

# Pharmacological Mechanism of Blood Activating Drug Astragalus Membranaceus in the Treatment of Diabetes Peripheral Vascular Disease

Yuying Zhao<sup>1</sup>, Hongxia Su<sup>2,\*</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

<sup>2</sup>Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

\*Correspondence Author

**Abstract:** *Diabetes, as a disease characterized by chronic progressive increase of blood sugar level, is known as “thirst quenching” in the field of traditional Chinese medicine. In clinic, the pathogenesis of diabetes is generally considered to be closely related to heredity, diet, mood, obesity and other factors. In recent years, with the development of social economy, people’s lifestyle has gradually changed, making diabetes one of the chronic diseases threatening human health worldwide. In addition, the number of people with diabetes peripheral vascular disease is on the rise, while in the treatment of diabetes and its complications, traditional Chinese medicine shows significant advantages. Astragalus membranaceus, as a kind of traditional Chinese medicine, has the effects of tonifying qi, promoting yang, promoting water, detumescence, supplementing health and strengthening appearance, and has been widely used in the clinical treatment of diabetes. This article reviews the main components and pharmacological effects of Astragalus membranaceus, analyzes the mechanism of Astragalus membranaceus in treating peripheral vascular diseases of diabetes, and explores the clinical progress of Astragalus membranaceus in treating diabetes.*

**Keywords:** Diabetes, Huangqi, Complication, Pharmacological mechanism.

## 1. Background of Diabetes Peripheral Vascular Disease

### 1.1 Epidemiological Characteristics and Complications of Diabetes

In recent years, with the continuous and comprehensive improvement of people’s material living standards, the prevalence and incidence rate of diabetes in China are rising, which has caused a heavy burden to patients, their families and society. Diabetes is one of the most common endocrine and metabolic diseases, which is characterized by the continuous increase of blood sugar levels. Its pathological factors involve many aspects, such as insufficient insulin secretion or resistance, genetic factors, abnormal metabolism of glucose by the liver, etc [1]. These factors can often interact to jointly lead to the occurrence and development of diabetes. Under the stimulation of continuous high blood sugar level, the body is extremely prone to produce various chronic complications of diabetes. Among them, diabetes related peripheral vascular disease mainly involves major arteries except coronary arteries and cerebral vessels. Its pathological characteristics include thickening, narrowing, occlusion, etc. of the arterial wall, which can lead to ischemic spasm or even necrosis of the local tissues at the distal end of the patient’s limbs. This is one of the most common and serious complications in diabetes. With the increase of the number of diabetes patients in the world, diabetes peripheral vascular disease has become one of the important issues of medical and social concern.

### 1.2 Understanding of Western Medicine on Peripheral Vascular Lesions of Diabetes

Diabetes peripheral vascular disease (DPVD) is one of the more common and serious complications in diabetes patients. It includes macrovascular disease and microvascular disease,

and is a lower limb venous thrombotic disease with high incidence rate [2]. Compared with non diabetes and people without high risk of vascular disease, the incidence of DPVD in diabetes patients and people with high risk of vascular disease has a significant upward trend. The occurrence of diabetes increases the risk of symptoms several times, leading to cardiovascular events and early mortality. 22%~26% of DPVD participants are diagnosed with diabetes [3]. Up to now, modern medicine believes that the basic pathological basis of the disease is mainly due to atherosclerosis. Due to the accumulation of a large number of lipid substances in the vascular intima, abnormal proliferation and contraction of the vascular wall occur [4], resulting in the formation of plaques and fibrous tissue, resulting in thickening of the vascular wall, loss of elasticity, narrowing and obstruction of the lumen, and ultimately leading to the formation of thrombus [5]. Long term illness is prone to intermittent claudication, ulcers, and even gangrene [6]. Because of metabolic disorder, diabetes entered atherosclerosis earlier, with younger age, faster course of disease development, and heavier degree of disease. According to reports, 62% of foot ulcers that are difficult to heal are related to ischemia, and 46% of amputations are related to it. In addition, peripheral vascular disease causes insufficient blood supply to the lower limbs and feet, leading to a decrease in the lower limbs’ resistance to infections. It is easy to be complicated with infection, and in severe cases, limb ischemic necrosis or ulcers may occur, which can become diabetes foot.

The occurrence of this disease is mostly related to unstable blood glucose control, the course of diabetes and neglect of early prevention and treatment. At present, the understanding of western medicine on the pathogenesis of diabetes peripheral vascular disease is still not completely clear, and more people believe that its occurrence may be related to autoimmune function, hemodynamic changes, metabolic disorders, genetic factors, and multi factor interaction. For the

treatment of this disease, Western medicine still lacks a systematic treatment plan [7]. Clinically, symptomatic basic plans such as controlling blood sugar, stabilizing blood pressure, and improving microcirculation are often used for regulation, but the treatment effect is not ideal. A survey study [8] found that the incidence of amputation surgery for severe limb ischemia patients who have not undergone lower limb revascularization is nearly 10% per year, and the clinical disability rate is relatively high.

### 1.3 Traditional Chinese Medicine's Understanding of Peripheral Vascular Lesions of Diabetes

There is no discussion directly corresponding to the name of DPVD in the ancient books of traditional Chinese medicine, but according to its symptoms and signs, it can be considered that diabetes peripheral vascular disease is one of the disease syndromes of diabetes, which belongs to the categories of "diabetes", "kidney elimination", "numbness", "blood stagnation", "collateral disease", "gangrene", and "pulseless disease". In the "Wang Xugao Clinical Medical Case", it is recorded that "after a long period of quenching thirst, numbness can be seen in the hands and feet, and the limbs are as cold as ice". The course of quenching thirst disease is long, and it is easy to experience symptoms such as numbness in the hands and feet, and coldness in the limbs; The book "Ancient and Modern Medical Mirror: Bi Disease" states: "People with Bi disease often experience pain in their hands and feet, but lack compassion." Bi disease patients often experience discomfort such as numbness and numbness in their hands and feet. It is mainly caused by congenital deficiency, stagnation of qi and blood, coagulation of phlegm and dampness in the blood vessels, loss of blood vessels balance, blood loss and meat decay, resulting in this disease. The term "Mai Bi" first appeared in the 43rd chapter of "Su Wen Bi Lun", which states that "wind, cold, and dampness are mixed together to form Bi". According to the different seasons and corresponding parts of the disease caused by evil qi, Bi syndrome is divided into tendon Bi, vein Bi, muscle Bi, bone Bi, and skin Bi, among which "those who encounter this in summer are called Mai Bi" [9]. "Dendrosis" was first recorded in the "Lingshu · Chapter of Carbuncle and Gangrene", which said: "It occurs in the toes of the feet, and is called" Dendrosis [10]. The discussion on the relationship between diabetes and Dendrosis was first seen in Dou Hanqing's Complete Book of Surgery of Dou's Family, Volume II, and the Theory on the Hair on the Back of the Nail" [11], which said: "It occurs on the back of the nail, and the disease from thirst to the fingers of the hands and feet, and is called "Dendrosis". Therefore, "pulse blockage" and "Dendrosis" are often used in clinical practice as the TCM names of DPVD.

## 2. Traditional Chinese Medicine Theoretical Basis and Modern Research Overview of Huangqi

### 2.1 Traditional Chinese Medicine Attributes of Huangqi and Theoretical Basis for "Treating from Stasis"

Huangqi, as a traditional Chinese medicinal herb, has a sweet taste, a slightly warm nature, and belongs to the lung and spleen meridians. It mainly has the effects of invigorating qi

and yang, consolidating the surface and stopping perspiration, promoting water and detumescence, etc. It has shown unique advantages in the field of diabetes treatment, which can help improve the blood sugar control of diabetes patients, reduce the amount of urine protein and reduce edema, thus helping to control diabetes and its complications. It can regulate the immune system, improve the body's resistance, and thus improve the microcirculation and immune function of patients with good blood sugar control [12].

### 2.2 Material Basis of Huangqi's "Promoting Blood Circulation and Removing Blood Stasis" Effect

The main components of Huangqi include Huangqi polysaccharides, Huangqi saponins, and Huangqi flavonoids. Astragalus polysaccharide has biological activities such as immune regulation, anti-oxidation, anti-inflammatory, etc. It will play an important role in the prevention and treatment of immune system diseases, diabetes, and cardiovascular diseases. Astragaloside has the functions of reducing blood sugar, blood lipid and cardiovascular protection, can promote insulin secretion, improve insulin sensitivity, reduce blood sugar level, has a good therapeutic effect on diabetes patients, and can also reduce the content of cholesterol and triglyceride in the blood, reduce the deposition of fat in the vascular wall, prevent and improve atherosclerosis and other cardiovascular diseases [13]. Huangqi flavonoids have various biological activities such as antioxidant, anti-inflammatory, and anti-tumor. Huangqi contains many flavonoids, including flavonoids, isoflavones, and isoflavones, which can clear free radicals in the body, inhibit oxidative stress reactions, and protect cells from damage. In the inflammatory response, Huangqi flavonoids can inhibit the activation of inflammatory cells and the production of inflammatory factors. At the same time, flavonoids can also inhibit the growth and spread of tumor cells, which has certain preventive and therapeutic effects on various cancers [14].

### 2.3 Pharmacological Mechanism of Astragalus in the Treatment of Diabetes Peripheral Vascular Disease

#### 2.3.1 Improving endothelial function of blood vessels

The active ingredients in Astragalus membranaceus, such as Astragalus polysaccharides and Astragaloside IV, can promote the release of nitric oxide from endothelial cells. NO can dilate blood vessels, improve vascular elasticity, and increase blood perfusion to surrounding tissues; Inhibit the production of vasoconstrictors such as ET-1, balance vascular relaxation function, and alleviate vascular spasm.

#### 2.3.2 Protection of $\beta$ -cells

During the treatment of diabetes, astragalus can protect pancreatic islet  $\beta$  cells, which are the only insulin secreting cells in the human body, and insulin is the key hormone to reduce blood sugar levels. In patients with diabetes, the function of pancreatic  $\beta$  cells is often damaged, which leads to insufficient insulin secretion and difficulty in effectively controlling the blood sugar level. The polysaccharide, saponin, flavone and other components in astragalus can protect pancreatic  $\beta$  cells and improve their function through various ways, thus enhancing the insulin secretion ability. The

experimental study showed that 36 diabetes mice were randomly divided into model group, astragalus group, astragalus flavone group, and astragalus polysaccharide group. All mice were modeled and gavaged. After gavage, the body weight, blood sugar, and islet number of the four groups of mice were observed. It was found that astragalus and the effective ingredients of astragalus had good therapeutic effects on diabetes mice, and would affect the blood sugar level and islet  $\beta$  cells of diabetes mice. After verification, astragalus flavone shows significant biological effect in diabetes mouse model, which can effectively reduce the blood sugar level and body mass of diabetes mice, while increasing the content of insulin and adiponectin, further preventing the apoptosis process of pancreatic islet cells [15].

### 2.3.3 Anti inflammatory effect

The excessive production and activity of inflammatory factors is considered to be the key factor in the development of diabetes and its complications. Inflammatory factors not only affect the normal secretion of insulin, but also may cause damage to the structure and function of pancreatic islet  $\beta$  cells through the complex interaction with fat endocrine system, immune system and oxidative stress, thus aggravating the condition of diabetes. Research has shown that polysaccharides, saponins, flavonoids, and other components in *Astragalus membranaceus* can inhibit the production and release of inflammatory factors, reduce the degree of inflammatory response, activate the body's immune regulatory system, and improve the body's anti-inflammatory ability; At the same time, astragaloside, astragaloside and other ingredients can inhibit the activation of inflammatory cells and the release of inflammatory factors, and reduce the damage of inflammatory reaction to neural tissue. These effects together enable astragalus to effectively control the excessive inflammatory reaction, alleviate the symptoms of neuralgia, and improve the quality of life of patients in the treatment of complications of diabetes [16]. Research has shown that *Astragalus polysaccharides* can alleviate renal tissue inflammation and damage by inhibiting the expression of inflammatory factors such as interleukin-18 (IL-18) and interleukin-1  $\beta$  (IL-1  $\beta$ ) secreted during the inflammatory response process.

### 2.3.4 Regulating Blood Sugar

In the research on the treatment of diabetes with astragalus, we found that astragalus can play a role in regulating blood sugar. In the study, researchers [17] randomly divided 30 experimental mice into three groups. The control group received a normal diet, the model group received a high-fat diet, and the astragalus polysaccharide group received a high-fat diet and was also fed with astragalus polysaccharide solution. The results showed that feeding mice with astragalus polysaccharide solution on a high-fat diet significantly reduced their blood glucose levels. Further research revealed the specific mechanism by which astragalus polysaccharide improves fasting blood glucose and insulin levels in mice. Due to the intake of *Astragalus polysaccharides*, the beneficial bacterial community in the intestinal tract of mice is increased while the harmful bacterial community is reduced. The optimization of this bacterial community structure helps

to improve the glucose metabolism status of mice. Due to the improvement of gut microbiota structure, it can improve the glucose metabolism of mice and lower their blood glucose levels.

### 2.3.5 Promoting angiogenesis and repair

Huangqi can upregulate the expression of angiogenic factors (VEGF, bFGF, Ang-1, etc.), activate angiogenesis related signaling pathways (PI3K/Akt, HIF-1  $\alpha$  pathway), regulate the phenotype of vascular smooth muscle cells (inhibit abnormal proliferation and migration), improve microcirculation perfusion (increase capillary density, reduce blood viscosity), thereby promoting angiogenesis and repair.

## 3. Clinical Research Evidence of Astragalus in the Treatment of Diabetes Peripheral Vascular Disease

In the treatment of diabetes, lower limb peripheral vascular disease is a problem that cannot be ignored, which will seriously affect the quality of life of patients, and even threaten life. In the treatment of vascular complications of diabetes, astragalus can be effectively used. Zhang Bailiang et al [18]. showed in their research that the modified Huangqi Guizhi Wuwu Decoction was used to treat patients with lower limb vascular disease of diabetes. Among them, 61 patients were mainly treated with aspirin enteric coated tablets and atorvastatin calcium tablets on the basis of conventional treatment methods, while the other 61 patients were treated with modified Huangqi Guizhi Wuwu Decoction on this basis. After two months of treatment, it was found that the combination of modified Huangqi Guizhi Wuwu Decoction and conventional western medicine therapy could effectively reduce patients' blood sugar levels, significantly improve patients' oxidative stress status, and optimize lower limb arterial hemodynamic indicators; This treatment method has good safety performance and high clinical application value, providing a new effective means for the treatment of lower limb vascular disease in type 2 diabetes. Ding Jingxian et al [19]. showed that patients with macroangiopathy of type 2 diabetes with deficiency of both qi and yin syndrome were treated with Huangqi Yiqi Decoction. During the treatment, the control group mainly took atorvastatin, while the study group used Huangqi Yiqi Decoction on the basis of the treatment of patients in the control group. During the treatment period, neither the control group nor the research group had nausea, dizziness, headache and other symptoms. The research results showed that the combination of the two methods of Huangqi Yiqi Decoction and atorvastatin [20] would play a significant role in the treatment of macroangiopathy in type 2 diabetes with deficiency of both qi and yin. This treatment scheme can effectively alleviate symptoms, improve the glucose and lipid metabolism of patients, and further reduce the vascular endothelial dysfunction of patients, showing high safety. It can be seen that the clinical exploration of *Astragalus* in the treatment of diabetes not only significantly improves the vascular disease, but also shows unique advantages in promoting the recovery of pancreatic islet function, protecting neural tissue and improving the overall quality of life.

#### 4. Summary and Outlook

Patients with diabetes are prone to peripheral vascular disease, causing higher mortality and affecting the quality of life. The mechanism of atherosclerosis caused by diabetes is multifaceted, including inflammatory reaction, various cell disorders in vascular wall, promoting coagulation and fibrinolysis inhibition. These factors increase the sensitivity and instability of blood vessels, which can easily cause plaque rupture or thrombus formation. Compared with most western medicines, they have adverse reactions and have less toxic and side effects. They can improve the symptoms of patients with diabetes surrounding blood vessels, delay the progress of the disease and improve the quality of life of patients through multiple ways and targets [21]. Although Astragalus membranaceus has shown significant effect in the treatment of diabetes and its complications, there are still some limitations. Because most studies are still in the basic pharmacology stage and lack large-scale clinical trials to validate their efficacy and safety. Moreover, further exploration is needed on the interaction and dosage selection of Huangqi with other drugs. With the increase of research methods and means in traditional Chinese medicine, as well as the deepening of the study of its mechanism of action, the development of traditional Chinese medicine tends towards scientific and standardized methods. The clinical application of traditional Chinese medicine will be more extensive and recognized by the world. However, in the future research, it is necessary to further strengthen the clinical research on astragalus in the treatment of diabetes and its complications, explore its mechanism of action, and optimize the treatment plan, so as to provide patients with a more safe and effective treatment plan.

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