Progress in Traditional Chinese Medicine on Treatment of Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR), a common and blinding diabetic microvascular complication, is a harmful metabolic effect caused by persistent hyperglycemia. Owing to the complex pathogenesis of DR, various clinical treatment methods cannot completely prevent its development and are accompanied by various complications. Therefore, there is an urgent need to identify new therapeutic drugs or complementary and alternative therapies. Traditional Chinese medicine (TCM) has the unique advantages of multi-level, multi-target, and minimal side effects. Accumulating evidence has proven that TCM may help delay or prevent the progression of DR. This paper reviews the effect and mechanism of representative TCMs (including extracts, identified compounds, and compound formulas) on DR in recent years and provides evidence for new drug development and clinical efficacy.

Keywords

traditional Chinese medicine, diabetic retinopathy, Xiaoke, diabetic complications, mechanism, progress

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Introduction

With the improvement in people’s living standards and lifestyle changes, the number of diabetic patients is increasing every year. According to statistics, there are 425 million diabetic patients worldwide, and it is estimated that this number will reach 629 million by 2045.¹ The incidence rate of diabetes is affected by many factors, including body weight, body fat, metabolic syndrome, and even the negative effects caused by working pressure and insufficient sleep will increase incidence rate.² Complications of diabetes can be classified into macrovascular complications such as cardiovascular, cerebrovascular, and peripheral vascular diseases and microvascular complications such as retina, kidney, and nervous system diseases, which may cause premature deaths in patients with diabetes. Diabetic retinopathy (DR) is a common and serious complication of microvascular injury in mellitus patients. It is one of the main causes of vision loss in working-age populations.³,⁴ It has been reported that the incidence rate of DR is more than 40% after 5 years of diabetes, which increases gradually with an increase in the disease course, and the incidence rate of DR can reach 87% after more than 20 years.⁴,⁵

DR has little effect on vision in the early stages and is generally difficult for patients to detect. However, once the disease develops to a later stage, it will cause irreversible visual damage and even lead to retinal detachment in severe cases, which can lead to blindness. According to the staging standard formulated by the Chinese Academic Conference on Fundus Diseases, DR is divided into 6 stages. Stages I-III are non-proliferative stages and stages IV-VI are proliferative stages. Non-proliferative diabetic retinopathy (NPDR) is an early stage of DR, with the main clinical symptoms being microaneurysms, hemorrhagic spots, yellow-white hard exudates, and white lint spots. Neovascularization represents the stage of the disease entering the middle and late stages, namely proliferative diabetic retinopathy (PDR).⁶,⁷ DR is a multifactorial disease with complex pathogenesis, and, although many efforts have been made in this regard, its pathogenesis has not been fully clarified. However, most researchers believe that the main pathogenesis of DR involves inflammation, persistent hyperglycemia, angiogenesis, apoptosis, advanced glycation end products (AGEs), oxidative stress, and the interaction between these factors.⁸,⁹ The clinical treatment of DR usually focuses on
Drugs, lasers, and surgery. However, these treatment methods have limitations and various complications. After anti-vascular endothelial growth factor (VEGF) drugs, such as ranibizumab and bevacizumab, were administered to patients, they had some adverse reactions such as endophthalmitis, intraocular inflammation, and rhegmatogenous retinal detachment. Frequent intravitreal injections increase the risk of cataract surgery and glaucoma drug treatment, and may also lead to intraocular bleeding, infection, retinal detachment, and corneal scar problems. In addition, laser and surgical treatment may lead to retinal atrophy, decreased color vision, choroidal neovascularization, and retinal scar formation.\(^5\)\(^6\)\(^8\)\(^9\) Therefore, it is necessary to find new drugs against DR with fewer adverse reactions or complementary and alternative therapies.

TCM has played an important role in Oriental medicine. For thousands of years, China and many Asian countries have always regarded TCM or integrated traditional Chinese and Western medicine as the main way to treat diseases. As per the theory of Yin and Yang, the 5 elements and the 5 internal organs constituted the theoretical basis of TCM, and there is a complementary relationship between them. Under normal circumstances, Yin and Yang are in a state of dynamic balance in the human body. When some external factors (such as glutony, emotional disorders, chronic illness, and exogenous poisons) affect the human body, it will cause an imbalance of Yin and Yang, which will lead to the functional disorder of the 5 internal organs, unable to produce sufficient nutrients such as water and grains to be distributed throughout the body, thereby causing damage to the human body.\(^11\)\(^12\)\(^13\) Diabetes belongs to the category of “Xiaoke” in TCM, and modern Chinese medicine scientists call it DR “Xiaoke eye disease.” As early as 2000 years ago, the Huangdi Neijing in the Qin and Han dynasties recorded Xiaoke disease. Although there was no specific name for DR in ancient times, the general theory of Xiaoke in Xuanming Lunfang said that “one syndrome of Xiaoke can be changed into Que eyes (it refers to a kind of disease with unclear vision at night) or internal barrier,” and the Hejian Liushu also said that “if a man has Xiaoke, he will most likely become deaf, blind, and have eye disease.” These records clearly point out that Xiaoke caused eye diseases, indicating that there has been some clinical experience in the prevention and treatment of DR in ancient times.\(^14\)\(^15\) The basic pathogenesis of Xiaoke eye disease is Yin deficiency and dryness-heat, which is based on Yin deficiency as the foundation and dryness-heat is the surface, which can cause body fluid and water to decrease, resulting in a decline in renal function. Because the liver and kidney have a common source, and the liver opens its orifices to the eyes, the reduction of body fluid and water will lead to the eyes losing nutrition, which causes the occurrence of DR. In addition, the reduction of body fluid and water will also make the blood sticky and the weak operation of Qi and blood, causing blood stasis and leading to DR. Figure 1 describes the pathogenesis of DR from the perspective of TCM.\(^12\)\(^13\)\(^16\) Currently, TCM has accumulated a lot of clinical experience and research data in the prevention and treatment of DR, and many TCMs have been proven to improve DR, but the sample size of its mechanism of action is small and not deep enough. This review will elaborate and analyze the recent research status against DR of TCM, to provide a scientific experimental basis and basic reference materials for the clinical use of TCM in the prevention and treatment of DR. The scientific evidence and mechanism of TCM against the DR effect are shown in Figure 2.

**Extracts and Identified Compounds of Traditional Chinese Medicine**

**Curcuma Wenyujin Y. H. Chen et C. Ling**

*Curcuma wenyujin*, which is mainly grown in southeast China, has been found, in a history of thousands of years, to have the effects of promoting blood circulation and removing blood stasis, boosting the flow of Qi, and relieving pain. Modern pharmacological research has shown that its extract has anti-inflammatory, anti-tumor, antioxidant, and inhibitory activities against platelet aggregation.\(^17\)\(^18\) Curcumolide is a sesquiterpene with a special 5/6/5 skeleton isolated from *Curcuma wenyujin*. Cai and associates observed the effects of curcumolide on retinal inflammation in streptozotoxin (STZ) induced diabetic rats. Curcumolide treatment reduced leukocyte adhesion and vascular leakage in the retina of diabetic rats, and also reduced the expression of pro-inflammatory mediators tumor necrosis factor-α (TNF-α) and intercellular adhesion molecule-1 (ICAM-1) in retinal tissue, which indicated the anti-inflammatory effect of curcumolide.\(^19\) Similarly, in the study of Dong and associates, the anti-inflammatory activity of curcumolide was confirmed by inhibiting the levels of pro-inflammatory mediators TNF-α, interleukin 1β (IL-1β), and IL-6.\(^17\) In addition to its anti-inflammatory effect, Lin and colleagues found that curcumolide inhibited the migration, proliferation, tube formation, and apoptosis of HUVECs induced by VEGF in vitro, which are the characteristics of angiogenesis. Further, fluorescein and HE staining showed an increase in neovascular clusters, avascular area, and neovascular lumens in the retina of oxygen-induced retinopathy (OIR) mice, and curcumolide effectively inhibited their development. These results demonstrated the anti-angiogenic potential of curcumolide in vivo and in vitro. Furthermore, Western blot analysis showed that curcumolide regulated VEGF-mediated angiogenesis.\(^20\) In conclusion, these results suggest that curcumolide plays an important role in retinal inflammation and neovascularization, and provides an experimental basis for the clinical application of curcumolide for the treatment of DR.

**Dendrobium chrysotoxum Lindl**

*Dendrobium chrysotoxum* (DC), a valuable medicinal material in ancient China, has antioxidant, anti-senescent, anticancer, and immune regulation activities.\(^21\) Gong and coworkers...
reported the effect of an ethanol extract of DC on STZ-induced diabetic rats. DC inhibited VEGF/VEGFR2 and other related angiogenic factors which mediated retinal angiogenesis. In addition, DC inhibited the phosphorylation of p65 and the expression of inflammatory factors IL-6 and IL-1β, indicating its anti-inflammatory effects. It is worth noting that Yu and his colleagues conducted a similar study on ethanolic extracts of DC, which inhibited the expression of inflammatory factors IL-6, IL-1β, and TNF-α in the retina of NPDR mice and alleviated BRB breakdown. Moreover, DC also inhibited angiogenesis by reducing the expression of VEGF and its related genes in the retina of DR mice. In further studies, Yu and his colleagues reported the activity against DR of erianin, a bibenzyl compound isolated from DC. Erianin alleviated the BRB breakdown of the retina of STZ-induced diabetic mice and restored the expression of occludin and claudin-1. In addition, erianin inhibited retinal inflammation induced by microglial cells, reduced cellular glucose uptake, and inhibited BRB breakdown mediated by the inflammatory factor TNF-α. In another study, erianin reduced retinal neovascularization in STZ-induced hyperglycemic mice and OIR mice models, which plays a role in inhibiting angiogenesis. The above studies ranged from the use of an ethanolic extract of DC to the specific bibenzyl compound erianin, demonstrating the ability of DC to exert both anti-inflammatory and anti-angiogenic effects, indicating the potential of DC for DR treatment.

Scutellaria barbata D. Don

*Scutellaria barbata* (SB) is a perennial herb, distributed in southern China. It is primarily used in the clinical adjuvant treatment of jaundice, sore throat, and various cancers. It is reported that SB has anti-cardiovascular disease, antitumor, antibacterial, antiviral, antioxidant, and anti-inflammatory activities. Mei and associates studied the use against DR of ethanol extract of herb SB in terms of its anti-inflammatory activity and reduction of tight junction proteins. The expression of tight junction proteins, such as claudin-1 and claudin-19, was decreased in the retinas of STZ-induced diabetic mice, while treatment with SB restored their levels, but had no significant effect on the increased
claudin-5 levels. The Evans blue (EB) leakage test showed that SB had the ability to reduce retinal vascular leakage. Meanwhile, SB inhibited the increased expression of the inflammatory mediators TNF-α, IL-1β, and ICAM-1, indicating its anti-inflammatory activity. These results suggest that SB blocks diabetes-mediated BRB breakdown. In a recent report, Li and Xiao found that polysaccharides isolated from SB inhibited the proliferation, migration, and angiogenesis of high glucose (HG)-induced human retinal vascular endothelial cells. Therefore, SB showed a certain potential for the treatment of DR by alleviating BRB breakdown and anti-angiogenesis activity. The DR activity of SB and its compounds needs further study.

**Fructus arctii**

*Fructus arctii* (FA) is the dried ripe fruit of *Arctium lappa* L. It is a traditional medicinal plant in China, Japan, India, and Iran, and mainly contains lignans, volatile oils, terpenes, and phenolic acids. Studies have shown that FA has hypoglycemic, hypolipidemic, anti-inflammatory, antioxidant, analgesic, and antitumor activities. Zhang and colleagues investigated the effects of total lignans from FA on STZ-induced DR in rats. The protective effect of FA on the retina of diabetic rats was confirmed by retinal histopathological examination and electron microscopy, and FA inhibited retinal cell apoptosis in diabetic rats in the TUNEL assay. FA also repaired BRB breakdown by reducing vascular leakage in the retina of diabetic rats. In addition, the protein and mRNA levels of VEGF and PKCβ2 were significantly increased in the retina of diabetic rats, whereas FA down-regulated their levels in a dose-dependent manner. In another report, Lu and coworkers investigated the compound arctii isolated from FA against the STZ-induced DR model in rats. Compared to diabetic rats, the expression of VEGF in the retina of arctii-treated diabetic rats was significantly reduced.

![Figure 2. The schematic diagram depicts Traditional Chinese medicine (TCM) (including extracts, identified compounds, and compound formulas) targeting each of these respective pathways that improve the process of DR.](image-url)
and arctii treatment had beneficial effects on retinal edema and retinal detachment. In other studies, arctii also showed the ability to significantly inhibit the high expression of VEGF in vitro. Therefore, in vivo and in vitro experiments suggest FA as a promising candidate drug for the treatment of DR, and may protect against DR by regulating the expression of VEGF.

_Cyclocarya paliurus_ (Batalin) Iljinsk

_Cyclocarya paliurus_ (CP) grows mainly in the subtropical mountainous areas of southern China, and is one of the key protected endangered plants. CP contains triterpenoids, flavonoids, phenolic derivatives, and polysaccharides. Experimental studies have shown that extracts and constituents of CP have pharmacological activities such as anti-tumor, anti-inflammatory, anti-oxidant, immunomodulatory, and hypolipidemic. In recent years, CP has attracted much attention as a functional food raw material with a hypoglycemic effect, and its extract has been reported to be active against diabetic nephropathy and diabetic cardiomyopathy. 

Puerarin is one of the most studied compounds isolated and extracted from _Pueraria lobata_. It has anti-inflammatory, anti-oxidant, anti-tumor, and analgesic effects, and has beneficial effects in vascular protection, cardioprotection, and neuroprotection. Owing to the stimulating effect of puerarin on islet sensitivity, it is widely used in the research of diabetes-related diseases. Previous reports have shown that puerarin inhibited DR through anti-inflammatory and anti-angiogenic effects, but Lv and associates proposed other views. In an N-methyl-D-aspartic acid (NMDA)-induced retinal ganglion cells (RGCs) model, puerarin treatment increased the expression of Bel-2 and decreased the expression of Bax and caspase-3. Puerarin also inhibited the production of reactive oxygen species (ROS) and MDA, and promoted the release of SOD. Furthermore, puerarin pretreatment inhibited the levels of NMDA-induced inOS and nNOS levels, and inhibited the release of NO. These results illustrate the anti-apoptotic and anti-oxidative stress capabilities of puerarin. In addition, the anti-oxidative stress activity of puerarin was similar to that observed in in vivo experiments. The effects of puerarin on oxidative stress in the retinas of STZ-induced diabetic rats were observed by Cai and coworkers. SOD activity decreased and MDA activity increased in the serum and retina of diabetic rats, whereas puerarin treatment reversed this effect and increased the T-AOC content in the retina. Based on the above in vivo and in vitro experimental results, it is suggested that puerarin may improve DR by reducing retinal oxidative stress injury.

**Other Potential Traditional Chinese Medicines**

Gypenoside XVII (Gyp-17) is a saponin isolated from _Panax notoginseng_ (Burk) F.H. Chen. Luo and colleagues recently reported that it alleviates early DR in db/db mice by regulating Müller cell apoptosis and autophagy. Gyp-17 increased the expression of SOD and glutathione peroxidase (GSH-px), and decreased the expression of MDA, indicating the anti-oxidative stress activity of Gyp-17. The disorder of apoptosis and autophagy can lead to damage to Müller cells. Gyp-17 reversed the increase of the expression levels of pro-apoptotic proteins Bax, caspase-3, and p62 in the retina of DR mice, and increased the expression of pro-autophagy-related proteins Bel-2, ATG-5, and Beclin1, and the transformation from LC3I to LC3II, indicating that Gyp-17 improved the apoptosis and autophagy of retinal Müller cells. In addition, Gyp-17 improved retinal morphological changes and vascular permeability. These results suggest that Gyp-17 prevents early DR via anti-oxidative stress and regulates Müller cell apoptosis and autophagy. In addition, Gao and coworkers conducted similar studies on the prevention of early DR with ginsenoside Rgl1 (GRg1), which reduced blood glucose and triglyceride (TG) levels and improved retinal permeability. GRg1 also reduced the expression of pro-apoptotic proteins caspase-3 and Bax, increased the expression of anti-apoptotic protein Bel-2 in GCL and INL, and increased the thickness of GCL and INL. These data demonstrate that GRg1 alleviates DR injury by reducing apoptosis in GCL and INL cells. In conclusion, Gyp-17 and GRg1 may be potential candidates for the treatment of early-stage DR, but there are few studies on their activity against DR at present, and the mechanisms need to be further studied.
observed the effect of *Zingiber officinale* extract standardized to 5% 6-gingerol (6-G) on retinopathy. Histopathological observations of the retina showed that 6-G reduced the thickness of the retinal basement membrane in diabetic rats. In terms of mechanism, 6-G produces direct anti-inflammatory and anti-angiogenic mechanisms by inhibiting the activities of TNF-α and VEGF.49

Radix *trichosanthis* (RT) is the dried root of either *Trichosanthes kirilowii* Maxim. or *T. rosthornii* Harms. It is a plant that can be used to treat diabetes and has the effect of clearing away heat and purging fire, generating saliva, and relieving thirst. Song and colleagues reported the effects of ethyl acetate extracts of RT on HG-induced retinal vascular endothelial cells (RVECs). RT reduced viability, migration, tube formation, and proliferation of RF/6A cells.5 Based on the results of the in vitro experiments, it was confirmed that RT improved the damage of HG-induced RVECs.

**Compound Formulas of Traditional Chinese Medicine**

In contrast to a single TCM, a TCM compound formula is composed of a variety of TCMs, and their complex interactions produce a synergistic effect that improves efficacy or reduces side effects. There are comparatively few studies on TCM compound formulas for the treatment of DR.

**Fufang Xueshuantong**

Fufang Xueshuantong (FXST), which is composed of *Panax notoginseng* (Burk) F. H. Chen, *Salvia miltiorrhiza* Bunge, *Astragalus membranaceus* Fisch. ex. Bunge, *Scrophularia ningpoensis* Hems., can be used to treat fundus vascular diseases clinically, especially in reducing exudation and improving vision.50 Xing and associates reported a protective effect of FXST against HG-induced RVECs. Similar to RT, FXST reduced RF/6A viability, migration, and tube formation. FXST also reduced the expression of YAP, VEGF, and VEGFR.51 In another in vivo experiment, Sun and associates observed the effects of FXST on the retinas of STZ-induced diabetic rats. Diabetes causes a decrease in the number of RGCs and an increase in apoptotic cells in rats, and FXST treatment reversed these changes. In addition, FXST also reduced the disorder and edema of the retinal structure, and improved the hemodynamics of the retina in diabetic rats.9 In vitro and in vivo experiments have proved that FXST has beneficial effects on DR and may be a potential TCM compound formula for the treatment of DR.

**LuoTong Formula**

LuoTong formula (LTF), derived from the Di Dang decoction, is composed of 5 TCMs, *Astragalus membranaceus* (Fisch.) Bunge, *Salvia miltiorrhiza* Bunge, *Panax notoginseng* (Burk) F.H. Chen, *Hirsutum nipponica* Whitman, and *Rheum palmatum* L. It has the effect of promoting blood circulation and dredging collaterals. Pang and coworkers observed the effect of LTF on retinal inflammation in diabetic rats induced by STZ. LTF significantly improved the pathological damage to the retina and pancreas. Moreover, the expression levels of the pro-inflammatory mediators TNF-α, ICAM-1, IL-1β, and MCP-1 were increased in the retina of diabetic rats, and LTF reversed this phenomenon.52 In another study, the different mechanisms of LTF against DR were investigated using the same animal model. LTF alleviated retinal histological abnormalities and improved hemorheological indices in diabetic rats. In addition, LTF improved vascular endothelial function by downregulating the expression of VEGF and PEDF, and upregulating the expression of Ang-1, Tie-2, and tight junction proteins ZO-1 and occludin, thereby reducing vascular leakage and BRB breakdown.53 Therefore, the alleviation of BRB breakdown and anti-inflammation may be related to the beneficial effects of LTF on DR, which has a strong potential to delay DR progression.

**Zhujing Pill**

Zhujing pill (ZJP), composed of the 3 TCMs *Cuscuta chinensis* Lam., the seed of *Plantago asiatica* L., and *Rehmannia glutinosa* (Gaertn.) DC., has the effect of nourishing the liver and kidney and increasing eyesight. Lei and colleagues studied the protective effect of ZJP after water extraction and alcohol precipitation on the retinas of diabetic rats induced by STZ. The retinal structure of diabetic rats is disordered, the number of retinal cells is reduced, the INL and outer plexiform layer appear to be vascularized, and the BRB permeability is increased. Treatment with ZJP improved these retinal injuries. ZJP increased the levels of SOD and GSH-px in the retina and serum of diabetic rats, and decreased the level of MDA, which reflects the anti-oxidative stress effect of ZJP. Aldose reductase (AR) is associated with the expression of various inflammatory factors and ZJP inhibited AR activity. In addition, ZJP downregulated the expression of inflammatory factors TNF-α, IL-6, and hsCRP in the serum of diabetic rats, and the expression of TNF-α, IL-1β, ICAM-1, VEGF, and AGEs in the retinas of diabetic rats.54 In conclusion, ZJP has the ability to ameliorate DR injury, and its mechanism may be related to its anti-inflammatory and anti-oxidative effects. The preclinical efficacy of TCM (including extracts, identified compounds, and compound formulas) is shown in Table 1.

**Discussion**

TCM is a traditional discipline that is completely different from modern medicine, and was established by ancient Chinese medicine experts after thousands of years of exploration. It has a complete theoretical system and a wide history of clinical practice. What differs from modern medicine is the holistic treatment view of TCM. Based on symptomatic treatment, doctors usually consider the transmission of diseases, as stated in the theory of TCM, if you see the disease of the liver, you know that the liver...
transmits to the spleen, and you should strengthen the spleen first, which means that the treatment effect will be better if you first regulate the spleen and then treat the liver disease. DR is a complication that may occur only when diabetes develops to a deeper degree, and patients with DR may also have other diabetic complications or diseases. The overall treatment is obviously a more appropriate approach based on the complex pathological state of patients with DR. In the past, there was no concept of extracts and identified compounds of TCM, and TCM was considered a herbal medicine. The most obvious feeling of patients with DR after taking TCM was the improvement in vision. However, we do not know how it plays this role, which is caused by the backwardness of people’s cognition and detection methods. With the development and updating of science and technology, more in-depth research has been conducted on TCM, and its function and mechanism in improving DR have been gradually excavated, which makes TCM more recognized. Furthermore, TCM has also made great progress in dosage forms, such as Compound Danshen Dropping Pills, compared with TCM decoction, which cannot only exert better and faster efficacy, but can also be carried around without decocting, which greatly facilitates the use by DR patients and indirectly improves the compliance of patients with medication. Currently, there is an increasing interest in the prevention and treatment of diseases with TCM. TCM not only has the advantages of good curative effect, low price, few side effects, and easy access, but it can also prescribe and determine the compatibility and dose of TCM according to the current physical condition of patients, and formulate a personalized administration plan. In addition, TCM also changes the treatment plan according to the situation to avoid the cumulative toxicity of the liver and kidney caused by long-term medication. It is obvious that TCM compounds directly treat DR or as an adjuvant combined with Western medicine, which is a complementary and alternative therapy with great potential. On the other hand, with the emergence of a large number of reports on the treatment of DR with TCM, we could screen out the TCMs against DR, carry out bioactivity-guided isolation and structural elucidation, or further modify the structure of active compounds, and convert these compounds into new treatment methods to improve DR, which is an effective way to discover new drugs against DR. In this review, we investigated the effects and mechanisms of representative TCMs (including extracts, identified compounds, and compound formulas) on DR. Through an analysis of the literature, it is mainly related to the reduction of VEGF levels, anti-inflammation, anti-oxidative stress, anti-apoptosis, and anti-angiogenesis. It is usually the result of the combined action of multiple factors, which also reflects the multi-level and multi-target characteristics of TCM. In addition, from the perspective of TCM, the main functions of these TCMs include clearing away heat and toxic material, anti-inflammation, anti-oxidative stress, anti-apoptosis, and anti-angiogenesis. For example, nourishing Yin corresponds to Yin deficiency, promoting the secretion of saliva or body fluid, which are closely related to the pathogenesis of Xiaoke eye disease. Note, DC, Dendrobium chrysotoxum Lindl.; LTF, LuoTong formula; ZJP, ZhiuJing pill; FA, Fructus arctii; CP, Cyclocarya paliurus (Batalin) Iljinsk.; Gyp-17, Gypenoside XVII; GRG1, Ginsenoside Rg1.

Table 1. The Preclinical Efficacy of TCM in the Treatment of DR.

| Mechanism | Agents | Biological effects | References |
|-----------|--------|-------------------|------------|
| Anti-inflammation | Curcumolide DC | Inhibits vascular leakage and leukostasis, and decreases expression of inflammatory factors | 17, 19 |
| Anti-inflammation | LTF | Inhibits vascular leakage and decreases expression of inflammatory factors | 22, 23, 25 |
| Anti-inflammation | ZJP | Decreases expression of AR and inflammatory factors | 52 |
| Anti-angiogenesis | Curcumolide DC | Reduces the increased neovascular clusters, avascular area, and neovascular lumens, and decreases expression of VEGF | 20 |
| Anti-angiogenesis | FA | Decreases expression of VEGF and VEGFR2 | 24, 26 |
| Anti-oxidative stress | Puerarin | Decreases expression of MDA and increases expression of SOD and HO-1 | 40, 42 |
| Anti-apoptosis | Gyp-17 | Decreases expression of Bax, caspase-3, and p62 | 7 |
| Anti-apoptosis | GRG1 | Decreases expression of Bax and caspase-3 and increases expression of Bel-2 | 47 |

Note. DC, Dendrobium chrysotoxum Lindl.; LTF, LuoTong formula; ZJP, ZhiuJing pill; FA, Fructus arctii; CP, Cyclocarya paliurus (Batalin) Iljinsk.; Gyp-17, Gypenoside XVII; GRG1, Ginsenoside Rg1.
believe that with the deepening of research, there will be more similarities and differences between TCM and Western medicine in the future, which will be confirmed experimentally. Therefore, we suggest that TCMs for clearing away heat and toxic material, promoting blood circulation and removing blood stasis, nourishing Yin, and promoting the secretion of saliva or body fluid can be focused on in future research on TCM against DR, and strengthen the research on its mechanism, so as to make a breakthrough contribution to the integrated traditional Chinese and Western medicine against DR. However, TCM is not omnipotent in the prevention and treatment of DR, and there are still some limitations. Firstly, although the effects of TCM extracts or identified compounds on DR have been demonstrated in animal and cellular models, there are few studies on patients with DR. Similarly, TCM compound formulas have been used to prevent and treat DR in the clinic, but the mechanism research in animal models is not deep enough. Secondly, genuine medicinal materials are due to the quality of TCM in different regions, which leads to differences in clinical efficacy. Thirdly, the presence of BRB prevents the drug from entering the ocular microcirculation, resulting in insufficient effective drug concentration. It is necessary to improve ocular drug concentration with the help of other technologies, such as changes in the drug dosage form. Finally, TCM is inherited from different teachers and schools, and their knowledge has a variety of different inheritance methods (such as oral presentation and systematic learning in schools), which leads to different TCM syndrome differentiation standards for the same patient, resulting in different clinical curative effects. In general, we believe that while learning from the achievements of modern medicine, TCM needs to establish a set of convincing TCM syndrome differentiation standards guided by the basic theory of TCM and grasp the quality standards of TCM, so as to better integrate with modern medicine and give full play to its own advantages while compensating for each other’s shortcomings.

Conclusion

In summary, TCM has a good application prospect in the treatment of VEGF levels, inflammation, oxidative stress, apoptosis, and angiogenesis in DR. It is believed that with more in-depth research on TCM, new drugs against DR with fewer adverse reactions or complementary and alternative therapies will be developed, thus providing more ideas and evidence for the clinical prevention and treatment of DR.

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