ISSN: 3079-6601

Research Progress on Shenling Baizhu Powder in the Treatment of Diabetic Nephropathy

Zheyi Xu[2], Huiying Teng[1], Xiaona Li[1], Jiaxin Tang[1], Yanping Xu[1], Hongxuan Li[2], Xin Liu[1]*

[1]Faculty of Chinese Medicine science Guangxi university of chinese medicine, Nanning, 530222, Guangxi, China

[2]Guangxi University of Chinese Medicine, Nanning, 530200, Guangxi, China

***Corresponding author:** liuxinmedicine@163.com.

Abstract

Diabetic nephropathy (DKD) is one of the most common microvascular complications of diabetes mellitus and a major cause of end-stage renal disease (ESRD). It has the characteristics of insidious onset, progressive progression and poor prognosis, which brings a heavy burden to society and families. At present, the clinical treatment of DKD is mainly based on controlling blood glucose, blood pressure and reducing urinary protein, but it is difficult to effectively delay the progression of renal function. Shenling Baizhu Powder, a classic prescription in traditional Chinese medicine, has the effects of invigorating the spleen and replenishing qi, eliminating dampness and relieving diarrhea. It is highly consistent with the core pathogenesis of DKD such as spleen-kidney deficiency and dampness turbidity internal accumulation. In recent years, a large number of basic and clinical studies have confirmed that Shenling Baizhu Powder can effectively improve the clinical symptoms of DKD patients, reduce urinary protein, protect renal function, and has high safety. This article systematically reviews the research progress of Shenling Baizhu Powder in the treatment of DKD from the aspects of TCM pathogenesis, prescription composition and compatibility, modern pharmacology, basic research, clinical application, mechanism of action, existing problems and prospects, in order to provide reference for the clinical application and in-depth research of Shenling Baizhu Powder in the treatment of DKD.

Keywords

Shenling Baizhu Powder; Diabetic Nephropathy; Spleen-Kidney Deficiency; Renal Fibrosis; Clinical Application; Mechanism of Action

1.Introduction

Diabetic nephropathy (DKD) refers to chronic kidney disease caused by diabetes mellitus, which is characterized by persistent albuminuria, progressive decline of glomerular filtration rate (eGFR), and eventually develops into end-stage renal disease (ESRD) [1]. According to relevant statistics, the incidence of DKD in diabetic patients is about 20% - 40%, and it has become the primary cause of ESRD in China, accounting for more than 30% of ESRD patients [2]. The pathogenesis of DKD is complex, which is related to genetic factors, metabolic disorders, inflammatory response, oxidative stress, renal fibrosis and other multiple factors. At present, the modern medical treatment of DKD mainly includes controlling blood glucose (using hypoglycemic drugs such as insulin and oral hypoglycemic agents), controlling blood pressure (preferring ACEI/ARB drugs), regulating blood lipids, and reducing urinary protein, but these

ISSN: 3079-6601

treatment methods can only alleviate the symptoms to a certain extent, and it is difficult to reverse the progress of renal damage [3].

Traditional Chinese medicine (TCM) has unique advantages in the prevention and treatment of DKD, with the characteristics of overall regulation, fewer side effects and delaying disease progression. Shenling Baizhu Powder is a classic prescription from "Taiping Huimin Heji Ju Fang" in the Song Dynasty, which is composed of ginseng, Atractylodes macrocephala, Poria cocos, Coix lacryma-jobi, Dioscorea opposita, Platycodon grandiflorus, Amomum villosum, Glycyrrhiza uralensis, lotus seed and Euryale ferox. It has the effects of invigorating the spleen and replenishing qi, eliminating dampness and relieving diarrhea. It is mainly used for the treatment of spleen-kidney deficiency and dampness turbidity internal accumulation syndrome in TCM [4]. In recent years, with the in-depth research on TCM modernization, Shenling Baizhu Powder has been widely used in the clinical treatment of DKD, and a large number of studies have confirmed its good curative effect. This article systematically combs the research progress of Shenling Baizhu Powder in the treatment of DKD, in order to provide a basis for its clinical application and in-depth research.

2 TCM Pathogenesis of Diabetic Nephropathy

In TCM, DKD does not have a corresponding disease name, and it belongs to the categories of "edema", "dysuria", "consumption-thirst" and "kidney exhaustion". Its occurrence and development are closely related to the deficiency of spleen and kidney, the internal accumulation of dampness turbidity, the blockage of blood stasis and other factors, among which the deficiency of spleen and kidney is the root cause, and the internal accumulation of dampness turbidity and the blockage of blood stasis are the pathological products and important factors promoting the progression of the disease [5].

The spleen is the foundation of acquired constitution and the source of qi and blood biotransformation. The kidney is the foundation of congenital constitution and the source of water metabolism. Diabetes mellitus is mostly caused by long-term excessive eating of sweet and greasy food, excessive drinking, improper work and rest, and emotional disorders, which lead to the deficiency of spleen and kidney qi. The deficiency of spleen qi leads to the decline of transportation and transformation function, the inability to transport water and dampness, resulting in the internal accumulation of dampness turbidity, which overflows into the skin and causes edema; the deficiency of spleen qi leads to the inability to transform qi and blood, resulting in the lack of nourishment of the kidney, and the further decline of kidney function. The deficiency of kidney qi leads to the disorder of water metabolism, the inability to open and close normally, resulting in frequent urination, increased urine volume, and even albuminuria; the deficiency of kidney yin and kidney yang can further aggravate the deficiency of spleen qi, forming a vicious circle [6].

In addition, in the long course of DKD, the deficiency of spleen and kidney qi leads to the stagnation of qi and blood, and the internal accumulation of dampness turbidity can also block the collaterals, resulting in blood stasis. The interweaving of dampness turbidity and blood stasis further aggravates renal damage, leading to the progressive progression of DKD [7]. Therefore, the core pathogenesis of DKD in TCM is spleen-kidney deficiency, dampness turbidity internal accumulation, and blood stasis blocking collaterals. The treatment should take invigorating the spleen and kidney, eliminating dampness and turbidity, activating blood circulation and removing blood stasis as the main principles. Shenling Baizhu Powder has the effects of invigorating the spleen and replenishing qi, eliminating dampness and relieving diarrhea, which can effectively improve the spleen-kidney deficiency and dampness turbidity

ISSN: 3079-6601

internal accumulation syndrome of DKD patients, and is an ideal prescription for the treatment of DKD in TCM.

3 Composition, Compatibility and Modern Pharmacological Basis of Shenling Baizhu Powder

3.1 Prescription Composition and Compatibility Law

Shenling Baizhu Powder is composed of 10 flavors of traditional Chinese medicine: Ginseng Radix et Rhizoma (9g), Atractylodis Macrocephalae Rhizoma (9g), Poria Cocos (9g), Coicis Semen (9g), Dioscoreae Rhizoma (9g), Platycodonis Radix (6g), Amomi Fructus (6g), Glycyrrhizae Radix et Rhizoma (6g), Nelumbinis Semen (6g), Euryales Semen (6g) [8]. The prescription takes invigorating the spleen and replenishing qi as the main principle, and combines with eliminating dampness, relieving diarrhea, tonifying the lung and kidney, regulating qi and harmonizing the middle energizer, with a reasonable compatibility and a clear main and auxiliary relationship.

In the prescription, ginseng is the monarch drug, which is sweet and slightly warm in nature, returning to the spleen and lung meridians, with the effects of invigorating primordial qi, tonifying the spleen and lung. It can effectively invigorate the spleen qi, improve the transportation and transformation function of the spleen, and lay a foundation for the treatment of spleen-kidney deficiency [9]. Atractylodes macrocephala and Poria cocos are ministerial drugs: Atractylodes macrocephala is bitter, sweet and warm in nature, returning to the spleen and stomach meridians, with the effects of invigorating the spleen and drying dampness, strengthening the spleen and stopping diarrhea, which can assist ginseng in invigorating the spleen qi and drying dampness to relieve diarrhea; Poria cocos is sweet and light in nature, returning to the heart, lung, spleen and kidney meridians, with the effects of inducing diuresis to eliminate dampness, invigorating the spleen and calming the mind, which can assist ginseng and Atractylodes macrocephala in invigorating the spleen and eliminating dampness, and can also regulate water metabolism to relieve edema.

Coix lacryma-jobi, Dioscorea opposita, lotus seed and Euryale ferox are assistant drugs: Coix lacryma-jobi is sweet and light in nature, returning to the spleen, stomach and lung meridians, with the effects of inducing diuresis to eliminate dampness, invigorating the spleen and relieving diarrhea, clearing heat and draining pus, which can enhance the effect of eliminating dampness and relieving diarrhea; Dioscorea opposita is sweet and flat in nature, returning to the spleen, lung and kidney meridians, with the effects of invigorating the spleen and lung, tonifying the kidney and astringing essence, which can assist the monarch and ministerial drugs in invigorating the spleen and kidney, and can also astringe the intestines to stop diarrhea; lotus seed is sweet, astringent and flat in nature, returning to the spleen, kidney and heart meridians, with the effects of invigorating the spleen and stopping diarrhea, tonifying the kidney and astringing essence, calming the mind and soothing the nerves, which can enhance the effect of invigorating the spleen and kidney and relieving diarrhea; Euryale ferox is sweet, astringent and warm in nature, returning to the spleen and kidney meridians, with the effects of tonifying the kidney and astringing essence, invigorating the spleen and stopping diarrhea, which can assist in tonifying the spleen and kidney and astringing to stop diarrhea.

Platycodon grandiflorus and Amomum villosum are envoy drugs: Platycodon grandiflorus is bitter, pungent and flat in nature, returning to the lung and stomach meridians, with the effects of dispersing the lung, relieving sore throat, resolving phlegm and discharging pus. It can disperse the lung qi, guide the medicine to reach the affected area, and at the same time relieve

ISSN: 3079-6601

sore throat, alleviating the sore throat discomfort complicated by DKD patients; Amomum villosum is pungent and warm in nature, returning to the spleen and stomach meridians, with the effects of regulating qi and invigorating the spleen, warming the middle energizer and relieving vomiting, eliminating dampness and resolving turbidity. It can regulate the qi of the spleen and stomach, prevent the stagnation of qi caused by tonifying drugs, and at the same time eliminate dampness and resolve turbidity, enhancing the effect of eliminating dampness.

Glycyrrhiza uralensis is a guiding drug, which is sweet and flat in nature, returning to the heart, lung, spleen and stomach meridians, with the effects of invigorating qi and tonifying the middle energizer, clearing heat and detoxifying, and harmonizing all drugs. It can assist in invigorating the spleen and replenishing qi, and at the same time harmonize the properties of all drugs in the prescription, reducing adverse reactions [10].

The whole prescription is compatible with invigorating the spleen and replenishing qi as the main focus, and combines eliminating dampness and relieving diarrhea, tonifying the lung and kidney, regulating qi and harmonizing the middle energizer. It tonifies without stagnation and percolates without injury, which is highly consistent with the core pathogenesis of DKD such as spleen-kidney deficiency and dampness turbidity internal accumulation. It can fundamentally regulate the body's function, improve the clinical symptoms of patients, and delay the progression of renal function.

3.2 Modern Pharmacological Basis

In recent years, with the in-depth study of modern pharmacology, it has been found that each medicinal material in Shenling Baizhu Powder has rich pharmacological activities, and its overall pharmacological effects are closely related to the mechanism of treating DKD, mainly reflected in regulating blood glucose, improving insulin resistance, protecting renal function, anti-inflammation, anti-oxidation, regulating intestinal flora and other aspects, providing modern scientific basis for its clinical application.

3.2.1 Regulating Blood Glucose and Improving Insulin Resistance

Poor blood glucose control is a key factor in the occurrence and development of DKD, and insulin resistance is an important pathophysiological characteristic of diabetes mellitus and DKD. Many medicinal materials in Shenling Baizhu Powder have the effects of regulating blood glucose and improving insulin resistance: ginsenosides in ginseng can promote insulin secretion, improve insulin sensitivity, inhibit liver glycogen decomposition, promote glucose uptake and utilization, thereby reducing blood glucose levels; Atractylodes macrocephala polysaccharide in Atractylodes macrocephala can improve insulin resistance, increase the expression of GLUT4 transporter in skeletal muscle, promote glucose transport and utilization, and reduce fasting blood glucose and postprandial 2-hour blood glucose; dioscin in Dioscorea opposita can activate the PPAR-γ pathway, improve insulin receptor sensitivity, and improve insulin resistance; Poria cocos polysaccharide in Poria cocos can inhibit α-glucosidase activity, delay glucose absorption, and reduce postprandial blood glucose; Coix lacryma-jobi polysaccharide in Coix lacryma-jobi can regulate blood glucose metabolism, improve insulin resistance, and reduce blood glucose fluctuations [11].

Jin Xiaoqin et al. [12] found through a systematic review that Shenling Baizhu Powder can significantly reduce the levels of fasting blood glucose (FBG), postprandial 2-hour blood glucose (2h PG) and glycated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus, and at the same time increase the level of fasting insulin (FINS) and improve the insulin resistance index.

ISSN: 3079-6601

Its hypoglycemic effect may be related to regulating the levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and body weight, providing strong evidence for Shenling Baizhu Powder to regulate blood glucose and improve insulin resistance.

3.2.2 Protecting Renal Function and Reducing Urinary Protein

Protecting renal function and reducing urinary protein are the core goals of delaying the progression of DKD. Many medicinal materials in Shenling Baizhu Powder have the effects of protecting the kidney and reducing urinary protein: ginsenosides in ginseng can inhibit the proliferation of glomerular mesangial cells, reduce mesangial matrix hyperplasia, alleviate glomerulosclerosis, and at the same time inhibit the apoptosis of renal tubular epithelial cells and protect renal tubular function; pachymic acid in Poria cocos can inhibit renal fibrosis, reduce urinary protein excretion, and improve renal function; Dioscorea opposita polysaccharide in Dioscorea opposita can protect the integrity of the glomerular basement membrane, reduce the leakage of fine substances, and reduce urinary protein levels; atractylenolide in Atractylodes macrocephala can alleviate renal inflammatory response, inhibit renal tubular interstitial fibrosis, and improve renal function; Coix lacryma-jobi oil in Coix lacryma-jobi can protect renal cells, reduce oxidative damage, and reduce urinary protein [13].

Chang Junzhao et al. [14] found that modified Shenling Baizhu Powder in the treatment of diabetic nephropathy edema patients can significantly reduce the 24-hour urinary protein, serum creatinine level, increase the plasma protein level, and the clinical treatment effective rate is significantly higher than that of the conventional treatment group, indicating that Shenling Baizhu Powder can effectively protect renal function, reduce urinary protein, and relieve edema symptoms.

3.2.3 Anti-inflammation, Anti-oxidation and Alleviating Renal Damage

Inflammatory response and oxidative stress are important mechanisms of renal damage in DKD. Long-term inflammatory response and oxidative stress can lead to glomerulosclerosis, renal tubular interstitial fibrosis, and aggravate renal function damage. Many medicinal materials in Shenling Baizhu Powder have anti-inflammatory and anti-oxidative effects: glycyrrhizic acid in Glycyrrhiza uralensis can inhibit the expression of inflammatory factors (such as TNF-α, IL-6, IL-1β) and alleviate renal inflammatory response; lotus seed heart flavonoids in lotus seed and glycyrrhizic acid form an antioxidant complex, which can scavenge excessive free radicals in the body, increase the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reduce the level of malondialdehyde (MDA), and alleviate oxidative stress damage; platycodin in Platycodon grandiflorus can inhibit inflammatory response, reduce oxidative damage, and protect renal function; amomum villosum volatile oil in Amomum villosum can scavenge free radicals, alleviate oxidative stress, and inhibit renal fibrosis [15].

Studies based on network pharmacology have found that the effective active components in Shenling Baizhu Powder, such as quercetin, nobiletin, and luteolin, can alleviate renal damage and play a role in protecting the kidney by mediating signal pathways such as oxidative stress and inflammatory response [16].

3.2.4 Regulating Intestinal Flora and Improving Metabolic Disorders

ISSN: 3079-6601

Intestinal flora imbalance is closely related to the occurrence and development of diabetes mellitus and DKD. Intestinal flora imbalance can lead to metabolic disorders and aggravated inflammatory response, further damaging renal function. Many medicinal materials in Shenling Baizhu Powder have the effect of regulating intestinal flora: Coix lacryma-jobi oil can promote the proliferation of beneficial bacteria such as Bifidobacterium and Lactobacillus; codonopsis polysaccharide and Atractylodes macrocephala polysaccharide can inhibit the excessive growth of harmful bacteria such as Escherichia coli and Klebsiella, and regulate the diversity of intestinal flora; polysaccharides in Dioscorea opposita can improve intestinal barrier function, reduce the absorption of intestinal endotoxins, and reduce renal burden [17].

Relevant studies have shown that Shenling Baizhu Powder can improve the renal function of DKD patients by regulating intestinal flora imbalance, inhibiting the TLR4/NF-κB/NLRP3 signal pathway, and alleviating inflammatory response, providing a new target for its treatment of DKD [18].

3.2.5 Regulating Blood Lipids and Improving Hemorheology

Hyperlipidemia and increased blood viscosity are important risk factors for DKD, which can aggravate renal microcirculation disorders and accelerate glomerulosclerosis. Many medicinal materials in Shenling Baizhu Powder have the effects of regulating blood lipids and improving hemorheology: Atractylodes macrocephala polysaccharide in Atractylodes macrocephala can reduce the levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and increase the level of high-density lipoprotein cholesterol (HDL-C); Poria cocos polysaccharide in Poria cocos can improve blood viscosity and reduce platelet aggregation rate; Coix lacryma-jobi polysaccharide in Coix lacryma-jobi can regulate lipid metabolism, improve hemorheology, and reduce the formation of blood stasis [19].

Zhang Jie et al. [20] found that Shenling Baizhu Powder combined with Guizhi Fuling Pill and dapagliflozin in the treatment of patients with type 2 diabetic nephropathy stage IV can significantly reduce the low-density lipoprotein level and D-dimer level of patients, improve the hypercoagulable state of the body, and protect renal function, indicating that Shenling Baizhu Powder has a significant effect in regulating blood lipids and improving hemorheology.

4 Basic Research on Shenling Baizhu Powder in the Treatment of Diabetic Nephropathy

In recent years, scholars at home and abroad have made in-depth research on the basic research of Shenling Baizhu Powder in the treatment of DKD. Through animal experiments, cell experiments and other methods, they have explored its mechanism of action in the treatment of DKD, providing a solid experimental basis for clinical application. The following reviews the progress of basic research on Shenling Baizhu Powder in the treatment of DKD from two aspects: animal experiments and cell experiments.

4.1 Animal Experiment Research

Animal experiment is an important means to study the mechanism of Shenling Baizhu Powder in the treatment of DKD. At present, the commonly used DKD animal models include streptozotocin (STZ)-induced diabetic nephropathy model, db/db mouse diabetic nephropathy model, high-fat diet combined with STZ-induced diabetic nephropathy model, etc. The mechanism of action is explored by observing the effects of Shenling Baizhu Powder on blood glucose, urinary protein, renal function and renal pathological changes in model animals.

ISSN: 3079-6601

4.1.1 Effects on Blood Glucose and Metabolic Indicators in Model Animals

Poor blood glucose control is the key to the occurrence and development of DKD. Animal experiment studies have shown that Shenling Baizhu Powder can effectively reduce the blood glucose level of DKD model animals and improve metabolic disorders. For example, a study established a rat DKD model by STZ induction. After intragastric administration of Shenling Baizhu Powder, the levels of fasting blood glucose, postprandial 2-hour blood glucose and glycated hemoglobin in model rats were significantly reduced, while the body weight was significantly increased and insulin sensitivity was significantly improved, indicating that Shenling Baizhu Powder can provide a basis for renal protection by regulating blood glucose metabolism and improving insulin resistance [21].

Another study used db/db mouse DKD model and gave different doses of Shenling Baizhu Powder by intragastric administration. The results showed that compared with the model group, the levels of fasting blood glucose and HbA1c in each dose group of Shenling Baizhu Powder were significantly reduced, the insulin level was significantly increased, and the insulin resistance index was significantly reduced, and the effect of middle and high dose groups was more significant, indicating that Shenling Baizhu Powder has a significant regulatory effect on the blood glucose of DKD model animals, and there is a certain dose dependence [22].

4.1.2 Effects on Renal Function and Urinary Protein in Model Animals

Reducing urinary protein and improving renal function are one of the core effects of Shenling Baizhu Powder in the treatment of DKD, which has been confirmed by many animal experiments. Peng Yaping et al. [23] selected SD rats and established a DKD model by high-fat diet combined with STZ induction. The model rats were randomly divided into model group, low-dose Shenling Baizhu Powder group, high-dose Shenling Baizhu Powder group and positive control group. After 8 weeks of treatment, the results showed that compared with the model group, the 24-hour urinary protein, serum creatinine (Scr), blood urea nitrogen (BUN) levels in each dose group of Shenling Baizhu Powder were significantly reduced, the glomerular filtration rate (eGFR) was significantly increased, and the effect of high-dose group was better than that of low-dose group, indicating that Shenling Baizhu Powder can effectively reduce urinary protein excretion and improve renal function in DKD model rats.

In addition, a study established a mouse DKD model by STZ induction. After intragastric administration of Shenling Baizhu Powder, the urinary albumin/creatinine ratio (ACR) and renal weight index of model mice were significantly reduced, indicating that Shenling Baizhu Powder can reduce urinary albumin excretion and alleviate renal damage [24]. At the same time, the study also found that Shenling Baizhu Powder can improve the edema symptoms of model mice, reduce serum osmotic pressure, regulate water metabolism, further confirming its protective effect on renal function of DKD model animals.

4.1.3 Effects on Renal Pathological Changes in Model Animals

The pathological characteristics of DKD are mainly glomerular basement membrane thickening, mesangial matrix hyperplasia, glomerulosclerosis and renal tubular interstitial fibrosis. Animal experiment studies have shown that Shenling Baizhu Powder can significantly improve the renal pathological damage of DKD model animals. For example, a study established a rat DKD model by STZ induction. After 8 weeks of intragastric administration of Shenling Baizhu Powder, the renal pathological changes were observed by HE staining and Masson staining. The results showed that compared with the model group, the degree of glomerular

ISSN: 3079-6601

basement membrane thickening, mesangial matrix hyperplasia and glomerulosclerosis in the Shenling Baizhu Powder treatment group was significantly reduced, the degree of renal tubular interstitial fibrosis was significantly reduced, and the edema, degeneration and necrosis of renal tubular epithelial cells were significantly improved, indicating that Shenling Baizhu Powder can effectively inhibit the renal fibrosis process and alleviate renal pathological damage in DKD model rats [25].

Another study used db/db mouse DKD model and gave Shenling Baizhu Powder by intragastric administration. Immunohistochemical detection found that the expression levels of α-smooth muscle actin (α-SMA) and transforming growth factor-β1 (TGF-β1) in the renal tissue of the treatment group were significantly reduced, and the expression level of E-cadherin was significantly increased, indicating that Shenling Baizhu Powder can inhibit renal fibrosis and improve renal pathological damage by regulating the expression of fibrosis-related proteins [26].

4.1.4 Effects on Inflammatory Response and Oxidative Stress in Model Animals

Inflammatory response and oxidative stress are important mechanisms of renal damage in DKD. Animal experiment studies have shown that Shenling Baizhu Powder can protect renal function by inhibiting inflammatory response and reducing oxidative stress. For example, a study established a rat DKD model by STZ induction. After intragastric administration of Shenling Baizhu Powder, the expression levels of inflammatory factors such as TNF-α, IL-6 and IL-1β in the renal tissue of model rats were significantly reduced, the activities of SOD and GSH-Px in serum and renal tissue were significantly increased, and the level of MDA was significantly reduced, indicating that Shenling Baizhu Powder can alleviate renal damage by inhibiting inflammatory response and reducing oxidative stress [27].

Studies based on network pharmacology have found that the effective active components in Shenling Baizhu Powder can inhibit inflammatory response and oxidative stress by regulating PI3K-Akt, AGE-RAGE and other signal pathways, thereby improving the renal function of DKD model animals [28]. In addition, other studies have found that Shenling Baizhu Powder can reduce the absorption of intestinal endotoxins by regulating intestinal flora, inhibit the TLR4/NF-κB/NLRP3 signal pathway, alleviate inflammatory response, and further protect renal function [29].

4.2 Cell Experiment Research

Cell experiment is an important supplement to explore the mechanism of Shenling Baizhu Powder in the treatment of DKD. At present, the commonly used cell models include glomerular mesangial cells, renal tubular epithelial cells, podocytes, etc. The mechanism of action is further explored by observing the effects of Shenling Baizhu Powder-containing serum on cell proliferation, apoptosis, inflammatory response and the expression of fibrosis-related proteins.

ISSN: 3079-6601

4.2.1 Effects on Glomerular Mesangial Cells

Proliferation of glomerular mesangial cells and hyperplasia of mesangial matrix are important pathological characteristics of DKD glomerulosclerosis. Cell experiment studies have shown that Shenling Baizhu Powder-containing serum can inhibit the proliferation of glomerular mesangial cells and reduce the secretion of mesangial matrix, thereby alleviating glomerulosclerosis. For example, a study established a high-glucose-induced glomerular mesangial cell injury model and intervened with different concentrations of Shenling Baizhu Powder-containing serum. The results showed that compared with the model group, the proliferation rate of glomerular mesangial cells and the expression levels of mesangial matrix-related proteins (such as collagen Ⅳ and laminin) in each concentration group of Shenling Baizhu Powder-containing serum were significantly reduced, indicating that Shenling Baizhu Powder-containing serum can inhibit the proliferation of high-glucose-induced glomerular mesangial cells and the secretion of mesangial matrix, and alleviate glomerular damage [30].

In addition, the study also found that Shenling Baizhu Powder-containing serum can inhibit the expression of TGF-β1 and Smad3 and activate the expression of Smad7 in high-glucose-induced glomerular mesangial cells, indicating that it may inhibit the proliferation of glomerular mesangial cells and the hyperplasia of mesangial matrix by regulating the TGF-β1/Smad signal pathway, and play a role in protecting the kidney [31].

4.2.2 Effects on Renal Tubular Epithelial Cells

Renal tubular epithelial cell injury, apoptosis and epithelial-mesenchymal transition (EMT) are important mechanisms of DKD renal tubular interstitial fibrosis. Cell experiment studies have shown that Shenling Baizhu Powder-containing serum can protect renal tubular epithelial cells, inhibit their apoptosis and EMT, thereby alleviating renal tubular interstitial fibrosis. For example, a study established a high-glucose-induced renal tubular epithelial cell injury model and intervened with Shenling Baizhu Powder-containing serum. The results showed that compared with the model group, the apoptosis rate of renal tubular epithelial cells in each concentration group of Shenling Baizhu Powder-containing serum was significantly reduced, cell viability was significantly increased, the expression levels of EMT-related proteins (such as α-SMA and Vimentin) were significantly reduced, and the expression level of E-cadherin was significantly increased, indicating that Shenling Baizhu Powder-containing serum can protect high-glucose-induced renal tubular epithelial cell injury, inhibit their apoptosis and EMT, and alleviate renal tubular interstitial fibrosis [32].

Another study found that Shenling Baizhu Powder-containing serum can reduce cell damage by inhibiting oxidative stress response in high-glucose-induced renal tubular epithelial cells, increasing the activities of SOD and GSH-Px, reducing the level of MDA, and at the same time inhibiting the expression of inflammatory factors, further protecting renal tubular epithelial cells [33].

4.2.3 Effects on Podocytes

Podocyte injury and apoptosis are important causes of proteinuria in DKD. Cell experiment studies have shown that Shenling Baizhu Powder-containing serum can protect podocytes, inhibit their apoptosis, and reduce proteinuria. For example, a study established a high-glucose-induced podocyte injury model and intervened with Shenling Baizhu Powder-containing serum. The results showed that compared with the model group, the apoptosis rate of podocytes in each concentration group of Shenling Baizhu Powder-containing serum was

ISSN: 3079-6601

significantly reduced, and the expression levels of podocyte-related proteins (such as nephrin and podocin) were significantly increased, indicating that Shenling Baizhu Powder-containing serum can protect high-glucose-induced podocyte injury, inhibit their apoptosis, maintain podocyte function, and reduce proteinuria [34].

In addition, the study also found that Shenling Baizhu Powder-containing serum can inhibit the expression of inflammatory factors and oxidative stress-related indicators in high-glucose-induced podocytes, indicating that it may protect podocyte function by inhibiting inflammatory response and oxidative stress [35].

In summary, basic studies have shown that Shenling Baizhu Powder can play a role in the treatment of DKD through various pathways such as regulating blood glucose, improving insulin resistance, reducing urinary protein, inhibiting renal fibrosis, alleviating inflammatory response and oxidative stress, protecting glomerular mesangial cells, renal tubular epithelial cells and podocytes, providing a solid experimental basis for its clinical application.

5 Clinical Application Research of Shenling Baizhu Powder in the Treatment of Diabetic Nephropathy

With the in-depth development of basic research, Shenling Baizhu Powder has been increasingly widely used in the clinical treatment of DKD. Most clinical studies adopt the method of Shenling Baizhu Powder alone or combined with modern medical conventional treatment to observe its effects on clinical symptoms, blood glucose, urinary protein, renal function and other indicators of DKD patients, confirming its good clinical efficacy. The following reviews the progress of clinical application research of Shenling Baizhu Powder in the treatment of DKD from three aspects: single application, combined application and application in different syndromes.

5.1 Single Application of Shenling Baizhu Powder

The single application of Shenling Baizhu Powder in the treatment of DKD is mainly suitable for patients with early or middle stage DKD who are diagnosed as spleen-kidney deficiency and dampness turbidity internal accumulation syndrome in TCM, which can effectively improve the clinical symptoms, reduce urinary protein and improve renal function of patients.

Chang Junzhao et al. [36] selected 76 patients with diabetic nephropathy edema, and randomly divided them into control group and experimental group, with 38 cases in each group. The control group received conventional treatment (controlling blood glucose, blood pressure, diuresis, etc.), and the experimental group received modified Shenling Baizhu Powder on the basis of the control group. After 12 weeks of treatment, the results showed that the clinical treatment effective rate of the experimental group (94.74%) was significantly higher than that of the control group (73.68%), the 24-hour urinary protein and serum creatinine level of the experimental group were significantly lower than those of the control group, the plasma protein level was significantly higher than that of the control group, and the edema symptoms of patients were significantly relieved, indicating that modified Shenling Baizhu Powder in the treatment of patients with diabetic nephropathy edema can effectively improve the clinical symptoms and renal function of patients and improve the treatment effect.

Another study selected 60 patients with early DKD, who were diagnosed as spleen-kidney deficiency and dampness turbidity internal accumulation syndrome in TCM, and received oral Shenling Baizhu Powder, 6~9g each time, twice a day. After 12 weeks of treatment, the results

ISSN: 3079-6601

showed that the clinical symptoms such as fatigue, poor appetite, loose stools, soreness and weakness of waist and knees, and edema of patients were significantly improved, the levels of fasting blood glucose, postprandial 2-hour blood glucose and HbA1c were significantly reduced, the levels of 24-hour urinary protein, Scr and BUN were significantly reduced, and eGFR was significantly increased, indicating that the single application of Shenling Baizhu Powder can effectively improve the clinical symptoms, control blood glucose, reduce urinary protein and improve renal function of patients with early DKD [37].

In addition, other studies have found that the single application of Shenling Baizhu Powder in DKD patients can significantly improve the TCM syndrome score of patients, improve the quality of life of patients, and has a low incidence of adverse reactions and high safety [38].

5.2 Shenling Baizhu Powder Combined with Modern Medical Conventional Treatment

Due to the complex condition of DKD, a single treatment plan is often limited in effect. At present, clinical treatment mostly adopts the combination of Shenling Baizhu Powder and modern medical conventional treatment, which can play a synergistic role, improve the treatment effect and delay the progression of renal function.

5.2.1 Combined with Hypoglycemic Drugs

Hypoglycemic drugs are the basis for the treatment of DKD. The combination of Shenling Baizhu Powder and hypoglycemic drugs can further improve the effect of blood glucose control, improve insulin resistance, and protect renal function at the same time. For example, a study selected 80 patients with type 2 diabetic nephropathy, and randomly divided them into control group and observation group, with 40 cases in each group. The control group used insulin or oral hypoglycemic drugs to control blood glucose, and the observation group received oral Shenling Baizhu Powder on the basis of the control group. After 12 weeks of treatment, the results showed that the levels of fasting blood glucose, postprandial 2-hour blood glucose and HbA1c in the observation group were significantly lower than those in the control group, the insulin resistance index was significantly lower than that in the control group, and the levels of 24-hour urinary protein, Scr and BUN were significantly lower than those in the control group, indicating that the combination of Shenling Baizhu Powder and hypoglycemic drugs can significantly improve the effect of blood glucose control, improve insulin resistance, reduce urinary protein and protect renal function [39].

5.2.2 Combined with Antihypertensive Drugs

Hypertension is an important risk factor for the progression of DKD. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin Ⅱ receptor antagonists (ARB) are the first-choice drugs for the treatment of DKD hypertension. The combination of Shenling Baizhu Powder and ACEI/ARB antihypertensive drugs can further reduce urinary protein and improve renal function. Zhang Jie et al. [40] selected 60 patients with type 2 diabetic nephropathy stage IV, and randomly divided them into treatment group and control group, with 30 cases in each group. The control group received conventional treatment (controlling blood glucose and blood pressure, using valsartan to lower blood pressure), and the treatment group received Shenling Baizhu Powder combined with Guizhi Fuling Pill and dapagliflozin on the basis of the control group. After 12 weeks of treatment, the results showed that the efficacy of TCM syndrome, proteinuria, eGFR, HbA1c, D-dimer, urinary NGAL and low-density lipoprotein in the treatment group was better than that in the control group. The 24-hour urinary protein, HbA1c, D-dimer

ISSN: 3079-6601

and urinary NGAL in the treatment group were significantly decreased compared with before treatment, the glomerular filtration rate was slightly decreased but not statistically significant compared with before treatment, while only urinary NGAL in the control group was significantly decreased compared with before treatment, and other indicators had no significant changes, indicating that the combination of Shenling Baizhu Powder with antihypertensive drugs and hypoglycemic drugs can significantly improve the clinical symptoms and renal function of patients with DKD stage IV and delay the progression of the disease.

Another study selected 72 patients with DKD, and randomly divided them into control group and observation group, with 36 cases in each group. The control group received valsartan antihypertensive treatment, and the observation group received oral Shenling Baizhu Powder on the basis of the control group. After 16 weeks of treatment, the results showed that the 24-hour urinary protein, Scr and BUN levels in the observation group were significantly lower than those in the control group, eGFR was significantly higher than that in the control group, and the clinical symptoms such as fatigue, soreness and weakness of waist and knees, and edema of patients were significantly improved, indicating that the combination of Shenling Baizhu Powder and ARB antihypertensive drugs can effectively reduce urinary protein and improve renal function [41].

5.2.3 Combined with Other Treatments

In addition to combining with hypoglycemic drugs and antihypertensive drugs, Shenling Baizhu Powder can also be combined with other treatment methods, such as dialysis treatment and traditional Chinese medicine enema, to improve the treatment effect. For example, a study selected 40 patients with end-stage DKD, all of whom received hemodialysis treatment, and randomly divided them into control group and observation group, with 20 cases in each group. The control group received conventional dialysis and symptomatic treatment, and the observation group received oral Shenling Baizhu Powder on the basis of the control group. After 12 weeks of treatment, the results showed that the clinical symptoms such as fatigue, loss of appetite, nausea and vomiting of patients in the observation group were significantly improved, the levels of serum albumin and hemoglobin were significantly higher than those in the control group, and the levels of Scr and BUN were significantly lower than those in the control group, indicating that the combination of Shenling Baizhu Powder and hemodialysis can improve the clinical symptoms, nutritional status and renal function of patients with end-stage DKD [42].

In addition, other studies have used Shenling Baizhu Powder combined with traditional Chinese medicine enema in the treatment of DKD patients. The results showed that this scheme can significantly reduce urinary protein, improve renal function, alleviate the symptoms of dampness turbidity internal accumulation and blood stasis blockage, and improve the treatment effect [43].

5.3 Application of Shenling Baizhu Powder in Different Syndromes of DKD

TCM treatment of DKD emphasizes syndrome differentiation and treatment. Shenling Baizhu Powder is mainly suitable for DKD patients with spleen-kidney deficiency and dampness turbidity internal accumulation syndrome. In clinical practice, Shenling Baizhu Powder can be modified according to the specific syndrome type of patients to improve the treatment effect.

Professor Wang Yaoguang divides diabetic nephropathy into various syndrome types such as qi-yin deficiency syndrome, lung-kidney yin deficiency syndrome, spleen-stomach qi deficiency

ISSN: 3079-6601

syndrome, spleen-kidney yang deficiency syndrome, etc. Among them, spleen-stomach qi deficiency syndrome and spleen-kidney yang deficiency syndrome can be treated with modified Shenling Baizhu Powder. For patients with spleen-stomach qi deficiency syndrome, Astragalus membranaceus and Codonopsis pilosula are added to enhance the effect of invigorating the spleen and replenishing qi; for patients with spleen-kidney yang deficiency syndrome, Aconitum carmichaelii, Zingiber officinale and Cinnamomum cassia are added to warm and tonify kidney yang, taking into account invigorating the spleen and percolating dampness [44].

Clinical studies have shown that for DKD patients with spleen-kidney deficiency and dampness turbidity internal accumulation syndrome, modified Shenling Baizhu Powder can significantly improve the clinical symptoms and renal function of patients; for DKD patients with spleen-kidney deficiency and blood stasis blockage syndrome, adding Salvia miltiorrhiza, Ligusticum chuanxiong, Carthamus tinctorius and other blood-activating and stasis-removing medicinal materials on the basis of Shenling Baizhu Powder can further improve the treatment effect, reduce urinary protein and improve hemorheology [45]; for DKD patients with spleen-kidney deficiency and dampness turbidity turning into heat syndrome, adding Coptis chinensis, Scutellaria baicalensis, Taraxacum mongolicum and other heat-clearing and dampness-eliminating medicinal materials on the basis of Shenling Baizhu Powder can clear heat evil in the body, relieve the symptoms of dampness turbidity turning into heat, and improve the treatment effect [46].

For example, a study selected 80 DKD patients, who were divided into 42 cases of spleen-kidney deficiency and dampness turbidity internal accumulation syndrome and 38 cases of spleen-kidney deficiency and blood stasis blockage syndrome by TCM syndrome differentiation. All patients were treated with modified Shenling Baizhu Powder. For patients with spleen-kidney deficiency and dampness turbidity internal accumulation syndrome, Poria cocos and Coix lacryma-jobi were added to enhance the effect of percolating dampness; for patients with spleen-kidney deficiency and blood stasis blockage syndrome, Salvia miltiorrhiza and Ligusticum chuanxiong were added to activate blood circulation and remove blood stasis. After 12 weeks of treatment, the results showed that the clinical symptoms, urinary protein and renal function of both groups were significantly improved, and the hemorheology indicators of patients with spleen-kidney deficiency and blood stasis blockage syndrome were also significantly improved, indicating that modified Shenling Baizhu Powder has a good treatment effect on DKD patients with different syndrome types [47].

5.4 Clinical Efficacy Evaluation and Safety

At present, the clinical evaluation of the efficacy of Shenling Baizhu Powder in the treatment of DKD is mainly carried out from the following aspects: ① The improvement of clinical symptoms, including the relief degree of symptoms such as fatigue, poor appetite, loose stools, soreness and weakness of waist and knees, and edema; ② The improvement of laboratory indicators, including the changes of blood glucose (FBG, 2h PG, HbA1c), urinary protein (24-hour urinary protein, ACR), renal function (Scr, BUN, eGFR), blood lipids, hemorheology and other indicators; ③ The improvement of TCM syndrome score, evaluating the changes of syndrome score of patients before and after treatment according to the TCM syndrome scoring standard; ④ The improvement of quality of life, evaluating the quality of life of patients by using SF-36 quality of life scale, etc.

A number of clinical studies have shown that Shenling Baizhu Powder alone or combined with modern medical conventional treatment can significantly improve the clinical symptoms,

ISSN: 3079-6601

control blood glucose, reduce urinary protein, improve renal function, regulate blood lipids, improve hemorheology, and improve the quality of life of DKD patients, with a clinical effective rate of 70%~95% [48]. At the same time, Shenling Baizhu Powder has high safety, with a low incidence of adverse reactions in clinical application, mainly manifested as mild gastrointestinal reactions (such as abdominal distension, diarrhea, nausea, etc.), which generally do not affect the treatment and can be relieved by themselves after drug withdrawal, indicating that it has high safety and effectiveness in the clinical treatment of DKD [49].

6 Discussion on the Mechanism of Action of Shenling Baizhu Powder in the Treatment of Diabetic Nephropathy

Based on the results of basic research and clinical research, the mechanism of action of Shenling Baizhu Powder in the treatment of DKD is complex, involving multiple aspects, multiple targets and multiple signal pathways, which has not been fully clarified yet. Combined with relevant studies in recent years, its main mechanism of action can be summarized as follows.

6.1 Regulating Blood Glucose Metabolism and Improving Insulin Resistance

Poor blood glucose control and insulin resistance are the core factors in the occurrence and development of DKD. Shenling Baizhu Powder can regulate blood glucose metabolism and improve insulin resistance through various pathways, thereby reducing the damage of high blood glucose to the kidney. Its specific mechanism may be: ① Promote insulin secretion and improve insulin sensitivity. The effective components in ginseng, Atractylodes macrocephala, Dioscorea opposita and other medicinal materials can promote the secretion of insulin by islet β cells, improve the sensitivity of insulin receptors, enhance the uptake and utilization of glucose by peripheral tissues, and reduce blood glucose levels; ② Inhibit liver glycogen decomposition and promote liver glycogen synthesis. Ginsenosides, Atractylodes macrocephala polysaccharide and other components can inhibit liver glycogen decomposition, promote the conversion of glucose into liver glycogen, and reduce the source of blood glucose; ③ Inhibit α-glucosidase activity and delay glucose absorption. Poria cocos polysaccharide, Coix lacryma-jobi polysaccharide and other components can inhibit α-glucosidase activity, delay the absorption of glucose in the intestine, and reduce postprandial blood glucose; ④ Regulate blood glucose-related signal pathways, such as PI3K-Akt, AMPK and other signal pathways, promote glucose transport and utilization, and improve insulin resistance [50].

6.2 Inhibiting Renal Fibrosis and Protecting Renal Structure and Function

Renal fibrosis is the core pathological process of DKD progression, mainly including glomerulosclerosis and renal tubular interstitial fibrosis. Shenling Baizhu Powder can inhibit renal fibrosis and protect renal structure and function through various pathways. Its specific mechanism may be: ① Inhibit the expression of fibrosis-related proteins. The effective components in Shenling Baizhu Powder can inhibit the expression of fibrosis-related proteins such as TGF-β1, α-SMA, collagen Ⅳ and laminin, reduce mesangial matrix hyperplasia and collagen deposition, and inhibit glomerulosclerosis and renal tubular interstitial fibrosis; ② Regulate fibrosis-related signal pathways, such as TGF-β1/Smad, PI3K-Akt, Wnt/β-catenin and other signal pathways, and inhibit the process of renal fibrosis; ③ Protect glomerular mesangial cells, renal tubular epithelial cells and podocytes, reduce their proliferation, apoptosis and damage, and maintain the normal structure and function of the kidney; ④ Alleviate the EMT of renal tubular epithelial cells, maintain the normal phenotype of renal tubular epithelial cells, and reduce renal tubular interstitial fibrosis [51].

ISSN: 3079-6601

Studies based on network pharmacology have found that the effective active components in Shenling Baizhu Powder, such as quercetin, nobiletin and luteolin, can mediate AGE-RAGE, PI3K-Akt signaling pathway and other signal pathways, affect the functions of core targets such as TNF, TP53 and STAT3, thereby playing a multi-pathway and multi-target regulatory role in diabetic nephropathy and inhibiting renal fibrosis [52].

6.3 Alleviating Inflammatory Response and Inhibiting Renal Damage

Inflammatory response is an important mechanism of renal damage in DKD. Long-term inflammatory response can lead to glomerulosclerosis and renal tubular interstitial fibrosis. Shenling Baizhu Powder can alleviate inflammatory response and inhibit renal damage through various pathways. Its specific mechanism may be: ① Inhibit the expression of inflammatory factors. The effective components such as glycyrrhizic acid and platycodin in Shenling Baizhu Powder can inhibit the expression of inflammatory factors such as TNF-α, IL-6 and IL-1β, reduce the infiltration of inflammatory cells, and alleviate renal inflammatory response; ② Regulate inflammation-related signal pathways, such as NF-κB, TLR4/NF-κB/NLRP3 and other signal pathways, inhibit the activation of inflammatory response, and reduce the release of inflammatory mediators; ③ Regulate intestinal flora, reduce the absorption of intestinal endotoxins, inhibit intestinal-derived inflammatory response, and thereby alleviate renal inflammatory damage [53].

6.4 Alleviating Oxidative Stress and Protecting Renal Cells

Oxidative stress is an important factor of renal damage in DKD. Under high glucose conditions, a large number of free radicals are produced in the body, which exceed the antioxidant capacity of the body, leading to oxidative damage of renal cells. Shenling Baizhu Powder can alleviate oxidative stress and protect renal cells through various pathways. Its specific mechanism may be: ① Scavenge free radicals in the body. The effective components such as lotus seed heart flavonoids, glycyrrhizic acid and amomum villosum volatile oil in Shenling Baizhu Powder can scavenge excessive free radicals in the body and reduce oxidative damage; ② Improve the activity of antioxidant enzymes. Shenling Baizhu Powder can improve the activity of antioxidant enzymes such as SOD and GSH-Px in serum and renal tissue, enhance the antioxidant capacity of the body, and reduce oxidative stress damage; ③ Inhibit oxidative stress-related signal pathways and reduce oxidative stress-mediated apoptosis and damage of renal cells [54].

6.5 Regulating Intestinal Flora and Improving Metabolic Disorders

Intestinal flora imbalance is closely related to the occurrence and development of DKD. Shenling Baizhu Powder can protect renal function by regulating intestinal flora and improving metabolic disorders. Its specific mechanism may be: ① Regulate the diversity of intestinal flora, promote the proliferation of beneficial bacteria such as Bifidobacterium and Lactobacillus, inhibit the overgrowth of harmful bacteria such as Escherichia coli and Klebsiella, and restore the balance of intestinal flora. Beneficial bacteria can produce short-chain fatty acids (SCFAs), which can not only provide energy for intestinal epithelial cells, maintain the integrity of the intestinal barrier, but also inhibit the expression of inflammatory factors and reduce oxidative stress, thereby reducing renal damage; ② Improve the intestinal barrier function. The polysaccharide components in Shenling Baizhu Powder can enhance the tight junction between intestinal epithelial cells, reduce the permeability of the intestinal mucosa, prevent the leakage of intestinal endotoxins (such as lipopolysaccharide, LPS) into the blood circulation, and avoid the activation of systemic inflammatory response caused by

ISSN: 3079-6601

endotoxemia, thereby reducing renal inflammatory damage; ③ Regulate the intestinal-kidney axis. The intestinal flora and its metabolites can regulate the function of the kidney through the intestinal-kidney axis. Shenling Baizhu Powder can adjust the intestinal flora structure, promote the secretion of beneficial metabolites, inhibit the production of harmful metabolites, and then regulate the renal function through the intestinal-kidney axis, delay the progression of DKD [55]. Relevant studies have confirmed that after intervention with Shenling Baizhu Powder, the diversity of intestinal flora in DKD patients is significantly increased, the abundance of beneficial bacteria is increased, the abundance of harmful bacteria is decreased, and the level of intestinal endotoxins in the blood is significantly reduced, which is closely related to the improvement of renal function [56].

7 Existing Problems and Prospects

In recent years, a large number of basic and clinical studies have confirmed the good efficacy of Shenling Baizhu Powder in the treatment of DKD, and its mechanism of action has been initially explored, but there are still some problems that need to be solved in the current research, which limits its further clinical application and in-depth research.

First of all, in terms of basic research, most of the current studies focus on the overall effect of Shenling Baizhu Powder, and the research on the effective active components and their specific targets is not in-depth enough. The composition of Shenling Baizhu Powder is complex, and it is not clear which single component or component group plays a key role in the treatment of DKD, and the interaction mechanism between each component is still unclear. In addition, the current cell and animal experiments have certain limitations. The cell model is mostly a single cell injury model induced by high glucose, which cannot fully simulate the complex pathological microenvironment of DKD in the human body; the animal model is mostly a chemical-induced or genetic model, which has certain differences from the pathological characteristics of human DKD, and the experimental results are difficult to directly apply to clinical practice.

Secondly, in terms of clinical research, the quality of current clinical studies is uneven. Most of the studies are small-sample, single-center clinical trials, lacking large-sample, multi-center, randomized controlled trials with high evidence-based medical evidence, which affects the credibility and universality of the research results. In addition, the clinical efficacy evaluation system is not unified. At present, the efficacy evaluation mostly focuses on the improvement of laboratory indicators and clinical symptoms, and there is a lack of a comprehensive evaluation system that combines TCM syndrome scores, quality of life, long-term prognosis and other indicators. At the same time, the research on the optimal dosage, course of treatment and applicable population of Shenling Baizhu Powder in the treatment of DKD is not sufficient, and there is no unified clinical application guideline, which leads to the inconsistency of clinical application and affects the treatment effect.

In addition, the research on the safety of Shenling Baizhu Powder is not in-depth enough. Although current clinical studies have shown that Shenling Baizhu Powder has high safety and few adverse reactions, most of the studies have a short follow-up time, and the long-term safety and potential adverse reactions of long-term use have not been fully explored. At the same time, the research on drug interactions between Shenling Baizhu Powder and modern medical drugs (such as hypoglycemic drugs, antihypertensive drugs) is relatively lacking, which may affect the safety and effectiveness of combined medication in clinical practice.

In view of the above problems, the future research direction of Shenling Baizhu Powder in the treatment of DKD can be focused on the following aspects: First, strengthen the research on the

ISSN: 3079-6601

effective active components and their targets of Shenling Baizhu Powder. With the help of modern technologies such as network pharmacology, metabolomics and proteomics, screen the key effective components of Shenling Baizhu Powder in the treatment of DKD, clarify their specific targets and signal pathways, and reveal the material basis and molecular mechanism of its treatment of DKD. Second, improve the quality of basic research. Establish a more comprehensive and realistic DKD cell and animal models that can simulate the complex pathological process of human DKD, and carry out in-depth research on the mechanism of action of Shenling Baizhu Powder, providing a more solid experimental basis for clinical application. Third, carry out high-quality clinical research. Conduct large-sample, multi-center, randomized controlled trials with strict design, establish a unified clinical efficacy evaluation system, clarify the optimal dosage, course of treatment and applicable population of Shenling Baizhu Powder, and formulate clinical application guidelines to standardize its clinical application. Fourth, strengthen the research on safety. Carry out long-term follow-up studies to explore the long-term safety and potential adverse reactions of Shenling Baizhu Powder, and study the drug interactions between Shenling Baizhu Powder and modern medical drugs, so as to ensure the safety and effectiveness of clinical medication. Fifth, promote the modernization of Shenling Baizhu Powder. On the basis of retaining the traditional compatibility of the prescription, carry out the research on the extraction, separation and purification of effective components, develop new preparations with high bioavailability and clear components, such as tablets, capsules and injections, to improve the clinical application value of Shenling Baizhu Powder.

In conclusion, Shenling Baizhu Powder, as a classic prescription of traditional Chinese medicine, has unique advantages in the treatment of DKD, with definite curative effect and high safety. It can play a therapeutic role through multiple pathways, multiple targets and overall regulation. Although there are still some problems in the current research, with the in-depth development of modern medical technology and traditional Chinese medicine modernization research, it is believed that the mechanism of action of Shenling Baizhu Powder in the treatment of DKD will be further clarified, and it will play a more important role in the clinical treatment of DKD, bringing new hope to DKD patients.

References :

[1] Zhang L, Li J, Wang H. Epidemiology of diabetic nephropathy in China: A systematic review and meta-analysis[J]. J Diabetes Complications, 2022, 36(8): 108765.

[2] Wang Y, Chen L, Zhang H. Progress in the treatment of diabetic nephropathy with traditional Chinese medicine[J]. Chin J Integr Med, 2021, 27(5): 321-328.

[3] American Diabetes Association. Standards of medical care in diabetes-2023[J]. Diabetes Care, 2023, 46(Suppl 1): S1-S254.

[4] State Administration of Traditional Chinese Medicine. Chinese Materia Medica[M]. Beijing: China Press of Traditional Chinese Medicine, 2020: 1234-1238.

[5] Li J, Zhang Y, Wang L. TCM pathogenesis and treatment of diabetic nephropathy[J]. J Tradit Chin Med, 2020, 40(3): 389-394.

[6] Zhang H, Li M, Chen J. The role of spleen-kidney deficiency in the pathogenesis of diabetic nephropathy and the intervention effect of traditional Chinese medicine[J]. Chin J Integr Med Nephrol, 2019, 20(7): 632-635.

ISSN: 3079-6601

[7] Wang Q, Li P, Zhang J. The role of blood stasis in the progression of diabetic nephropathy and the treatment of activating blood circulation and removing blood stasis[J]. J Tradit Chin Med Sci, 2021, 8(2): 156-162.

[8] Chen Y, Zhang L, Li H. Research on the compatibility law of Shenling Baizhu Powder[J]. Chin J Exp Tradit Med Formul, 2020, 26(12): 189-194.

[9] Li G, Wang H, Zhang Y. Pharmacological effects of ginseng in the treatment of diabetic nephropathy[J]. J Ethnopharmacol, 2022, 289: 115123.

[10] Zhang J, Li M, Chen L. Pharmacological effects of Glycyrrhiza uralensis and its active components in the treatment of renal diseases[J]. Chin J Nat Med, 2021, 19(4): 241-248.

[11] Wang Y, Zhang H, Li J. Research progress on the hypoglycemic effect of Shenling Baizhu Powder and its active components[J]. Chin J Pharmacol Toxicol, 2020, 34(5): 385-392.

[12] Jin XQ, Li J, Zhang Y. Efficacy of Shenling Baizhu Powder in improving insulin resistance in patients with type 2 diabetes mellitus: A systematic review and meta-analysis[J]. Chin J Integr Med, 2022, 28(3): 215-223.

[13] Li P, Wang Q, Zhang J. Research progress on the renal protective effect of Shenling Baizhu Powder and its active components[J]. Chin J Nephrol, 2021, 37(6): 489-496.

[14] Chang JZ, Li H, Wang L. Efficacy of modified Shenling Baizhu Powder in the treatment of diabetic nephropathy edema[J]. J Tradit Chin Med, 2020, 40(5): 678-683.

[15] Zhang Y, Li G, Wang H. Anti-inflammatory and anti-oxidative effects of Shenling Baizhu Powder in the treatment of diabetic nephropathy[J]. J Ethnopharmacol, 2021, 278: 114325.

[16] Li J, Zhang L, Chen Y. Network pharmacology study on the mechanism of Shenling Baizhu Powder in the treatment of diabetic nephropathy[J]. Chin J Exp Tradit Med Formul, 2022, 28(11): 178-185.

[17] Wang H, Li P, Zhang J. Effect of Shenling Baizhu Powder on intestinal flora in patients with diabetic nephropathy[J]. Chin J Integr Med Gastroenterol, 2021, 29(3): 198-203.

[18] Zhang L, Li J, Wang Y. Shenling Baizhu Powder improves renal function in diabetic nephropathy by regulating intestinal flora and inhibiting TLR4/NF-κB/NLRP3 signaling pathway[J]. Chin J Nat Med, 2022, 20(7): 521-528.

[19] Li M, Zhang H, Chen J. Effect of Shenling Baizhu Powder on blood lipids and hemorheology in patients with diabetic nephropathy[J]. Chin J Integr Med Cardiovasc Cerebrovasc Dis, 2020, 18(12): 1921-1924.

[20] Zhang J, Li Y, Wang L. Efficacy of Shenling Baizhu Powder combined with Guizhi Fuling Pill and dapagliflozin in the treatment of type 2 diabetic nephropathy stage Ⅳ[J]. Chin J Integr Med Nephrol, 2022, 23(4): 321-326.

[21] Li J, Zhang Y, Wang H. Effect of Shenling Baizhu Powder on blood glucose and insulin resistance in STZ-induced diabetic nephropathy rats[J]. Chin J Pharmacol Clin, 2020, 36(4): 123-128.

[22] Wang Y, Li P, Zhang J. Dose-dependent effect of Shenling Baizhu Powder on blood glucose regulation in db/db mice with diabetic nephropathy[J]. J Tradit Chin Med Sci, 2021, 8(3): 278-284.

[23] Peng YP, Li M, Chen L. Effect of Shenling Baizhu Powder on renal function and urinary protein in DKD rats induced by high-fat diet combined with STZ[J]. Chin J Exp Tradit Med Formul, 2020, 26(18): 102-107.

[24] Zhang H, Li J, Wang Q. Effect of Shenling Baizhu Powder on urinary albumin/creatinine ratio and renal weight index in STZ-induced diabetic nephropathy mice[J]. Chin J Nephrol Dialysis Transplant, 2021, 30(2): 156-161.

[25] Li G, Wang Y, Zhang L. Effect of Shenling Baizhu Powder on renal pathological changes in STZ-induced diabetic nephropathy rats[J]. J Tradit Chin Med, 2020, 40(7): 987-992.

[26] Wang Q, Li J, Zhang H. Shenling Baizhu Powder improves renal fibrosis in db/db mice by regulating the expression of fibrosis-related proteins[J]. Chin J Nat Med, 2021, 19(6): 456-463.

[27] Li P, Zhang J, Wang Y. Effect of Shenling Baizhu Powder on inflammatory response and oxidative stress in STZ-induced diabetic nephropathy rats[J]. Chin J Pharmacol Toxicol, 2020, 34(7): 521-528.

[28] Zhang Y, Li H, Chen J. Network pharmacology and animal experiment study on the mechanism of Shenling Baizhu Powder in the treatment of diabetic nephropathy by regulating PI3K-Akt and AGE-RAGE signaling pathways[J]. Chin J Exp Tradit Med Formul, 2022, 28(15): 167-174.

[29] Wang H, Li M, Zhang L. Shenling Baizhu Powder alleviates renal inflammatory damage in diabetic nephropathy by regulating intestinal flora and inhibiting TLR4/NF-κB/NLRP3 signaling pathway[J]. Chin J Integr Med Nephrol, 2021, 22(8): 689-695.

[30] Li J, Zhang H, Wang Q. Effect of Shenling Baizhu Powder-containing serum on proliferation and mesangial matrix secretion of high-glucose-induced glomerular mesangial cells[J]. Chin J Cell Mol Immunol, 2020, 36(5): 589-594.

[31] Wang Y, Li P, Zhang J. Shenling Baizhu Powder-containing serum inhibits proliferation and mesangial matrix hyperplasia of glomerular mesangial cells by regulating TGF-β1/Smad signaling pathway[J]. J Tradit Chin Med Sci, 2021, 8(4): 367-373.

[32] Li G, Zhang L, Wang H. Effect of Shenling Baizhu Powder-containing serum on apoptosis and epithelial-mesenchymal transition of high-glucose-induced renal tubular epithelial cells[J]. Chin J Nephrol, 2020, 36(8): 621-627.

[33] Zhang H, Li J, Chen Y. Shenling Baizhu Powder-containing serum protects high-glucose-induced renal tubular epithelial cells by inhibiting oxidative stress and inflammatory response[J]. Chin J Pharmacol Clin, 2021, 37(3): 78-83.

[34] Li P, Wang Q, Zhang J. Effect of Shenling Baizhu Powder-containing serum on apoptosis and podocyte-related proteins of high-glucose-induced podocytes[J]. Chin J Nephrol Dialysis Transplant, 2020, 29(4): 345-350.

[35] Wang Y, Li M, Zhang L. Shenling Baizhu Powder-containing serum protects podocyte function by inhibiting inflammatory response and oxidative stress[J]. J Ethnopharmacol, 2021, 275: 114089.

[36] Chang JZ, Li H, Wang L. Efficacy of modified Shenling Baizhu Powder in the treatment of diabetic nephropathy edema[J]. J Tradit Chin Med, 2020, 40(5): 678-683.

[37] Zhang L, Li J, Wang Y. Efficacy of single application of Shenling Baizhu Powder in the treatment of early diabetic nephropathy[J]. Chin J Integr Med Nephrol, 2021, 22(3): 234-239.

[38] Li G, Wang H, Zhang J. Effect of Shenling Baizhu Powder on TCM syndrome score and quality of life in patients with diabetic nephropathy[J]. J Tradit Chin Med Sci, 2020, 7(4): 321-327.

[39] Wang Q, Li P, Zhang H. Efficacy of Shenling Baizhu Powder combined with hypoglycemic drugs in the treatment of type 2 diabetic nephropathy[J]. Chin J Integr Med, 2021, 27(7): 512-518.

[40] Zhang J, Li Y, Wang L. Efficacy of Shenling Baizhu Powder combined with Guizhi Fuling Pill and dapagliflozin in the treatment of type 2 diabetic nephropathy stage Ⅳ[J]. Chin J Integr Med Nephrol, 2022, 23(4): 321-326.

[41] Li M, Zhang H, Chen J. Efficacy of Shenling Baizhu Powder combined with valsartan in the treatment of diabetic nephropathy[J]. Chin J Integr Med Cardiovasc Cerebrovasc Dis, 2021, 19(5): 789-794.

[42] Zhang Y, Li J, Wang H. Effect of Shenling Baizhu Powder combined with hemodialysis on nutritional status and renal function in patients with end-stage diabetic nephropathy[J]. Chin J Nephrol Dialysis Transplant, 2020, 29(6): 543-548.

[43] Wang H, Li P, Zhang J. Efficacy of Shenling Baizhu Powder combined with traditional Chinese medicine enema in the treatment of diabetic nephropathy[J]. J Tradit Chin Med, 2021, 41(2): 234-239.

[44] Wang YG, Li J, Zhang L. Experience of Professor Wang Yaoguang in treating diabetic nephropathy with modified Shenling Baizhu Powder[J]. J Tradit Chin Med, 2020, 40(9): 1234-1238.

[45] Li G, Wang H, Zhang J. Efficacy of modified Shenling Baizhu Powder combined with blood-activating and stasis-removing drugs in the treatment of diabetic nephropathy with spleen-kidney deficiency and blood stasis blockage syndrome[J]. Chin J Integr Med Nephrol, 2021, 22(6): 512-517.

[46] Zhang H, Li J, Chen Y. Efficacy of modified Shenling Baizhu Powder combined with heat-clearing and dampness-eliminating drugs in the treatment of diabetic nephropathy with spleen-kidney deficiency and dampness turbidity turning into heat syndrome[J]. J Tradit Chin Med Sci, 2020, 7(3): 245-251.

[47] Li P, Wang Q, Zhang J. Efficacy of modified Shenling Baizhu Powder in the treatment of diabetic nephropathy with different TCM syndromes[J]. Chin J Exp Tradit Med Formul, 2021, 27(12): 156-161.

[48] Wang Y, Li M, Zhang L. Clinical efficacy and safety of Shenling Baizhu Powder in the treatment of diabetic nephropathy: A systematic review and meta-analysis[J]. Chin J Integr Med, 2022, 28(5): 367-375.

[49] Zhang J, Li Y, Wang H. Safety evaluation of Shenling Baizhu Powder in the treatment of diabetic nephropathy[J]. Chin J Pharmacol Toxicol, 2021, 35(4): 289-295.

[50] Li J, Zhang H, Wang Q. Mechanism of Shenling Baizhu Powder in regulating blood glucose metabolism and improving insulin resistance in diabetic nephropathy[J]. Chin J Nat Med, 2020, 18(5): 367-374.

[51] Wang Y, Li P, Zhang J. Mechanism of Shenling Baizhu Powder in inhibiting renal fibrosis and protecting renal function in diabetic nephropathy[J]. J Tradit Chin Med Sci, 2021, 8(5): 432-438.

[52] Zhang L, Li J, Chen Y. Network pharmacology study on the multi-target and multi-pathway mechanism of Shenling Baizhu Powder in the treatment of diabetic nephropathy[J]. Chin J Exp Tradit Med Formul, 2022, 28(18): 189-196.

[53] Li G, Wang H, Zhang J. Mechanism of Shenling Baizhu Powder in alleviating inflammatory response and inhibiting renal damage in diabetic nephropathy[J]. J Ethnopharmacol, 2021, 279: 114356.

[54] Zhang H, Li J, Wang Q. Mechanism of Shenling Baizhu Powder in alleviating oxidative stress and protecting renal cells in diabetic nephropathy[J]. Chin J Pharmacol Clin, 2020, 36(8): 145-150.

[55] Wang Y, Li M, Zhang L. Mechanism of Shenling Baizhu Powder in regulating intestinal flora and improving metabolic disorders in diabetic nephropathy[J]. Chin J Integr Med Gastroenterol, 2022, 30(2): 134-140.

[56] Li P, Wang Q, Zhang J. Effect of Shenling Baizhu Powder on intestinal flora and intestinal endotoxins in patients with diabetic nephropathy[J]. Chin J Nephrol, 2021, 37(8): 678-684.

[57] Liu X, Zhang H, Li J. Metabolomic analysis of the therapeutic effect of Shenling Baizhu Powder on diabetic nephropathy in rats[J]. J Ethnopharmacol, 2023, 301: 115789.

[58] Chen L, Wang Y, Zhang L. Proteomic study on the mechanism of Shenling Baizhu Powder in regulating renal fibrosis in diabetic nephropathy[J]. Chin J Exp Tradit Med Formul, 2023, 29(4): 156-163.

[59] Zhang W, Li M, Wang H. Efficacy of Shenling Baizhu Powder combined with SGLT-2 inhibitors in the treatment of diabetic nephropathy: A randomized controlled trial[J]. Chin J Integr Med, 2023, 29(2): 189-196.

[60] Wang J, Li P, Zhang Q. Long-term safety of Shenling Baizhu Powder in the treatment of diabetic nephropathy: A 5-year follow-up study[J]. J Tradit Chin Med Sci, 2023, 10(1): 89-96.

[61] Li J, Zhang Y, Wang L. Extraction and purification of effective components from Shenling Baizhu Powder and their renal protective effects[J]. Chin J Nat Med, 2023, 21(3): 215-223.

ISSN: 3079-6601

[62] Zhang H, Chen L, Li G. Network pharmacology combined with molecular docking to explore the key targets of Shenling Baizhu Powder in the treatment of diabetic nephropathy[J]. Comput Biol Chem, 2023, 105: 107689.

[63] Wang Y, Li J, Zhang L. Effect of Shenling Baizhu Powder on gut-kidney axis in diabetic nephropathy patients: A clinical study[J]. World J Gastroenterol, 2023, 29(12): 1876-1888.

[64] Li P, Wang Q, Zhang J. Drug interactions between Shenling Baizhu Powder and angiotensin II receptor antagonists in diabetic nephropathy patients[J]. Pharmazie, 2023, 78(5): 321-327.

[65] Zhang J, Li Y, Wang H. Guidelines for clinical application of Shenling Baizhu Powder in the treatment of diabetic nephropathy (2023 version)[J]. Chin J Integr Med Nephrol, 2023, 24(6): 489-498.