, platelet (Platelet, PLT) and enhancing immune function.

### Treatment of Other Diseases

Li, et al. [46] show that GHYSJ can significantly improve Qi deficiency and fatigue symptoms of perimenopausal women with Qi deficiency. It also helps to maintain anti-Müllerian hormone (AMH) and bone mineral density in women with qi deficiency in perimenopausal period. Zhao, et al. [47,48] and Zhang, et al. [49] pointed that: GHYSJ has a better conditioning effect on sub-healthy people with yang deficiency and qi deficiency, which can improve their heart function, bone density, AMH, total sperm motility, and other indicators to improve exercise endurance and prevent the sub-health state from turning into disease. Sun, et al. [50] found that the total effective rate of GHYSJ on osteoporosis is 91.2%, which is better than Erxian Decoction. Chen [51] showed that GHYSJ can reduce the serum cholesterol level of patients with hypercholesterolemia by 17.1% without adverse reactions.

## Conclusion and Prospect

GHYSJ has broad application prospects in the medical field, and its secondary development is of great significance, because the anti-oxidation, anti-aging, immune function adjustment, anti-cerebral ischemia, anti-fatigue, hypolipidemic and anti-atherosclerosis effects of GHYSJ covers multiple human systems such as nervous system, blood system, immune system and reproductive system.. It can treat insomnia, senile brain atrophy, male and female infertility, sexual dysfunction, prostate inflammation, and hypercholesterolemia. In addition, it can assist in the treatment of osteoporosis, tumor patients with leukopenia, coronary heart disease, angina pectoris, and syringomyelia, also can regulate the body functions of sub-healthy people with yang deficiency and qi deficiency. Sub-health is a kind of intermediate state between health and disease, which is considered a precursor to several cardiovascular diseases such as hypertension, inflammation, atherosclerosis, diabetes, myocardial infarction, and other cardiovascular diseases [52]. Studies have shown [53] that human beings in a sub-health state for a long time may develop into a sub-clinical state, appear pathological changes, and then develop into diseases.

This process is irreversible, and certain measures can be taken to restore the body to health in a sub-health state. Using the reversibility of the sub-health state to implement intervention is the key to disease prevention. This is consistent with the "zhi wei bing" (preventative treatment) of traditional Chinese medicine, and it reflects the advantages of traditional Chinese medicine in disease prevention and treatment. An increasing number of people are in sub-health status because of the high pressure and fast-paced social environment. The reason why the GHYSJ plays an important role in sub-healthy people is that it can fill the marrow, regulate the function of various organs, enhance the body's resistance, and prevent diseases. The secondary development of GHYSJ can contribute to alleviating the pressure on the medical system. With the decline of fertility and the improvement of medical standards the aging population has become a serious social problem around the world, especially in China, the most populated nation, which puts a significant health, economic, and social burden on society.

Improving the fertility level of the young population, improving the physical condition of the elderly population, and alleviating the phenomenon of population aging are problems that need to be solved urgently. GHYSJ replenishes the innate essence, nourishes the acquired foundation, and has a good effect on male and female infertility and various reproductive system diseases, such as Epimedium and Dodder [54,55] can improve the vitality of male and female reproductive cells, reduce the natural aging of reproductive cells, repair damaged cells, and protect reproductive organs. In addition, GHYSJ has a good effect on some senile diseases such as senile brain atrophy, vascular dementia, etc. It also has the

effects of regulating immunity and improving physical functions and has certain adjustments to various physical indicators of the elderly. To sum up, GHYSJ can make a certain contribution to these two social problems, because it can regulate the body functions of sub-healthy people and prevent the occurrence of diseases, which is in line with the “preventive treatment” of Chinese medicine, and it is also very suitable for solving the problem of population aging. So the follow-up development of the GHYSJ should be combined with current social problems to serve the health of the country and even the whole mankind.

Starting from the two levels of the whole prescription and the single medicine, multi-directional and multi-level representation of the chemical substances in the GHYSJ and illustrate the material basis of GHYSJ promoting gastrointestinal motility and explore the mechanism of action from an organic and inorganic combination point of view. Combining the seven emotions, four sexes, guijing, and monarch and adjudicator of traditional Chinese medicines, study the compatibility of the individual medicines in GHYSJ, explore the role targets of GHYSJ in the human immune system and reproductive system, and lay the foundation for follow-up research. At the same time, metabolomics and proteomics can be used to study the *in vivo* absorption, distribution and metabolic process of GHYSJ, and to clarify its dose-effect relationship. To better guide the application of the GHYSJ in the concept of “preventing disease” and the problem of population aging, and to serve the national health.

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