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Review

Research progress in pharmacological and clinical application of Jingui Shenqi pill

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Highlights

Combining the pharmacology with the clinical research of Jingui Shenqi pill can provide ideas for more scientific and rational application of the prescription in the treatment of diseases.

Abstract

Objective: To provide ideas for more scientific and rational application of Jingui Shenqi pill in the treatment of diseases. **Methods:** We searched and analyzed the literatures about the composition principle, pharmacology and clinical researches of Jingui Shenqi pill. **Conclusion:** The pharmacology mechanism researches about Jingui Shenqi pill were extensive and in-depth. Combining the pharmacology with the clinical research should become a new direction of Jingui Shenqi pill, and can also provide reference for clinical use of this prescription.
Keywords: Jingui Shenqi pill, Bawei Shenqi pill, pharmacology research, clinical research.

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Background

Jingui Shenqi pill, also known as Bawei Shenqi pill, originated from "*Synopsis of the Golden Chamber*" written by the medical sage Zhang Zhongjing. This book clearly mentions that Jingui Shenqi pill can be used in five kinds of diseases, including dermatophytosis, the backache caused by consumptive disease, the short of Qi and fluid mobility disorder, the diabetes and the poor urination during pregnancy. Such diseases are all caused by the insufficiency of the kidney-essence, the deficiency of kidney-Yang and the anomaly of Qi-transforming function. The collocation of Jingui Shenqi pill was so exquisite that it had been highly praised by generations of physicians. In addition, the convention of traditional Chinese medicine (TCM) are focusing on the inheritance of classic, so the diseases that can be treated by Jingui Shenqi pill are much more than those recorded in the "Synopsis of the Golden Chamber". With the development of modern pharmacology, the clinical application of Jingui Shenqi pill can be directed by the study of pharmacological action mechanism. This paper is a summary of the composition principle, the pharmacological mechanism and the corresponding clinical research about Jingui Shenqi pill in the past years.

The composition principle and ancient development of Jingui Shenqi pill

The original prescription of Jingui Shenqi pill includes eight taels of *Radix Rehmanniae*, four taels each of *Rhizoma Dioscoreae* and *Fructus Corni*, three taels each of *Poria*, *Rhizoma Alismatis*, *Cortex Moutan*, one tael each of *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata*. The sovereign drug in the prescription is *Radix Rehmanniae*, which can nourish the kidney- Yin and fill the marrow. *Radix Rehmanniae* was also described as the best medicine for tonifying kidney and benefiting Yin and blood in *Bencao Jingshu. Rhizoma Dioscoreae* and *Fructus Corni* are the minister drugs, invigorating spleen and kidney, reducing the consumption of kidney essence and benefiting Qi. The combination of sovereign drugs and minister drugs can achieve the goal of "drawing Yang from yin". The assistant drugs are *Poria and Rhizoma Alismatis,* which can excrete dampness and dredge or regulate water passage. Meanwhile, the *Cortex Moutan* can clear deficient heat, descend ministerial fire, limit the deficient Yang with upper manifestation, resulting to make the triple energizer work well and also make kidney-Yang sufficient combined with *Poria and Rhizoma Alismatis*. The envoy drugs are a small amount of *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata,* which can warm kidney-Yang and enrich kidney-Qi. And the combination of all of the envoy drugs are characterized by mild but not strong, called little kidney-Yang giving birth to the kidney-Qi. As Ke Qin said, "The purpose of putting a small amount of *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata* into a large number of Yin nourishing drugs is to warm the kidney slightly instead of supplementing the kidney- fire, that is, to generate kidney- Qi. And Qian Yi also said, " The focus of Shenqi pill is on Qi, therefore there are so small *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata* to draw a fulcrum from their feature of gentleness to invigorate the kidney-Yang." In the prescription, using *Radix Aconiti Lateralis Preparata* and *Radix Rehmanniae* to reconcile Yin and Yang. *Radix Aconiti Lateralis Preparata* and *Cortex Moutan*, the former is used to dispel cold and the latter to clear heat. *Ramulus Cinnamomi* and *Cortex Moutan* are used to invigorate Qi and nourish blood. *Poria and Rhizoma Alismatis*, are used to reinforce and enrich water. *Fructus Corni* and *Rhizoma Alismatis*, the former is used to enrich the body and the latter to catharsis. At the same time, *Radix Rehmanniae*, *Rhizoma Dioscoreae* and *Fructus Corni* nourish the liver, the Spleen and the kidney collectively. *Poria*, *Rhizoma Alismatis and Cortex Moutan* clear the liver heat away, reduce the deficiency fire and remove the pathogenic factor. There are three supplements and three diarrhea which can be compatible with Yin and Yang, cold and heat, Qi and blood, purgation and tonification, both astringent therapy and diuresis, and also coordinate the liver, spleen, kidney and other organs, making Yin and Yang alternate and Qi-transforming stronger eventually.

The development of Jingui Shenqi pill started from Liuwei Dihuang pill. Qian Yi in the Song Dynasty was deeply influenced by Luxin Jing, and according to the saying of "Infantile bodies of pure Yang and do not need to tonify kidney-fire in children." He used prescription to reduce the amount of warm-dryness *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata*, with emphasizing on the soft and moist use, creating Liuwei Dihuang pill, which focused on tonifying kidney-Yin. Influenced by the theory that kidney is the source of edema, Yan Yonghe in the Southern Song Dynasty developed three new prescriptions on the basis of Shenqi pill, namely Jisheng Shenqi pill, Shibu pill and Jiajian Shenqi pill. In the Yuan Dynasty, Zhu Danxi held the saying that "Yang is usually redundant while Yin is frequently deficient", advocated "Do not reduce the fire of kidney-Yang, preserve kidney-Yin essence", and created Dabu Yin pill, Ziyin Dabu pill and Bawu Shenqi pill. To the Ming dynasty, Xue Ji influenced by the theory "Supplementation of kidney-Yin can help to restrict the overactive Yang caused by Yin deficiency, while supplementation of kidney-Yang can dissipate the diffuse shade of Yin pathogen", "the cold is not

cold, blame its no water", "the heat is not hot, blame its no fire", he combined Jingui Shenqi pill with Xiaoyao pill, added some *Schisandra* and created a new prescription, named Zishui Qinggan Yin, treating menstrual and emotional diseases caused by the mood disorders and the dysfunction of poor liver and spleen. Zhang Jingyue perfected the Qi-monism and supplemented the Yang-deficiency, put forward the theory of water and fire in life- gate, and developed the theory of tonifying the kidney to its heyday. He was not only good at warming and tonifying the kidney-Yang, but also pay attention to nourishing Yin. And he created Zuogui pill, Yougui pill, Zuogui yin, Yougui yin, Dabu Yuanjian and Danggui Dihuang pill on the basis of Jingui Shenqi pill. Zhao Xianke supplemented and developed the theory of Mingmen, and believed that Liuwei Dihuang pill and Shenqi pill were the main prescription for replenishment of true fire and true water. In the Qing Dynasty, Gao Gufeng *et al* founded Qiwei Duqi pill and Zishui Qinggan Yin on the basis of predecessors. Wu Qian *etc.* created Zhibai Dihuang pill, Qiju Dihuang pill, Baxian Changshou pill and so on. Therefore, the development of Jingui Shenqi pill is becoming perfect day by day. The successive dynasties development of it is shown in Figure 1

Figure 1. The Development of Jingui Shenqi pill

Development of modern pharmacology of Jingui Shenqi pill

Modern pharmacology research finds that Jingui Shenqi pill has the function of protecting nerve, lowering lipid and glucose, relieving kidney damage and so on.

The neuroprotective effect of is mainly reflected in the hippocampal nerve and gastric sinus nerve, which can (1) enhance the expression of NOS positive neurons in CA1 area of brain horse region [1], (2) reverse the RNA and protein expression of mGluR5[2], (3) reduce the positive rate of NgmRNA and protein expression [3], (4) promote the expression of substance P in the nerve plexus in the muscle of gastric antrum [4]. The hypoglycemic and lipid-lowering effects are mainly reflected in the pancreas and β cells, which can (1) hypoglycemic and insulin-lowering, and increase the content of C-peptide [5] and induce (2) hypoglycemic and lipid-lowering by reducing HOMA-IR and increasing ISI [6]. The effect of relieving renal damage is mainly reflected in the kidney and renal blood vessels, which can (1) reduce the levels of SCr, BUN, UA, urine MA, β2-MG and ET in renal tissue [7] , (2) increase IGF-1, promote NO secretion, reduce ET, improve perfusion, filtration and vascular injury [8]. The regulation of endocrine disorders is mainly reflected in gonadal and prostate vascular endothelial cells and the hypothalamus-pituitary-adrenal cortex axis, which can (1) reduce serum T level, and increase E2 and E2/T level [9] , (2) inhibit VEGF and IGF-1 mRNA levels, and regulate the expression of growth factors [10], (3) increase serum TSH, and decrease hypothalamic TRH, serum T3 and T4 [11]. Anti-inflammatory effects are mainly reflected in prostatic vesicle, glandular cavity, stroma, fibrous tissue and genes, which can (1) reduce serum TNF- α level, inhibit iNOS expression, reduce inflammatory response [12], (2) down-regulate inflammatory/immune genes, up-regulate cell cycle/cell structure genes, promote the up-regulation of hormones and melanin, and promote cell proliferation [13]. The regulation of reproduction is mainly reflected in gene expression, hypothalamic-pituitary-gonadal axis, target gland axis, telomerase and gonads, which can (1) up-regulate azoospermia deletion gene (DAZ) -related protein 1, epididymal specific α- mannose glycosidase precursor and sperm cation channel 1 [14], (2) improve testicular structure, increase the number of spermatogenic tubules, spermatogenic cells and spermatogenesis, restore the number of mesenchymal cells, and increase the eosinophilic intensity [15], (3) affect cell proliferation signaling pathway and stimulate spermatogenic cell regeneration [16], (4) improve the microenvironment of ovarian function, reconstruct reproductive endocrine system [17], (5) restore telomerase activity in testicular tissue [18], (6) regulate GH and IGF-1 levels, affecting growth and development [19]. The regulation of immune function is mainly reflected in brain protein expression, immune organs and immune cells, which can (1) regulate cytokines TNF-α, TGF-β, IL-17 [20], (2) improve T, B lymphocyte proliferation ability and IFN- λ content [21], (3) increase the count of CD+4, CD+8, T cell, macrophage phagocytosis rate, thymus and spleen index in the blood [22]. The anti-stress effect is mainly reflected in the HPA axis and genes, which can (1) regulate neurotransmitter and hormone metabolism, inhibit the synthesis of adrenalin glucocorticoid, increase plasma 5-HT, thus enhance the anti-stress ability [23], (2) reduce the hypermethylation level of Ntf3 gene caused by PTSD [24]. The protective effect is mainly reflected in the spinal cord and gene expression, which can 1) improve the apoptosis index of spinal cord cells and have prednisone-like effects [25], (2) up-regulate osteogenic differentiation genes and down-regulate lipogenic differentiation genes, promote osteoblast differentiation and inhibit lipoblast differentiation [26].

The group prescription medicine that afore-mentioned of Jingui Shenqi pill is *Radix Rehmanniae*, *Rhizoma Dioscoreae, Fructus Corni*, *Poria*, *Rhizoma Alismatis*, *Cortex Moutan*, *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata*. Pharmacological studies found that the main components of *Radix Rehmanniae* are catalpol, triterpenes and rehmannii polysaccharides, the main effects of which include cytotoxicity, anti - inflammation, lowering blood sugar and lipid. The mechanism of its cytotoxic activity is that catalpa protects the apoptosis of SH-SY5Y cells in human neuroma cell line induced by high glucose [27]. Anti-inflammatory mechanism is to inhibit the production of NO, the phosphorylation of extracellular signal ERK1/2 and nuclear translocation of NF-κ 65 protein, and the release of inflammatory mediating agent with 2, 5-dihydroxyacetophenone [28]. The mechanism of immune regulation is to (1) have immune-enhancing activity [29], (2) rehmannia glutinosa can promote dendritic cell maturation and enhance immunity [30]. The mechanism of hypoglycemic and lipid-lowering effect is to (1) regulate glucose and lipid metabolism in fat cells [31], (2) promot GLP-1 and GIP secretion to treat obese diabetic rats [32]. The anti-osteoporosis mechanism is to (1) improve the proliferation and differentiation ability of osteoblast line MC3T3-E1 cells [33], (2) inhibit the differentiation and the formation of osteoclasts and reduce bone loss [34]. The mechanism of organ protection is to (1) prevent liver damage related to reactive oxygen species [35], (2) promote the expression of surface antigens CD29,

CD44, CD90 and CD105 [36]. The protective mechanism of cardiovascular, cerebrovascular and central nervous system is to (1) promote angiogenesis by caffeic acid in rehmannia glutinis [37], (2) activate the PI3K/ AKT-B signaling pathway in alzheimer's disease [38], (3) protect cerebrovascular units and promote recovery of nerve function after cerebral ischemia [39], (4) up-regulate the expression of p-AKT, inhibit the white matter injury caused by chronic cerebral ischemia [40], (5) increase the production of physiological NO, reduce the production of ONOO(-), and improve myocardial ischemia reperfusion injury [41], (6) stimulate Bcl-2 expression, inhibit Bax protein expression, and protect lps-induced neuronal apoptosis by catalpa [42], (7) reduce MDA accumulation in serum and hippocampal tissues of dementia rats and the level of glutamate, and increase SOD activity by rehmannia glutinosa oligosaccharide [43].

The main components of *Fructus Corni* are cycloene, ether terpene, polysaccharide, and its main functions are myocardial protection, glucose and lipid lowering, antioxidant, etc. The mechanism of total glycosides from cornus officinalis in myocardial protection is to inhibit myocardial cell apoptosis [44]. The mechanism of lowering glucose and lipid is to (1) cure sugar kidney in early stage by cornus officinalis granule [45], (2) reduce serum triglyceride and insulin levels by fructus corni in mice [46]. The mechanism of antioxidant action is to remove DPPH free radicals and improve the total antioxidant capacity FRAP value [47]. The neuroprotective mechanism is that cycloallyl ether terpene glycosides can improve the learning and memory ability of ischemic rats and the expression of BDNF in the hippocampus [48]. The anti-tumor effect was reflected in the inhibition of polysaccharide of dogwood on the growth of S180 sarcoma mice, increasing the number of T cells $CD4^+$ and decreasing the $CD8^+$ [49].

The main components of *Rhizoma Dioscoreae* are polysaccharides, saponins, pigments, etc. And hypoglycemic, anti-tumor, immune regulation are the main functions. The hypoglycemic mechanism is to (1) increase the content of C-peptide [50], (2) reduce the blood glucose and increase the activity of HK, SDH and MDH of diabetic mice [51]. The anti-tumor mechanism is to (1) water-soluble yam polysaccharide have anti-proliferation ability for colon cancer cells [52], (2) dioscin inhibit proliferation of human liver cancer cells [53]. The immune regulation mechanism is to (1) Chinese yam crude polysaccharide inhibit gastric emptying and small intestine propulsion, and increase the index of spleen and thymus in mice with spleen deficiency [54], (2) reduce MDA content, improve the ability of the body to produce NO and IL-l β, and enhance immunity [55]. The anti-aging mechanism is that polysaccharide of purple yam increases GSH, decrease MDA and inhibit the expression of aging genes P53 and P21 in D-galactose aging rats [56]. The antioxidant mechanism of diosgenin is to (1) diosgenin improve the activity of antioxidant enzymes, scavenging free radicals, and reduce the formation of peroxidation lipid in aging mice [57], (2) polysaccharide of Chinese yam increase the activity of SOD and gsh-px in kidney tissue, and decrease the level of MDA [58].

Poria mainly consists of poria cocos, gum and choline, which can diuretic, improve immunity and fight tumors. Its diuretic mechanism is reflected in (1) poria cocos water decoction can diuretize rats under normal saline load [59], (2) increase the urine volume in rabbits, and present a positive vector validity relationship [60]. The immune mechanism of triterpenes is (1) triterpenes improve the phagocytosis [61], (2) promote the proliferation of T lymphocytes and inhibit the proliferation of esterification derivatives [62], (3) tuckaolin inhibit lymphocyte transformation induced by PHA, LPS and ConA, and inhibit skin contact hypersensitivity [63]. The anti-tumor mechanism is poria cocos polysaccharide inhibits Lewis lung cancer mice spontaneous lung metastasis and increases the expression of WBCCD11b and CD18 mRNA in peripheral blood [64]. The anti-aging mechanisms is (1) poria cocos polysaccharide can increase the activity of T-SOD and Cu-SOD, and reduce the content of MDA in serum of rats, (2) the substance extracted from poria cocos can regulate tyrosine RNA level [65].

The main components of *Rhizoma Alismatis* are polysaccharides, terpenes, nicotinamide and 4-pyrazin-2-yl-but-3-ene-1, 2-diol, and the main effects are diuretic, antioxidant, immune regulation, etc. Diuretic effect is reflected in alcohol extract, water extract, 24-acetyl alismatil. A diuretic can promote diuretic effect [66]. The mechanism of anti-oxidation and vascular protection is to enhance NO secretion, increase SOD activity and inhibit endothelial cell apoptosis [67]. Anti-calculus was manifested by triterpene extracts that inhibited the formation of urinary calcium oxalate stones in rats [68]. The mechanism of immune regulation and anti-inflammation is (1) methanol hot extract can exert anti-nephritis activity and inhibit complications in rats of IC nephritis [69], (2) alisma can inhibit NO production in lipopolysaccharide activated macrophages, and enhance the function of reticuloendothelial system [70]. The effects of the extract on blood pressure and lipid lowering are shown in (1) the extract reduces blood lipid in hyperlipidemia mice [71], (2) alcohol extract protects pancreatic islets and reduces blood glucose and lipid levels in glucose rats [72], (3) terpenes inhibit sympathetic NA release, block Ca2+, and alissinol

inhibits the increase of blood pressure caused by aorta and vasoconstriction [73]. The mechanism of anti-tumor is (1) alisma improves anti-tumor immunity [74], (2) alisol B can induce the Bax nuclear translocation and apoptosis in PC-3 cells of hormone-resistant prostate cancer [75].

The main components of *Cortex Moutan* are paeonol, total glycoside of paeonicin, and polysaccharide of paeonicin, and its main effects are anti-inflammatory, cognitive improvement, antioxidant, etc. The anti-inflammatory mechanism is that the decoction inhibits many kinds of bacteria such as staphylococcus aureus and escherichia coli [76]. The mechanism of improving cognitive function is that paeonol could reduce the neurotoxicity induced by D-galactose and improve cognitive function. The mechanism of anti-asthma is to reduce airway hyperresponsiveness and serum IgE level in asthmatic rats [77]. The anti-tumor mechanism is (1) the pill increases sensitivity to radiation [78], (2) paeonol inhibits the proliferation of human liver cancer cells, breast cancer cells, and rat gastric cancer cells, and always induces an apoptosis [79], (3) inhibits tumor angiogenesis, tumor invasion and metastasis [80]. The antioxidant mechanism is that paeonol regulates the expression of acetylase SIRT1 protein and its substrate, protects inner epidermal cells and fights premature aging [81].Immune regulation is manifested by (1) up-regulating the expression of autophagy protein LC 3, preventing and treating liver injury caused by second-degree scald [82], (2) improving the percentage of ANAE positive lymphocytes and the release of WBC mobility factor in peripheral blood [83].

The main components of *Ramulus Cinnamomi* are cinnamaldehyde, calamus ene, acetic acid and other meat ester, which has the functions of diuretic, phlegm relieving cough, anti-inflammatory and sensitization, etc. Among them, diuretic effect is manifested by intravenous injection of cassia twig by dogs, which could increase urine volume [84]. The mechanism of removing phlegm and relieving cough is that cinnamon oil is excreted through the lung to dilute the concentration of secretions. Anti-sensitivity was manifested as the inhibition of IgE induced mast cell granule reaction by volatile oil [85]. Anti-inflammatory performance of cinnamaldehyde inhibition of auricle swelling in mice caused by xylene and increased peritoneal capillary permeability [86]. The antiviral manifestations are (1) the decoction of cassia twig inhibits orphan virus and Asian influenza a strain of kynidae 68-1, (2) volatile oil and cinnamaldehyde inhibit the proliferation of H1N1 virus in MDCK cells [87]. Antipyretic and analgesic manifestations include cinnamaldehyde and sodium cinnamate dilating skin vessels, ncreasing heat dissipation and blood circulation [88].

The main components of *Radix Aconiti Lateralis Preparata* are polysaccharides, saponins, aconite alkaloids, and its main functions are heart strengthening, lipid lowering, anti-depression, etc. The mechanism of improving asthma is that euphrine activates β2 receptors and relaxes tracheal smooth muscle [89]. The lipid lowering mechanism is that polysaccharide from aconite can reduce cholesterol content in rats [90]. The mechanism of anti-depression is reflected in (1) polysaccharide from aconite can increase BDNF in hippocampus of mice with social failure [91], (2) aconite alkaloid can fight depression more quickly and aconite polysaccharide has better long-term effect. The anti-rheumatism mechanism is that aconitine can down-regulate the signal pathway of NF-κB and inhibit the production of osteoclasts [92]. The mechanism of cardiac activity is that 45 compounds such as alkanolamine-diterpene alkaloids and monoester-diterpene alkaloids can activate β2 receptors [93]. The mechanism of protection of myocardium is that polysaccharide from aconite can increase autophagy and reduce apoptosis of myocardium in H9c2 myocardium through activating AMPK/mTOR signaling pathway [94].

To sum up, the whole prescription of Jingui Shenqi pill and its constituent drugs have many pharmacological effects. In order to illustrate the function of the constituent drugs of Jingui Shenqi pill, we summarized the active components and action targets of the whole prescription and its constituent drugs. The pharmacological mechanism and targets are shown in Figure 2.

The whole prescription pharmacology mechanism and function of Jingui Shenqi pill are not exactly correspond to its constituent drugs. The pharmacological effect of the whole prescription emphasizes the regulation of reproduction, but there is little mention of such function in the pharmacological research of its constituent drugs, which may be related to the synergistic effect of drugs, and it is also the essence of TCM to pay attention to the compatibility of "monarch, minister, assistant and guide". Pharmacological analysis of its constituent drugs showed that many drugs, including *Rhizoma Dioscoreae, Fructus Corni*, *Poria*, *Rhizoma Alismatis and Cortex Moutan,* had anti-tumor effects, but the whole prescription had not been involved in the pharmacological analysis, which may be related to drug antagonism in the pharmacological effect, and it was also a manifestation of the "mutual inhibition" effect stressed by TCM. And such problems need to be further studied and confirmed by more comprehensive pharmacological experiments, and also the aspects to be improved in the follow-up experiments.

In general, although the compatibility of prescription is more concerned about synergistic

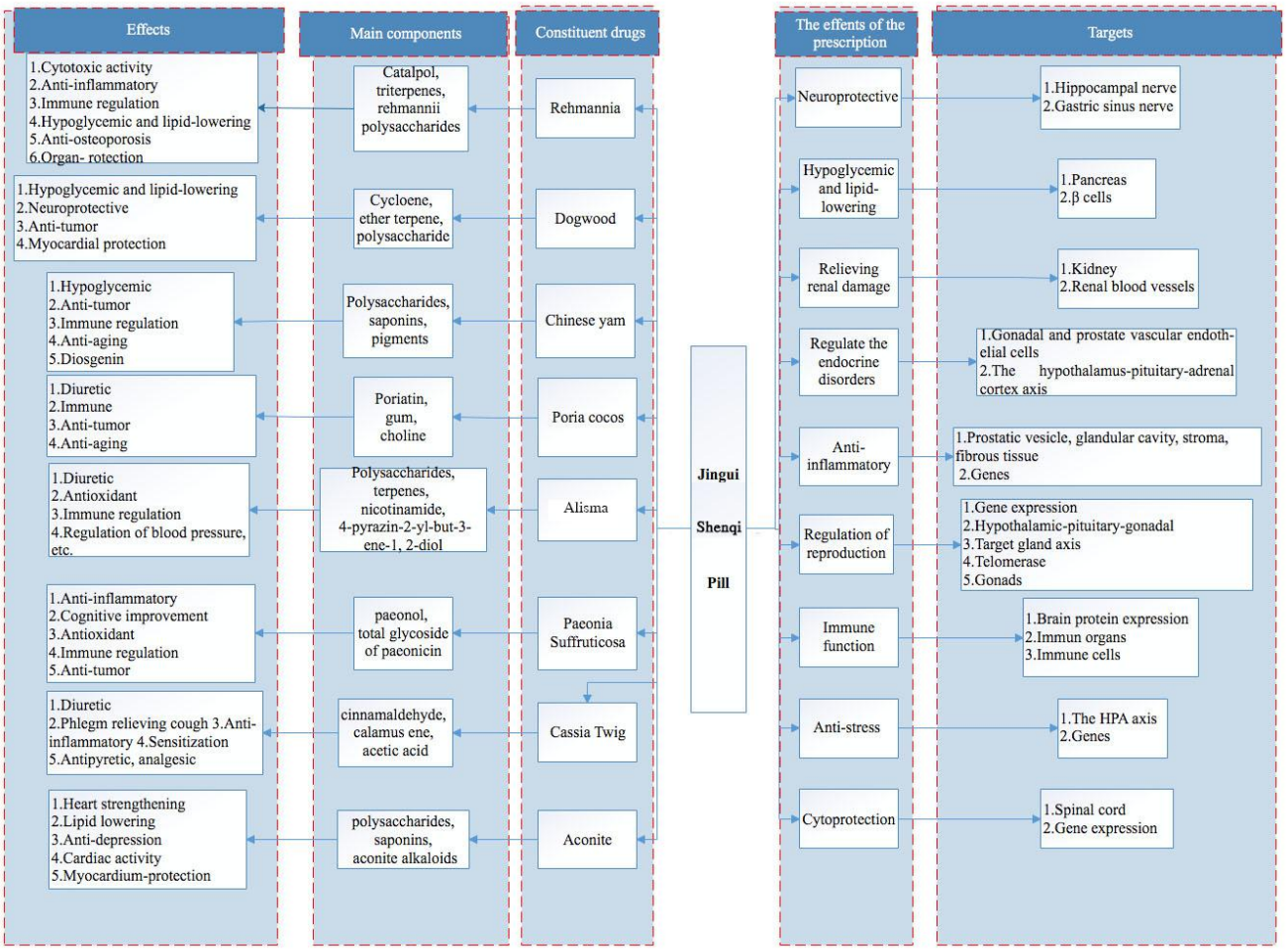

Figure 2. The Pharmacological Mechanism and Targets of the Prescription

effect than a certain effect of its constituent drugs, in the compatibility of "monarch, minister, assistant and guide", the effects of constituent drugs are followed by the whole prescription. Only by understanding how the single of the constituent drugs works can we explore the mechanism of the whole prescription completely.

Therefore, the research on the pharmacological mechanism of the constituent drugs and the whole prescription is definitely the direction of the gradual development and improvement of TCM, and it is also another way for the better and more scientific service in clinical practice.

Clinical application

In the TCM, under the guidance of the principle of syndrome differentiation and treatment, Jingui Shenqi pill is used in the treatment of various diseases. As described in *Yizong Jinjian*, "Putting a small amount of *Ramulus Cinnamomi* and *Radix Aconiti Lateralis Preparata* into a large number of Yin nourishing drugs is to warm the kidney slightly instead of supplementing the kidney-fire, that is, to generate kidney- Qi." Jingui Shenqi pill focus on drawing Yang from Yin, making both of which sufficient. And the curative effect is distinct in the treatment of kidney disease, mainly for the difficulty in urination, bloody urine, drench, etc. *Gezhi Yulun·Xianghuo lun* puts forward that the heart pertains to fire in the five elements and is located in the upper energizer, the kidney pertains to water in the five elements and is located in the lower. Heart-fire has to descend to the kidney to warm kidney-Yang and prevents abnormal of water; kidney-water has to ascend to nourish heart-Yin and prevents hyperactivity of heart-Yang. One descends and another ascends, in this way can guarantee the continuity of life. The relationship between heart and kidney is manifested in the dynamic balance of blood, Yin and Yang, water and fire so that Jingui Shengqi pill can also be used in the treatment of heart disease such as palpitation, angina and so on. The lung pertains to metal, and the kidney pertains to water, the metal gives birth to water and the water moistens metal in turn. The relationship between the lung and

kidney is signified by respiration and fluid metabolism. This shows the physiological dependence and pathological correlation of lung and kidney, so when it comes to treating respiratory system disease, treating kidney at the same is much better. Jingui Shenqi pill is often used to treat cough, lung distension, pulmonary tuberculosis, pulmonary carbuncle, etc. In addition, it also can be used for the treatment of other diseases which reflects the theory of treating different diseases with the same method and treats the same syndrome with the same methods.

Jingui Shenqi pill plays an important role in many aspects of physiological process according to the mechanism of modern pharmacology. Its pharmacological mechanism and clinical effects are shown in **Table 1.**

Conclusion

Table 1 Corresponding Clinical Application and Pharmacological Analysis of Jingui Shenqi pill and Its Constituent Drugs

Pharmacological effects	Clinical application
Neuroprotection effect	① Combined with Buyang Huanwu decoction in the treatment of diabetic peripheral neuropathy, the effective rate is significantly better than the mecobalamine group [95]. ② The treatment of neurogenic bladder is better than that of mecobalamine combined with vitamin B group [96]. ③ Combined with modern medical methods and Buyang Huanwu decoction in the treatment of traumatic cervical spinal cord injury, the ASIA score is superior to the modern treatment alone [97].
Regulate secretion and metabolism	① Treatment of SCH can improve the high level of TCHO and LDL and inhibit the overexpression of TSH [98]. ② Combined thyrine for hashimoto thyroiditis with hypothyroidism, increased FT3 and FT4, and decreased TSH, the total effective rate is higher than that of levothyroxine tablets group [99]. ③ The levels of FBG, PBG, HbA1C, TC, TG and ldl-c were significantly reduced in the treatment of diabetes, and the total effective rate was better than that of the metformin group [100]. ④ Combined with Xuehiang capsules for hyperlipidemia, the reduction of TC and TG and the increase of HDL-c are significantly better than those of Xuezhikang group [101]. ⑤ Combined hemodialysis treatment of uremia, in small molecule toxin (BUN, Scr) is statistically significant [102]. ⑥ Treatment of hyperuricemia significantly improved UA, Scr, BUN and blood β2-MG [103]. ⑦ To treat pap, increase the expression of GR-α in skin lesions, reduce the expression of GR-β, and improve the sensitivity of GR [104].
Delayed renal damage	① Treatment of DN, the SF-36 score and total effective rate were higher than western medicine treatment group [105]. ② In the treatment of gouty nephropathy, the changes of WBC, N%, Scr, BUN and 24h-TP are significantly better than those of allopurinol group [106]. ③ In the treatment of chronic renal failure, the effective rate and decrease trend of BUN and Cr are better than western medicine treatment [107].
Anti-inflammatory effects	① The combination of western medicine in the treatment of bronchial asthma in the elderly can reduce airway inflammation and improve the level of immunoglobulin, which is better than the use of western medicine alone [108]. ②Combined hemodialysis treatment of hemodialysis patients, effectively improve the microinflammatory performance [109].

	③ Combined with clarithromycin to treat chronic prostatitis in the elderly, the improvement of total response rate, WBC count, NIH-COSI score and sIgA level is better than that of clarithromycin group [110]. ④ Treating knee osteoarthritis, the effective rate is higher than the modern medicine triple methods [111]. ⑤ Combined western medicine treatment of chronic bronchitis, the total effective rate is superior than pure western medicine treatment [112].
Regulation of reproduction	① In the treatment of polycystic ovary syndrome, LH, FSH, PRL, prolactin, ovarian volume and other improvements are better than those of eparylestradiol cyprogesterone tablet group [113]. ② Sperm count, motility and motility rate are improved and the total effective rate was better than that of clomiphene citrate capsule combined inosine tablet group in patients with low or weak sperm [114]. ③ Treatment of infertility, increased FSH, LH and testosterone [115]. ④ In the treatment of male partial androgen deficiency, serum testosterone level and follicle-stimulating hormone increase significantly, which may play a role by improving the balance of pituitary-gonadal axis [116].
Immunomodulation	① In the treatment of nephrotic syndrome, the time of urine protein negative transition, edema resolution and infection is better than that of Qihuang granule + prednisone group [117]. ② Combined with western medicine to treat bronchial asthma in remission, the result suggests that the IL-2 and IFN-γ are higher than western medicine group, and IL-4, IL-5, IgE and complement C are lower than western medicine group, so as to optimize cellular and humoral immunity [118]. ③ Combined with levothyroxine sodium in the treatment of hypothyroidism, the result shows that the levels of TPOAb and TgAb are lower than those of western medicine group [129]. ④ Combined with reenqing for the treatment of chronic urinary tract infection in the elderly, the results demonstrate that the improvement of immune function was better than that of the Relinqing group [120].
Reduce blood pressure, protect heart and improve circulation	①Combined with CCB drugs, the results suggest that the control of blood pressure and improvement of blood lipids are better than western medicine group [121]. ② Combined with western medicine to treat chronic cardiac insufficiency, the improvement of cardiac function, myocardial hypoxia ability, blood viscosity and blood lipid are better than western medicine group [122]. ③Combined western medicine treatment for coronary heart disease after PCI, the results demonstrate that the MLHFQ scale, 6mWT, SAQ, doppler echocardiography, safety test and TCM syndrome improvement are significantly superior than the control group [123]. ④ Treatment of pulmonary heart disease right heart failure with linggui zhugan decoction, the result shoes that the improvement degree of PaO2, PaCO2, BNP and RVEF are better than that of the control group [124].
Anti-stress	① Combined with paroxetine for PTSD, the result shows that PCL and PSQI scores are lower than those of paroxetine group [125]. ② Treatment of neurasthenia with flupentixol-melitracen, the result shows that the sleep quality, depression and anxiety scores and serum correlation indexes are better than the melitracen group [126].

Brain cell protection	① In the treatment of mild cognitive impairment in the elderly, the improvement degree is better than that of Nimodipine group [127]. ② In the treatment of senile dementia, ADL, FAQ score and total effective rate are significantly higher than those of naofukang tablet group [128].
Antineoplastic	① The effective rate of treating cancer fever is higher than indomethacin enteric-coated tablets [129]. ② In the treatment of head and neck tumors, symptom improvement and KPS score are significantly improved [130]. ③ Combined acupuncture treatment of postoperative urinary retention after cancer, the total effective rate is higher than acupuncture group [131].

In conclusion, making good use of the research outcomes of modern pharmacology to lay the foundation of TCM and combining both for the complementary effects in applications are of prime importance. That gives us new insights into suitable clinical applications, ranging from clinical applications of drugs using modern pharmacological mechanism to inferring the correlated pharmacological functions in clinical applications.

However, there are still some problems to be improved and solved, including the following three aspects. Firstly, it lacks of data on the relevant pharmacological mechanism research, and the modeling, target and pharmacological mechanism are not comprehensive enough in the whole prescription pharmacological analysis research, and the interaction mechanism between prescription drugs need in-depth experimental exploration. Secondly, the research methods of scientific research, such as randomization and double-blind, are not perfect enough in many clinical studies and it also lacks of prospective studies, therefore the generalizability of the results is uncertain. Thirdly, the combination of pharmacological mechanism analysis results and clinical application are not closely enough, and it lacks of relevant data to deduce the pharmacological mechanism from the clinical research. In view of the above problems, we should improve the level of the pharmacological mechanism research, the standard of combing pharmacological mechanism with clinical research, so as to provide a reliable basis for the more accurate and scientific application of Jingui Shenqi pill to prevent and treat diseases.

Abbreviations

TCM, Traditional Chinese Medicine.

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Competing interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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