

# Research Progress of Traditional Chinese Medicine in the Treatment of Diabetic Retinopathy

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**Abstract:** *Diabetic retinopathy (DR) is one of the microvascular complications of diabetes. If it is not treated effectively in time, it will cause great damage and is a common blind eye disease. This article analyzes the understanding of traditional Chinese medicine of DR, summarizes the current situation of traditional Chinese medicine treatment of DR, and the research on the mechanism of traditional Chinese medicine treatment of DR. Clinically, traditional Chinese medicine adheres to the pathology, combines movement and static, and divides yin and yang, distinguishes viscera, and recognizes diseases with the overall concept. According to the main contradictions of patients, choosing the appropriate traditional Chinese medicine treatment has the advantages of improving clinical efficacy and reducing some complications of Western medicine treatment. However, there are still certain shortcomings and difficulties at present. For example, there is no consensus on the early pathological identification method of DR, the impact of the "metabolic memory" effect on the prevention and treatment of DR in diabetic patients has not been solved, and the diagnosis and treatment syndrome differentiation of DR has not been unified. This article has made a certain discussion and outlook on the above content, with a view to providing new ideas for clinical work.*

**Keywords:** Traditional Chinese medicine, Diabetic retinopathy, Research progress.

## 1. Introduction

Diabetic retinopathy (DR) is a chronic, progressive eye disease characterized by retinal microvascular damage caused by long-term hyperglycemia and other abnormalities related to diabetes (such as hypertension, hyperlipidemia, etc.). It often leads to vision loss, visual field defects, glass volume blood, and even traction retinal detachment in severe cases, and eventually blindness. DR is the main cause of visual impairment in adults [1]. DR can cause changes in ocular blood vessels. The disease is clinically characterized by intraretinal hemorrhage, hard exudation, cotton spots, macular edema, microhemangioma, etc. In severe cases, there may be pulling retinal detachment, visual impairment, and even blindness. As a fundus microvascular disease, DR is the result of the combined effect of various factors inside and outside the body. Many factors such as intestinal flora changes, oxidative stress, cell apoptosis, cell death, cell autophagy, etc. can lead to damage to eye blood vessels [2]. According to the latest survey [3], the prevalence of DR, NPDR and PDR in Chinese diabetic patients is 22.4%, 20.2% and 2.3% respectively. The number of DR population is constantly expanding, which seriously affects the normal life of diabetic patients and brings a certain economic burden to the family. Therefore, early diagnosis and treatment are particularly important to effectively delay the progression of lesions and avoid vision loss. The systematic review of YAU JW and other [4] included people in the United States, Australia, Europe and Asia. The results showed that the total incidence of DR reached 34.6%, among which the incidence of DR in the proliferative period of adult DM patients (20-79 years old) was 6.96%, and the incidence of diabetic macular edema The rate is 6.81%. In the past 20 years, the number of blind people caused by DR worldwide has increased by 27%, and DR-related visual impairment has increased by 64% [5]. It can be seen that the disease of DR is still developing rapidly, and DR still needs to be further explored. Therefore, it is one of the important tasks to actively explore the pathogenesis of DR and find the exact treatment. In recent years, with the

continuous development of traditional Chinese medicine, the advantages of traditional Chinese medicine treatment DR have become increasingly prominent. Based on the overall concept of traditional Chinese medicine and the characteristics of dialectical treatment, traditional Chinese medicine starts from the whole, multi-link, multi-level, multi-target and multi-channel treatment, and reconciles yin and yang qi and blood, so as to achieve the goal of "positive qi is inside, and evil qi cannot be dry". Therefore, more and more attention has been paid to the prevention and treatment of diabetic retinopathy with traditional Chinese medicine. The progress of traditional Chinese medicine in the treatment of diabetic retinopathy in recent years is reviewed.

## 2. Etiology and Pathogenesis

DR belongs to the category of "anti-through barrier" in traditional Chinese medicine ophthalmology. Although ancient doctors did not specifically describe DR, it has realized that quenching thirst can eventually lead to blindness. For example, the "Sanxiao Lun" pointed out: "The long-term uncontrolled hyperglycemia of patients can lead to a variety of complications, including but not limited to vision problems (such as deafness and blindness), skin diseases (such as ringworm, acne), etc...", etc. Therefore, its evolution cannot be separated from the pathological evolution of diabetes qi and yin deficiency-yin deficiency and yang-yang deficiency. The eyes are the trick of the liver, the water wheel belongs to the kidney, quench thirst for a long time, the liver and kidney yin deficiency, the eyes loss of nourishment, coupled with qi and yin consumption, qi deficiency and handsome blood weakness, yin deficiency and blood stagnation, all of which can lead to eye stasis. Blood stasis can cause micro hemangioma, exudation, edema, bleeding, etc. in the fundus. If the blood overflows outside the collaterals, it can overflow into the divine ointment and seep into the pupil god. If the stasis in the eyes does not go aside for a long time, the blood stasis causes heat or quenches thirst and heat, the liquid becomes phlegm, or the spleen and kidney yang deficiency,

the phlegm is turbid and endogenous, causing phlegm and blood stasis to connect with each other, and finally forming a retinal vitreous proliferative disease.

### 3. Clinical Characteristics

Main clinical characteristics of DR: There are usually no obvious symptoms in the early stage. As the disease progresses, microvascular lesions occur, which are manifested in microaneurysms, bleeding points, rigid exudation, cotton floccules, etc., retinal edema is characterized by macular edema, diffuse edema, etc., retinal ischemia and hypoxia induces neovascular production, which may also cause fiber proliferation, leading to traction retinal detachment. As the disease worsens, vitreous bleeding, neovascular glaucoma and other complications that seriously affect vision may occur.

### 4. Dialectical Treatment

At present, there is no unified standard for the syndrome differentiation of DR. According to the latest "Guidelines for the Combined Diagnosis and Treatment of Diabetes Retinopathy Syndromes" published by World Medicine [6] According to the basic pathology evolution of DR: the transformation characteristics of Qi and Yin deficiency - Kidney deficiency - Yin and Yang deficiency and the three important pathogenic factors of deficiency, phlegm and blood stasis, it is proposed to be staged into early, middle and late, so as to combine disease symptoms and treat it in stages. For the early and middle stages, there are four types of syndrome: (1) Yin deficiency and dry heat, and the eyes are unfavorable. Choose Yuquan pills with white tiger and ginseng soup to nourish yin and clear heat. (2) Qi and yin are weak, and the veins and blood stasis are blocked. The prescription is selected to replenish qi and nourish yin, and promote blood circulation. (3) Liver and kidney deficiency, eye collateral loss syndrome, choose Liuwei Dihuang pills to nourish the liver and kidney, moisten the dryness and collaterals; (4) Liver yang hyperphyperity, heat injury eye collateral syndrome, the prescription to choose rhinoceros horn Dihuang soup to calm the liver and brighten the eyes, clear the heat and cool the blood. In addition, the guidelines also enrich the treatment of symptom differentiation and syndrome differentiation therapy, and summarize the 15 special prescriptions for the treatment of DR, 11 groups of drugs, 6 groups of keratin drugs, 5 proprietary Chinese medicines and 7 flavors of traditional Chinese medicines to improve DR microcirculation disorders. Different expert professors also have their own unique opinions. Professor Li Zhiying [7] believes that DR is mainly divided into three syndromes of qi and yin deficiency, blood stasis and qi stagnation of yin and yang, which are related to the length of the course of the disease. Those within 5 years are mostly qi and yin deficiency syndromes; those who have been 5 to 10 years are mostly blood stasis and qi stagnation syndrome; those who have been more than 10 years are mostly yin and yang deficiency syndromes. And the syndrome type mostly transforms along the law of deficiency of qi and yin → blood stasis and qi stagnation → deficiency of yin and yang. The treatment is based on the principle of nourishing yin and clearing away heat, nourishing the liver and kidney, nourishing qi and strengthening the spleen.

## 5. Traditional Chinese Medicine Treatment

DR mostly causes changes in vascular microcirculation in nerve and eye tissue due to insulin metabolism disorders, causing visual function and eye nutritional impairment. The occurrence of DR is the result of a combination of multiple mechanisms, involving many molecular and biochemical mechanisms, and interactions between various mechanisms, which jointly affect the physical state of retinal blood vessels and cells in the internal environment, mainly including vascular mechanisms and neurological mechanisms [8]. Research shows that the mechanism of traditional Chinese medicine for treating DR is to improve blood vessels and nerves by antioxidant, anti-inflammatory, anti-cellular apoptosis, reducing VEGF expression, and improving hormone levels, so as to improve or delay the degree of fundus lesions in DR patients and effectively improve their symptoms [9].

### 5.1 Mechanism of Traditional Chinese Medicine Treatment of DR

At present, the pathogenesis of DR mainly includes non-enzymatic glycosylation, inflammation, cytokines, oxidative stress, hemodynamics, etc. The retinal cells involved include photoreceptor cells, retinal pigment epithelial cells, vascular endothelial cells, pericapillary cells, Müller cells, microglial cells, etc. Because traditional Chinese medicine has the characteristics of multi-component and multi-target, it can mediate multiple pathogenesis of DR at the same time and play a therapeutic role. For example, Bodhisattva ultrafine powder can not only reduce the expression of vascular endothelial growth factor (VEGF) and alkaline fibroblast factor and other cytokines in the retina of DM rats [10], but also inhibit the inflammatory response of the retina of DM rats by inhibiting the nuclear transcription factor- $\kappa$ B signaling related to inflammation, and play a protective role in the retinal nerve tissue [11]. Compound thrombo capsule can inhibit the loss of periretinal cells, reduce the number of non-cellular blood vessels, reduce the expression of VEGF, improve hemodynamics, and antioxidant stress response [12]. Proteomics is a discipline that analyzes the composition, function and interaction between all proteins in cells, tissues and body fluids through high-throughput, rapid identification and quantitative analysis [13]. Xie Mengjun [14] Based on the integrated analysis and experimental verification of network pharmacology technology and metabolomics technology, it was found that kidney tonic and blood circulation can inhibit the expression of interleukin and tumor necrosis factors in the serum of DR rat model.

### 5.2 Traditional Chinese Medicine Monomer Treatment DR

High sugar can damage mitochondria and cause excessive apoptosis of cells, while astragalosine IV can inhibit the expression of miR-138-5p, restore the activity of silent information regulator 1 (silent information regulator 1, SIRT1) / nuclear factor E2 related factor 2 (nuclear factor erythroid 2-related factor 2, Nrf2) to reduce abnormal apoptosis of cells, and at the same time, increase the expression of miR-128, regulate phosphatidylinositol 3 kinase / protein kinase B

(PI3K/Akt) signaling pathway, protect retinal cells [15] astragalus polysaccharides can regulate miR-240, miR-195, miR-182 and other related miRNA, affecting SIRT1/Nrf2 and B-cell lymphoma 2 (B-cell lymphoma-2, Bcl-2) signal, reduce cell apoptosis induced by mitochondrial function damage [16]. Interleukin-1 $\beta$  (interleukin-1 $\beta$ , IL-1 $\beta$ ) can up-adjust the expression of BAX, down the gene expression of Bcl-2, and effectively activate Caspase-3. The study found that puerarin significantly inhibited IL-1 $\beta$ -induced apoptosis and reduced the damage of retinal endothelial cells. After puerarin treatment, the expression level of Bcl-2-related X-protein (BAX), Bcl-2 and Caspase-3 was significantly reversed [17]. It has been confirmed that the main targets of hyperglycemia and oxidative stress in the DR state are NF- $\kappa$ B, Chen Fang, etc. [18] It has been found that puerarin may protect the retina by inhibiting the activation of NF- $\kappa$ B in the retina, reducing the production of oxygen free radicals, reducing the oxidative stress response, and inhibiting the apoptosis of retinal nerve cells. EVO can reduce blood sugar, retinal ganglion cell apoptosis rate, malondialdehyde (MDA), tumor necrosis factor  $\alpha$  (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ ), interleukin-6 (interleukin-6, IL-6), Bax protein, P53 protein expression by regulating the signaling pathway of cyclic adenosine phosphate (cAMP)/protein protein (cAMP)/protein kinase A (PKA), and increase the expression levels of superoxide dismutase (SOD), cAMP and p-PKA/PKA protein, thus reducing the pathological damage of retinal tissue in diabetic rats [19]. Angelica polysaccharides can improve the expression level of antioxidant Nrf2 in cells by blocking the Akt/GSK-3 $\beta$  pathway, thus inhibiting high-sugar-induced retinal ganglion cells (RGC)-5 apoptosis and reduce the level of intracellular oxidative stress [20]. Feng Wanguo et al. [21] found that burdoside can inhibit high-sugar-induced RGC oxidative damage and apoptosis, inhibit retinal nerve degenerative lesions, and treat DR. By regulating the AMPK/mTOR pathway, lanthin promotes autophagy, inhibits apoptosis, and improves the damage of high-sugar-induced cone cells and pigment epithelial cells [22].

### 5.3 Traditional Chinese Medicine Compound Treatment DR

Wang Zhiyong [23] believes that the deficiency of qi and yin is the basic pathology of diabetic retinopathy, and the whole course of the disease is accompanied by blood stasis symptoms. The key to the pathology is qi and yin deficiency and blood stasis block. He collected 80 DR patients and divided them into 35 cases in the Western medicine group and 45 cases in the traditional Chinese medicine group according to the single-blind method. Western medicine group treated orally with calcium hydroxybenzene sulfonate capsules, and the Chinese medicine group gave Damingyin treatment. Prescription: 10g each of Sanqi, astragalus, Chaihu, Zhizhihuang, wolfberry, Huangjing and Sichuan astragalus. 1 dose/d, 300mL of water-fried juice, divided into breakfast and dinner for about half an hour. After 4 weeks of continuous treatment for the two groups, four aspects were observed, including the vision level of the two groups before and after treatment, the comparison of traditional Chinese medicine syndrome points, the efficacy of traditional Chinese medicine syndrome, and clinical efficacy. The results showed that the traditional Chinese medicine group was better than the Western medicine group. It shows that Dayuan Drink has the

effect of improving the eye symptoms of DR patients, improving their vision level, and increasing clinical efficiency. Shi Wei et al. [24] randomly divided 200 DR patients into two groups and 100 cases each. The control group was treated with conventional western medicine. On the basis of the control group, the treatment group added Shengqing-reducing turbidity Tongluo Mingmu prescription: astragalus 50g, Atractylodes 15g, Rhubarb 6g, Aungshi 10g, Houpu 10, Cinnamon 3g, Xuanshen 30g, Yam 30g, Danshen 30g, Zelan 15g, Sanqi 6g, Motherwort 15g, Hawthorn 15g, etc., 2 times/d, 200mL at a time. After 8 weeks, the fundus lesions and vision of the two groups of patients were observed, and it was found that there were differences in the curative effect and vision improvement of the two groups, and the curative effect of the treatment group was better than that of the control group. The use of Chinese herbal medicine can not only improve the clinical symptoms of patients and improve vision, but also improve the degree of fundus lesions. Buyang Wu Decoction can improve the retinal mitochondrial respiratory chain function of DR rats, regulate the process of cell apoptosis, significantly reduce the relative expression level of CytC, Bax and Caspase-3 proteins in the retina, improve the relative expression level of Bcl-2 protein and mitochondrial membrane potential (MMP), inhibit the apoptosis of retinal cells in diabetic rats, and improve the structure and function of all layers of the retina through anti-apoptosis pathway in the treatment of DR, so as to effectively alleviate the structural and functional damage of high-sugar to the retina and improve the retinal microcirculation of diabetic rats [25]. By regulating the PI3K/Akt signaling pathway, upregulating PI3K, Akt, downgrading the expression of Bax, Caspase-8, Caspase-3 and Bid, inhibiting the apoptosis of early DR rats retinal microperiovascular cells, thus giving full play to its protective role in the apoptosis of early DR retinal microvascular cells [26]. Musk Baoxin Pills can improve retinal hard exudation and macular edema, and reduce apoptosis and barrier damage in the retina. Reduce the expression of apoptosis pathogen Caspase-3, reduce the damage and apoptosis of retinal RGCs cells, and significantly improve retinopathy in diabetic rats [27].

### 5.4 Treatment of DR with Traditional Chinese Patent Medicines and Simple Preparations

Zheng Xuehui [28] collected 87 DR patients and randomly divided them into a control group and a research group. Both groups were given routine control of blood sugar, and paid attention to diabetes diet to reduce blood pressure and blood lipids. The research group administered Compound Danshen Dripping Pills orally, 10 pills each time, 3 times a day. After 8 weeks of treatment, the improvement of fundus lesions (edema, bleeding, exudation) and the degree of visual improvement were observed. The results showed that the effective rate of the study group was higher than that of the control group, indicating that oral administration of compound Danshen dripping pills can improve the efficacy and improve the vascular condition of the patient's fundus. Traditional Chinese patent medicines and simple preparations is easy to take and carry, and its therapeutic effect is also significant. And relevant analysis shows that [29], Compound Xueshuantong Capsule, Compound Danshen Dripping Pill, Qiming Granules, Hexue Mingmu Tablets, Shuangdan Mingmu Tablets, Mingmu Dihuang Pills, these traditional

Chinese patent medicines and simple preparations have unique roles in improving eyesight, improving fundus diseases, reducing the area of fundus hemorrhage spots, reducing the thickness of macula, and reducing the volume of hemangioma. Traditional Chinese patent medicines and simple preparations can improve the symptoms of DR patients from multiple aspects. National diabetes prevention and treatment guide [30]. The first increase of traditional Chinese medicine for diabetes retinopathy can apply Qiming granules, compound Danshen dropping pills, etc. on the basis of routine treatment.

### 5.5 Traditional Chinese Medicine Ion Introduction Therapy for DR

Wang Xin [31] divided 60 patients with diabetes retinopathy into two groups, and the two groups were given conventional drugs such as hypoglycemic, lipid-lowering, and hypotensive control for adjuvant treatment. 30 cases in the control group were treated with amiodarone eye drops for eye drops, while the treatment group received a self-made Quyu Sanjie Tang with a prescription of 1.5g each for Chaihu, Taoren, and Honghua, 2.5g each for Haizao, Kunbu, and Jinei, 10g each for Pueraria, Mimoso, and Yujin, and 15g each for Huangqi, Codonopsis, and Angelica, and direct current iontophoresis was used to treat patients, with a treatment period of 15 days as one course of treatment. After 3 courses of treatment, the changes in visual acuity and fundus were compared between the two groups of patients before and after treatment. It was found that both treatment groups were effective, and the effectiveness rate of the treatment group was higher than that of the control group. Traditional Chinese medicine iontophoresis is an effective external treatment method in traditional Chinese medicine to improve vision and alleviate retinal lesions. Ion introduction is the directed attraction of highly effective drug factors extracted from traditional Chinese medicine through electrodes, allowing them to directly reach the affected area of eye diseases. It is superior to conventional administration methods in terms of drug concentration, duration, and absorption efficiency.

### 5.6 Traditional Chinese Medicine Eye Nebulization Treatment

Yu Dongdong et al. [32] randomly divided 66 DR patients into an observation group and a control group, with 33 patients in each group. The control group received conventional drug treatment, while the observation group received eye nebulization of breviscapine in addition to conventional treatment for 20 minutes each time, once a day, for a course of 12 days. After treatment, it was found that the observation group had better visual acuity, fundus condition, and TCM syndrome score than the control group. Lamplighter has anti platelet aggregation, anticoagulant, and microcirculation improving effects, which can enhance the antioxidant capacity of retinal tissue, inhibit retinal cell apoptosis, and delay the progression of diabetic retinopathy.

### 5.7 Acupuncture and Moxibustion Treatment

Wang Yong [33] collected 92 cases and randomly divided them into a control group and an experimental group; The control group was treated with a conventional Western

medicine treatment plan, which involved intravenous injection of 400mg of quercetin mixed with 250mL of sodium chloride injection, and the use of calcium dobesilate, three times a day, with 500mg each time. On the basis of the control group, the experimental group selected Jingming point, Chengxie point, Cunzhu point, Sizhukong point, Tongziliao point, and Temple as the main acupoints, and Hegu point, Zusanli point, Xuehai point, Taichong point, Sanyinjiao point, and Ganshu point as the matching acupoints. After 30 days of treatment, the clinical efficacy and visual acuity of both groups of patients were compared. It was found that the visual acuity of both groups improved significantly after treatment, but the experimental group was significantly higher than the control group. Acupuncture and moxibustion has its specific efficacy and advantages in the treatment of DR.

## 6. Summary and Prospect

With the increasing prevalence of diabetes, the number of patients with retinopathy complicated by diabetes is also increasing year by year. Retinopathy in diabetes patients will aggravate the pain of patients, reduce their quality of life, even lead to blindness, and increase the investment in medical costs. It is a difficult problem to be solved urgently in diabetes research and clinical research. This study mainly reviewed the pathogenesis of DR and the progress of traditional Chinese medicine in the treatment of diabetes retinopathy, with a view to improving the prevention and treatment strategies of DR. High blood sugar, disrupted gut microbiota, oxidative stress, autophagy, pyroptosis, and apoptosis are all important pathological mechanisms leading to the occurrence of diabetic retinopathy. Various complex pathological reactions interact with each other, leading to the occurrence and evolution of DR. The existing treatment methods, such as dietary adjustments and lifestyle improvements, can alleviate patients' symptoms to a certain extent, but it is difficult to restore them to normal. Long term use of chemical drugs has problems such as reduced efficacy and significant adverse reactions. With the discovery of effective ingredients of traditional Chinese medicine and the deepening of mechanism research, it has been found that a variety of traditional Chinese medicine and compound prescriptions can play a role in preventing and treating DR through multiple ways. Traditional Chinese medicine will provide new effective strategies for the treatment of DR. Traditional Chinese medicine treatment is based on the theory of traditional Chinese medicine and the characteristics of patients' syndromes to develop flexible and personalized treatment strategies, which are very effective for many complex diseases, such as cardiovascular disease, cancer, diabetes complicated diseases, etc.

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