Review Articles

Acupuncture and Herbal Medicine

The beneficial effects of Traditional Chinese Medicine on diabetic retinopathy: mechanisms, therapeutics, and prospects

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Abstract

Diabetic retinopathy (DR) is a common microvascular sequela of diabetes mellitus. Chronic hyperglycemia contributes to progressive retinal microvascular damage, thereby increasing the risk of visual impairment and irreversible blindness. Traditional Chinese Medicine (TCM) has historically been effective against diabetes and related diseases such as retinopathy. It treats DR based on syndrome differentiation, with individualized regimens tailored to patients' specific conditions and physical constitutions. This review discusses the pathogenesis of DR in modern medicine and TCM. It also summarizes four therapies for DR, including formulas, Chinese herbs, active components, and acupuncture. We systematically gathered and arranged the pertinent literature on DR from various databases, including PubMed, Web of Science, and ScienceDirect. We analyzed and summarized research advances in TCM for the treatment of DR. Moreover, the GSE60436 dataset was chosen to dissect the variations in gene expression and signaling pathways connected to DR, employing Gene Ontology (GO) enrichment analysis and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database. Bioinformatics studies have indicated a potential link between the development of DR and the phosphatidylinositol 3-kinases-protein kinase B (PI3K-Akt) and advanced glycation end products (AGE)-receptors for advanced glycation end products (RAGE) pathways. At the same time, we emphasized the cutting-edge targets and strategies for DR treatment interventions. TCM exhibits a distinctive therapeutic efficacy in preventing and treating ocular conditions and mitigating DR *via* various mechanisms and routes. According to the principle of holistic treatment based on syndrome differentiation in TCM, choosing appropriate TCM treatments has the advantage of improving the clinical efficacy and mitigating adverse effects of Western medications.

Keywords: Diabetic retinopathy, Pathogenesis, PI3K, Traditional Chinese Medicine

Graphical Abstract: https://links.lww.com/AHM/A210

Introduction

Diabetic retinopathy (DR) is a common diabetes-related consequence that can inflict permanent harm to the retinal microvasculature. It is the primary cause of blindness among diabetics and the most rapidly increasing source of visual impairment in working-age adults. DR can be divided into two stages according to disease progression: non-proliferative DR (NPDR) and proliferative DR (PDR), which correspond to the early and late stages, respectively[1]. Early morphological signs of NPDR include the formation of small aneurysms. As the disease progresses, retinal hemorrhage, hard exudates, and cotton-wool spots are observed[2]. PDR involves the creation of new retinal blood vessels and frequently leads to severe complications. As the disease progresses, retinal detachment, bleeding, and irreversible vision loss may occur[3]. Over the past two decades, the number of individuals experiencing blindness owing to DR has increased by 27% globally. In addition, DR-related visual impairment increased by 64%[4]. Therefore, urgent attention and proactive measures for medical intervention and prevention are imperative. Currently, laser-assisted therapy and vitrectomy represent the predominant treatments for DR. However, it is important to note that these interventions can potentially result in retinal damage and scarring[5–6]. According to traditional Chinese medicine (TCM), the pathogenesis of DR stems from the disrupted circulation of *qi*, *xue*, and fluids, coupled with an organ yin-yang imbalance. These factors collectively lead to a pathological state characterized by *yin* deficiency, dryness, and heat[7]. In addition, Chinese herbs exert antioxidant and anti-inflammatory effects, improve microcirculation, and regulate blood glucose and lipid levels. Growing evidence indicates that common diabetes-related

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complications are effectively mitigated with few adverse effects using herbal remedies[8]. TCM can slow the development of DR through a mechanism involving multiple targets and pathways. We conducted a literature review to identify published studies on the role of traditional TCM in the prevention and treatment of DR. A comprehensive literature search was performed in the PubMed, Web of Science, and ScienceDirect databases. This review examines TCM's therapeutic mechanisms and impacts on DR from four perspectives: herbal formulas, raw herbs, active compounds, and acupuncture techniques. We further employed bioinformatics to identify the differentially expressed genes and signaling pathways implicated in DR, providing new insights into its pathogenesis.

Pathogenesis of DR

Modern medicine perspective

The potential mechanisms underlying DR remain unclear. It has been speculated that the mechanism mainly involves hyperglycemia, oxidative stress, inflammatory reactions, innate immune dysfunction, extracellular vesicles (EVs), and apoptosis. Progress in understanding the pathogenesis of DR has enabled early and novel interventions and prevention.

Hyperglycemia and oxidative stress

DR is closely related to hyperglycemia, which is an important driving factor in its onset and development. Long-term hyperglycemia directly damages the retinal microvasculature and neural tissue *via* multiple pathways[9]. Oxidative stress harms cell structure and contributes to the development of various illnesses. Diabetes is linked to increased generation of reactive oxygen species (ROS)[10]. Overabundance of ROS triggers mitochondrial impairment, apoptosis, inflammatory responses, and retinal structural and functional alterations[11]. Hyperglycemia, a primary ROS contributor, disrupts the electron transport chain and induces ROS generation in retinal vascular endothelial cells (RVECs) mitochondria[12]. Four typical metabolic abnormalities are associated with oxidative damage to the retina caused by hyperglycemia: accumulation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), increased flux in the polyol pathway and hexosamine pathway, thereby increasing the production of ROS, triggering oxidative stress, and activating a series of reactions closely related to the progression of DR[13], while oxidative stress worsens these metabolic pathway irregularities, perpetuating a cycle (Figure 1).

Inflammation

Inflammation is pivotal in the development of DR. In animal models of diabetes and in clinical cases, inflammatory responses have been demonstrated to be widely present throughout all stages of DR development[14–15]. Persistent low-level inflammation triggers a cascade of cellular irregularities and tissue damage, culminating in retinal degradation. This is due to the marked escalation and extensive involvement of proinflammatory cytokines, adhesion proteins, chemokines, and growth factors, all of which play key roles in the development of DR[16–18]. Inflammation represents a generalized reaction to damage or strain and involves multiple functions and molecular mediators. Pathogens are recognized by receptors such as toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE)[18]. Triggering TLR signaling pathways can unleash the nuclear factor κB (NF-κB) transcription factor from its restraints, prompting its journey to the cell nucleus, where it kicks into high gear, ramping up the production of inflammatory mediators and chemotactic signals[19]. During the course of diabetes, NF-κB is activated, leading to inflammation and exacerbation of DR. Additionally, multiple interrelated biochemical pathways altered during diabetes activate glial cells, and glial cell abnormalities are thought to trigger coordinated pathological changes in cells within the neurovascular unit in DR[20]. In the presence of diabetes, microglia, Müller cells, and astrocytes are riled up and start going through a whirlwind of alterations. They activate a medley of cytokines, chemokines, matrix metalloproteinases (MMPs), and pieces of the complement cascade, all of which contribute to the neuron's downhill slide[19]. Neurodegeneration prompts glial cells to modify their growth factor expression (eg, vascular endothelial growth factor [VEGF]), thereby intensifying DR progression[21]. In summary, inflammation has an impact on the occurrence and progression of DR. Its mechanism is shown in Figure 2.

Innate immune system

The retina is an immune-privileged tissue, and the clinical symptoms of DR are usually associated with the loss of retinal immune privilege[22]. The onset and progression of DR are closely related to a congenital immune activation imbalance[23]. Innate immune cells and inflammatory responses play key roles in the vascular damage and neurodegeneration in DR[24–25]. Microglia serve as the primary immune cells within the retina and typically maintain an inactive state. Stimuli such as hyperglycemia and oxidative stress can activate microglia[26]. When the retinal immune response enters the "damage phase," active microglia release proinflammatory mediators, which damage retinal cells[22]. Beyond the resident microglia, peripheral innate immune cell infiltration (neutrophils and macrophages) characteristically advances the progression of DR[27–28]. The NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome is a core molecule involved in the activation of innate immunity. In DR, hyperglycemia and the accumulation of ROS and AGEs activate the NLRP3 inflammasome[29–30]. Zou et al.[31] found that NLRP3 promotes tubular structure formation and angiogenesis in retinal microvascular endothelial cells. Activation of NLRP3 triggers the inflammatory complex to initiate a proinflammatory response in DR[32]. Chai et al.[33] reported that NLRP3 blockade inhibits the secretion of proinflammatory and proangiogenic cytokines in DR. Therefore, NLRP3 plays a key role in activating innate immunity in DR, leading to worsening and prolongation of inflammation. The complement system is an important branch of innate immunity and dysfunctional complement activation contributes significantly to the progression[34]. Increased deposition of complement components, such as C3, has been detected in the

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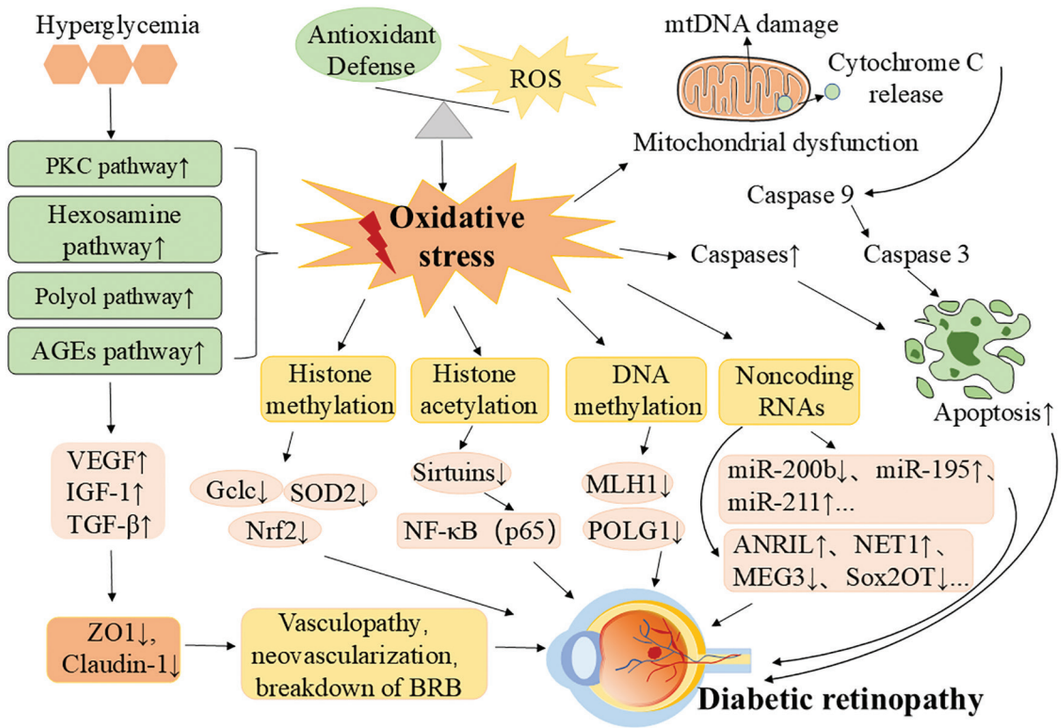


Figure 1. Mechanisms of oxidative stress in DR. AGE: Advanced glycation end product; ANRIL: Antisense noncoding RNA at the INK4 locus; BRB: Blood retina barrier; DR: Diabetic retinopathy; Gclc: Glutamate-cysteine Ligase; MEG: Maternally expressed gene; MLH1: MutL homolog 1; NET: Neuroepithelial cell transforming; NF-κB: Nuclear factor κB;Nrf2: Nuclear factor erythroid 2-related factor 2; PKC: Protein kinase C; POLG: Polymerase gamma; ROS: Reactive oxygen species; SOD2: Superoxide dismutase 2; Sox2OT: Restricted expression toward brain; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor.

vitreous of eyes with PDR, contributing to retinal cell apoptosis and vascular dysfunction[35]. Complement fragments, such as C3a and C5a, can activate microglia and other cells, releasing more inflammatory factors and triggering a strong inflammatory response. Both substances show an upward trend in the vitreous humor of patients with diabetes[36]. The abnormal activation of the innate immune system is a key driver of DR pathology. It mediates retinal inflammation, vascular damage, and neovascularization through multiple pathways, including microglial activation, NLRP3 inflammasome activation, complement system overactivation, and peripheral immune cell infiltration.

Extracellular vesicles

EVs are pivotal in the emergence and evolution of DR. They participate in intercellular communication by carrying biologically active molecules such as proteins, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and lipids, thereby influencing RVECs, pericytes, glial cells, and inflammatory responses, and promoting the pathological progression of DR. A series of studies have found that abnormally circulating EVs are involved in vascular damage during the development of DR. Mazzeo et al.[37] found that EVs in the plasma of DR patients can induce pericyte detachment and pericyte/endothelial cell migration, increasing cellular permeability and promoting vascular formation. Huang et al.[38] reported that diabetic plasma EVs induce complement activation, leading to membrane attack complex (MAC) accumulation within human retinal endothelial cells (HREC) and consequently harming these cells. In DR, there may be an association between neurodegeneration and EVs derived from activated glial cells. Zhu et al.[39] demonstrated that oxidative stress can induce autophagy in retinal astrocytic cells (RACs) and promote RACs to regulate ECs function through the release of EVs, showing the potential for promoting neovascularization. Liu et al.[40] experimentally verified that dysregulated miR-9-3p expression in Müller glial cell–derived vesicles intensified vascular impairment under hyperglycemic settings. A large body of research indicates that EVs are involved in various pathologies associated with DR, including vascular damage, retinal neuronal apoptosis, and glial cell dysfunction. Although EVs mediate damage signaling in the pathological process of DR, they also serve as potential diagnostic markers and therapeutic tools. The content of EVs (such as miRNAs) exhibits tissue specificity and pathology-state dependence, making them suitable biomarkers for the early diagnosis of DR. For example, loss of pericytes is an early indicator of DR, and alterations in EVs originating from pericytes in diabetic settings could serve as promising early biomarkers for DR[41]. During the initial progression of DR, EVs can exert a protective effect by preventing the rapid progression of retinal damage. Recent studies have shown that small EVs from mesenchymal stem cells (MSCs) are able to effectively inhibit the activation process of NLRP3 inflammatory vesicles by delivering the miR-22-3p molecule, resulting in a therapeutic effect on DR[42]. Another study showed that miR-192 released from MSCs delayed inflammation

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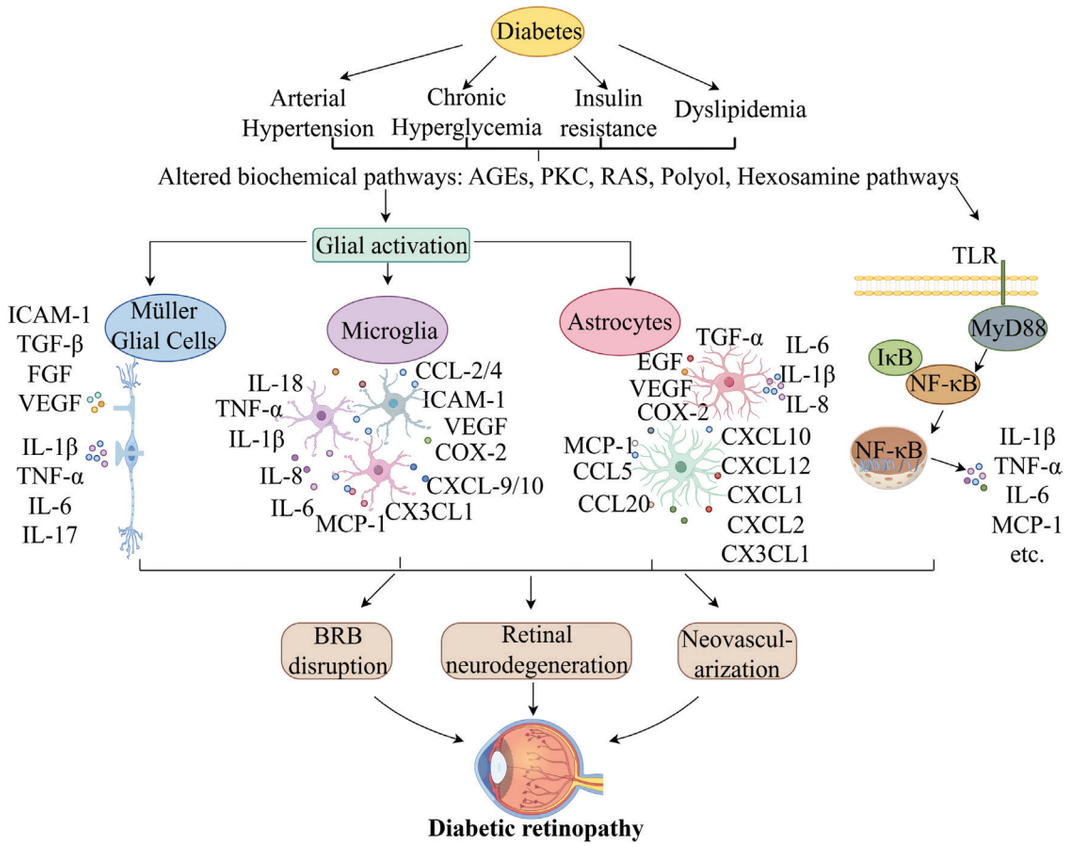


Figure 2. Mechanisms of inflammation in DR. AGE: Advanced glycation end product; CCL: CC motif ligand; COX: Cyclooxygenase; DR: Diabetic retinopathy; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; ICAM: Intercellular cell adhesion molecule; IL: Interleukin; MCP: Monocyte chemoattractant protein; PKC: Protein kinase C; RAS: Renin-angiotensin system; TGF: Transforming growth factor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

and blood vessel formation in DR, and may represent a potential therapeutic approach for treating DR[43]. EVs are gaining prominence as critical factors in DR development, influencing inflammation, new blood vessel formation, and cell-to-cell interactions within the retina. EVs offer capabilities for the early diagnosis and prognostic assessment of DR.

Apoptosis

Apoptosis, or programmed cell death, is a distinct cellular death process. Studies have shown that apoptosis causes retinal tissue damage and diabetes-related complications[44]. The caspase pathway is crucial for apoptosis. Caspase-3, also known as the "cell death executor," significantly increases its expression, which is one of the reasons for DR[45]. Tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β overexpression induces caspase-1/2 production and activates caspase-3, ultimately resulting in retinal cellular apoptosis[46]. Moreover, the increase in the number of cells undergoing apoptosis within the retinal ganglion layer substantiates apoptosis as a contributor to DR.

Pathogenesis of DR in TCM

According to TCM theory, DR is a complication of "Xiao Ke" disease, as recorded in the classic Chinese medical text *Huangdi Neijing* from the Qin and Han dynasties[47]. Patients with diabetes have *yin* deficiency and dry heat. DR is secondary to diabetes mellitus, mostly in the "long illness" stage of the body, and stems from liver, spleen, and kidney insufficiencies. Treatment should focus on addressing the root causes, including dryness-heat, phlegm, and stasis, as well as deficiency and excess complex patterns.

Many ophthalmologists believe that the long-term damage to the retina caused by high blood sugar is a typical feature of DR[48].

Integration of TCM theory with modern mechanisms

TCM's "imbalance of *yin* and *yang*" is associated with modern internal environmental homeostasis disorders. Studies have shown that in the *yin* deficiency and internal heat syndrome model, ATP synthesis, cellular oxygen consumption rates, and superoxide dismutase (SOD) activity decrease, indicating a weakened ability to clear oxygen-free radicals within cells[49]. A separate investigation revealed elevated serum IL-6 and TNF-α in individuals with *yin* deficiency and dry heat syndrome, which Sangpi decoction treatment effectively lowered. Molecular associations between *qi* stagnation and *xue* stasis, microcirculatory disorders, and endothelial dysfunction[50]. In TCM, "*qi* stagnation"

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is associated with vascular vasomotor dysfunction. Endothelin-1 (ET-1) and nitric oxide (NO) are primary vasoconstrictor and vasodilator factors synthesized by vascular endothelial cells, respectively. Compound Danshen Drops reduced ET-1 levels by 35% and increased NO levels by 28% in patients with *qi* Stagnation and *Xue* Stasis-type angina pectoris[51]. *Xue* stasis is akin to conditions such as thrombosis, ischemic stroke, and microcirculatory impairment in contemporary medical understanding[52].

Therapeutic effects of TCM on DR

Classical herbal formulae

TCM formulae are blends of various medicinal substances in specific proportions. Compared with raw herbs and individual compounds, formulas are known for their ability to enhance efficacy and reduce adverse reactions. Different TCM formulations invigorate *qi* and promote fluid production, clear collaterals, improve eyesight, activate *xue* circulation, and alleviate *xue* stasis. This can significantly reduce the discomfort experienced by patients with DR[53]. While DR is rooted in deficiencies of the spleen, liver, and kidney as well as deficiencies of *qi*, *yin*, and *yang*, its pathogenesis evolves dynamically throughout the disease. Consequently, for the management of ailments, prescriptions are individually adjusted according to the respective therapeutic methodologies derived from syndrome analysis. When the disease manifests as *yin* deficiency with dryness and heat, the treatment should emphasize *yin* nourishment and heat clearance. When the clinical syndrome presents with *yin* deficiency, options such as the Qiju Dihuang Pill[54] can be considered. However, it is important to note that the Heying Qingre formula should only be used in cases of pronounced heat. The centuries-old Heying Qingre formula, effective for vasculopathy by expelling heat and boosting circulation, is composed primarily of seven raw herbs: *Lonicera japonica* Thunb., *Scrophularia ningpoensi* Hemsl., *Angelica sinensis* Oliv., *Rehmannia glutinosa* Libosch, *Lycium barbarum* L., *Taraxacum mongolicum* Hand, *Polygonatum sibiricum* F. (Rhizome). *Taraxacum mongolicum* Hand. and other plants assisted *Lonicera japonica* Thunb. to clear heat and detoxify, whereas *Rehmannia glutinosa* Libosch was paired with *Polygonatum sibiricum* F. (rhizome) to nourish *yin*, increase fluid, and promote *xue* circulation. Zhang et al.[55] demonstrated the potential of the Heying Qingre formula and luteolin as a therapy for DR. This approach primarily inhibits oxidative stress by blocking the acetylation of proteins within the retinal pigment epithelium and through the action of the SIRT1/P53 signaling pathway[55]. Zhang et al.[56] used various methods to assess the therapeutic efficacy of the Heying Qingre formula for DR *in vitro* and *in vivo*. These findings demonstrate that the Heying Qingre formula serves as an effective therapeutic strategy for treating DR by targeting the inhibition of retinal neurodegeneration, particularly retinal ganglion cell apoptosis, through the suppression of oxidative stress pathways linked to both endoplasmic reticulum and mitochondrial dysfunction[56]. When there is a dual deficiency of *qi* and *yin*, the treatment typically involves nourishing both *qi* and *yin*. The commonly used prescription for this condition includes the Yi-qi-yang-yin decoction[57]. Clinical evidence demonstrates that patients with DR can be differentiated into spleen-, liver-, and kidney-related patterns. For patients with spleen deficiency, Guipi decoction[58] is commonly employed to tonify the spleen and *qi*. Zhujing pills[59] can be considered an option for patients with liver and kidney dysfunction. It is essential to address the role of *xue* stasis in the pathogenesis of DR. Xuefu Zhuyu decoction[60] or Danhong Huayu oral liquid[61] can be used for patients presenting with *qi* stagnation and *xue* stasis. Additionally, Shiquan Dabu decoction[62] can be considered for treating individuals with both *qi* deficiency and *xue* stasis. Danggui Buxue decoction[63] and Bushen Huoxue prescription[64] both possess a blood-tonifying effect that exhibits therapeutic efficacy in managing DR (Table 1).

TCM treatment for DR has shown significant efficacy in clinical applications and has several clinical advantages. In clinical practice, TCM practitioners adjust herbal combinations and dosages according to the specific conditions of each patient. Table 2 shows eight different TCM prescriptions derived from empirical prescriptions used by modern Chinese medicine practitioners for the treatment of DR, which have shown significant efficacy in clinical trials for DR treatment. The ingredients of the Qiming granules were extracted from *Astragalus membranaceus* (Fisch.) Bge., *Rehmannia glutinosa* Libusch, *Pueraria lobata* (Willd.) Ohwi, *Lycium barbarum* L., and other herbs. *Astragalus membranaceus* (Fisch.) Bge. was used to supplement the energy, whereas *Pueraria lobata* (Willd.) Ohwi is used to relieve thirst and promote fluid balance. The combination of these two benefits *qi* by promoting fluid circulation. Given that the basic pathogenesis of DR involves *qi* and *yin* deficiencies, supplementation without stagnation is the primary method for treating the disease. *Lycium barbarum* L. nourishes *yin* and *xue*, benefiting the liver and eyes, whereas *Rehmannia glutinosa* Libusch nourishes *yin* and *xue* as well as the liver and kidneys. When combined with principal medicines, they enhance the effects of invigorating *qi* and nourishing *yin*. Together, these two herbs facilitate *qi* circulation and *xue* flow, which promotes normal *xue* circulation, nourishes *yin*, and promotes fluid balance, thereby improving retinal circulation. In their analysis of 360 DR patients who underwent fluorescence fundus angiography 3 months post-treatment, Luo et al.[65] demonstrated the significant efficacy of Qiming granules in the treatment of DR. The results of the study showed that the therapy was not only effective in promoting retinal *xue* flow, but also in restoring normal *xue* circulation[65]. Zhenwu decoction has also shown beneficial effects in DR. In an initial double-blind trial among 80 older individuals with type 2 diabetes–related retinopathy, Wei et al.[66] found that Zhenwu decoction significantly improved efficacy after 3 months of treatment and effectively reduced plasma endothelin levels. A 36-month randomized, double-blind, controlled trial was conducted to assess the efficacy of Liuwei Dihuang Wan in

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Table 1

Effects of Chinese classic herbal formulae on DR

Name	Composition	Model	Mechanism of action	Refs.
Qiju Dihuang Pill	Gou Qi Zi (*Lycium barbarum* L.), Ju Hua (*Chrysanthemum morifolium* Ramat.), Shan Zhu Yu (C*ornus officinalis* Sieb. et Zucc.), Shu Di Huang (*Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. & C.A.Mey.), Mu Dan Pi (*Paeonia suffruticosa* Andrews.), Fu Ling (*Poria*), Shan Yao (*Dioscorea polystachya* Turcz.), Ze Xie (*Alisma orientale* (Sam.) Juzep.).	Rat	Improved antioxidant enzyme activity and inhibited aldose reductase activation.	[54]
Heying Qingre formula	Jin Yin Hua (*Lonicera japonica* Thunb.), Xuan Shen (*Scrophularia ningpoensis* Hemsl.), Dang Gui (*Angelica sinensis* Oliv.), Di Huang (*Rehmannia glutinosa* Libosch), Gou Qi Zi (*Lycium barbarum* L.), Huang Jing (*Polygonatum sibiricum* F. (Rhizome)), Pu Gong Ying (*Taraxacum mongolicum* Hand.).	Mouse	Inhibited protein acetylation and oxidative stress in retinal pigment epithelial cells. Prevented apoptosis and retinal microvascular and structural degeneration.	[55–56]
Yi-qi-yang-yin decoction	Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Nü Zhen Zi (*Ligustri lucidi* fructus), Sha Yuan Zi (*Astragalus complanatus* R.Br.), Chong Wei Zi (*Leonurus japonicus* Houtt.), Sang Shen (*Morus alba* L.)	Rat; mouse	Improved HbA1C, reduced vascular branching points, and alleviated damage to retinal tissue.	[57]
Guipi Decoction	Bai Zhu (*Atractylodes macrocephala* Koidz.), Fu Ling (*Poria*), Dang Gui (*Angelica sinensis* Oliv.), Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Yuan Zhi (*Polygala tenuifolia* Willd.), Long Yan (*Dimocarpus longan* Lour.), Suan Zao Ren (*Ziziphi Spinosae Semen*), Ren Shen (*Panax ginseng* C. A. Mey.), Mu Xiang (*Aucklandia lappa* Decne.), Gan Cao (*Glycyrrhiza uralensis* Fisch.)	Mouse	Reduced VEGF in the eyes of mice with oxygen-induced retinopathy.	[58]
Zhujing pill	Tu Si Zi (*Cuscuta chinensis* Lam.), Che Qian Zi (*Plantago asiatica* L.)., Shu Di Huang (*Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. et Mey.).	Rat	Antioxidant and anti-inflammatory effects	[59]
Xuefu Zhuyu Decoction	Tao Ren (*Prunus persica* (L.) Batsch), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Di Huang ((*Rehmannia glutinosa* Libosch), Hong Hua (*Carthamus tinctorius* L.), Chi Shao (*Paeonia lactiflora* Pall.), Niu Xi (*Achyranthes bidentata* Bl.), Chuan Xiong (*Ligusticum chuanxiong* Hort.), Jie Geng (*Platycodon grandiflorus* (Jacq.) A. DC.), Zhi Ke (*Citrus aurantium* L.), Gan Cao (*Glycyrrhiza uralensis* Fisch.), Chai Hu (*Bupleurum chinense* DC).	Rat	Reduced oxidative stress, thereby inhibiting the signaling pathway of ERK1/2.	[60]
Danhong Huayu Koufuye	Dang Shen (*Salvia miltiorrhiza* Bge.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Chuan Xiong (*Ligusticum chuanxiong* Hort.), Tao Ren (*Prunus persica* (L.) Batsch), Hong Hua (*Carthamus tinctorius* L.), Chai Hu (*Bupleurum chinense* DC), Zhi Ke (*Citrus aurantium* L.).	Rat	Suppressed inflammation and oxidative stress responses.	[61]
Shiquan Dabu Decoction	Ren Shen (*Panax ginseng* C. A. Mey.), Fu Ling (*Poria*), Bai Zhu (*Atractylodes macrocephala* (Koidz.), Gan Cao (*Glycyrrhiza uralensis* Fisch.), Chuan Xiong (*Ligusticum chuanxiong* Hort.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Bai Shao (*Cynanchum otophyllum* Schneid.), Shu Di Huang (*Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. et Mey.), Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Rou Gui (*Cinnamomum cassia* Presl)	Mouse	Suppressed the expression of platelet-derived growth factor.	[62]
Danggui Buxue Decoction	Dang Gui (*Angelica sinensis* (Oliv.) Diels), Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.)	Rat	Elevated VEGF concentrations in serum and vitreous were reinstated.	[63]

(Continued)

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Table1

(Continued)

Name	Composition	Model	Mechanism of action	Refs.
Bushen Huoxue prescription	Bu Gu Zhi (*Psoralea corylifolia* Linn.), Shu Di Huang (*Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. & C.A.Mey.), Tu Si Zi (*Cuscuta chinensis* Lam.), Gou Qi Zi (*Lycium barbarum* L.), Du Zhong (*Eucommia ulmoides* Oliver), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Shan Zhu Yu (*Cornus officinalis* Siebold & Zucc.), Cong Rong (*Cistanches Herba*), Mo Yao (*Commiphora myrrha* Engl.), Du Huo (*Heracleum hemsleyanum* Diels), Hong Hua (*Carthamus tinctorius* L.)	Rat	Lowered retinal oxidative damage in DR rats.	[64]

DR: Diabetic retinopathy; ERK: Extracellular regulated protein kinases; HbA1C: Hemoglobin A1C; VEGF: Vascular endothelial growth factor.

combination with Ginkgo biloba leaves in the prevention and treatment of vascular complications in type 2 diabetes mellitus, in addition to conventional treatment. The results of this study showed that the prevalence of DR was significantly lower in the Liuwei Dihuang Wan and Ginkgo Biloba Leaf groups than in the control group[67]. In addition, in a clinical investigation involving 80 patients with DR, acupuncture paired with the Chinese herbal decoction, Mingmu Wuzi, showed good efficacy and was superior to Western medicine alone[68]. The Heying Qingre formula[69], Jiawei Buyanghuanwu decoction[70] and Compound Danshen Dripping Pill[71] have demonstrated clear efficacy in clinical studies on NPDR. Tang Wang's Prescription has shown efficacy in the treatment of type 2 NPDR[72].

Chinese herbs

In addition to the aforementioned formulations, Chinese herbs hold promise as therapeutic agents for the treatment of DR. Typhae Pollen (TP) is a Chinese herb with a long history of clinical use in TCM. Because it activates *xue* circulation, removes *xue* stasis, cools *xue,* and stops bleeding, it is widely used in the treatment of ocular diseases such as hemorrhagic fundus and *xue* stasis[73]. The active ingredients of TP include flavonoids, polysaccharides, and organic acid[74], which play roles in promoting the two-way regulation of coagulation and anticoagulation, improving microcirculation, lowering blood lipids, anti-atherosclerosis, and other pharmacological effects[75–76]. Zhou et al.[77] analyzed the interventional effects of TP on DR using network pharmacology and molecular docking techniques. They revealed that TP may act on core targets such as AKT1 and EGFR through key active ingredients and exert protective effects against DR by regulating multiple signaling pathways such as VEGF and PI3K-Akt[77]. Lei et al.[73] demonstrated through *in vivo* experiments that TPP, one of the main active components of TP, could improve DR by decreasing inflammation levels and improving *xue* circulation. In TCM, *Dendrobium Chrysostom* Lindl (DC) is an important *yin* nourishing herb that is mainly used to treat gastric *yin* deficiency and *yin* deficiency with internal heat, which can alleviate vision loss due to yin deficiency in the liver and kidney[78–79]. It contains a variety of active ingredients, such as mullein and polysaccharides, and has various pharmacological activities, including immunomodulatory, antioxidant, hypoglycemic, antidiabetic, and anticancer[80–81]. Gong et al.[82] experimentally explored the ameliorative effects and mechanism of action of a DC ethanol extract on retinopathy in diabetic rats. The results showed that DC extract alleviated pathological retinal angiogenesis by inhibiting the VEGF/VEGFR2 signaling pathway and the expression of proangiogenic factors. In addition, DC extract attenuated the inflammatory response in the diabetic retina[82–83]. Another study suggests that DC ethanol extract ameliorates retinopathy in diabetic rats by reducing inflammation and increasing expression of tight junction proteins[82,84]. These studies suggest the potential use of DC in DR treatment and explain the ocular improvement capabilities of medicinal DC that have been used for centuries.

Astragalus membranaceus (AM) is used to treat various ailments. Research has shown that it has antiaging, antiviral, antibacterial, blood sugar-regulating, and antidiabetic effects[85]. Using network pharmacology, Jin et al.[86] found that AM exhibits multicomponent, multitarget, and multipathway characteristics in treating DR. Astragalin, the active ingredient of AM, inhibits VEGF overexpression and attenuates hyperglycemic injury in Müller cells, thereby combating DR[87]. Cheng et al.[88] found that AM and its formulations are superior to other drugs used to treat DR in improving vision and fundus appearance and lowering fasting blood glucose (FBG), triglyceride (TG), RBC aggravation index (RAI), and plasma viscosity. Therefore, AM may serve as a novel therapeutic option for diabetic DR.

Moreover, additional Chinese herbs have demonstrated effectiveness in both animal models and clinics for DR, such as *Zingiber zerumbetmagnum* Elmer[89], *Scutellaria barbata* D. Don[90], *Polygonum cuspidatum* var. *spectabile* Noter[91], which exerts a therapeutic effect on DR through its anti-inflammatory effects. For example, *Lonicera japonica* Thunb[92]., and total lignans from *Arctium lappa* L[93]. can inhibit DR angiogenesis by promoting VEGF expression. Table 3 lists the specific mechanisms of action of crude anti-DR drugs. The analysis showed that multiple Chinese herbs have significant potential for the prevention and treatment of DR.

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Table 2

Clinical observations of Chinese medicinal formulae for the treatment of DR

Name	Composition	DR stage	Results	Refs.
Qiming Granules	Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Di Huang (*Rehmannia glutinosa* Libusch), Ge Gen (*Pueraria lobata* (Willd.) Ohwi), Gou Qi Zi (*Lycium barbarum* L.), Jue Ming Zi (*Cassia tora L.*), Chong Wei Zi (*Leonurus japonicus* Houtt), Pu Huang (*Typha angustifolia* L.), Shui Zhi (*Hirudo*).	DR	The ARCT decreased in the examined group, exhibiting a statistically considerable change following treatment ($P < 0.01$).	[65]
Zhenwu Decoction	Fu Zi (*Aconitum carmichaelii* Debx.), Bai Zhu (*Atractylodes macrocephala* Koidz.), Sheng Jiang (*Zingiber officinale* Roscoe), Fu Ling (*Poria*), Bai Shao (*Paeonia lactiflora* Pall.)	DR	Plasma endothelin levels were lower in the treatment group compared to controls, who demonstrated a reduced overall response rate ($P < 0.05$).	[66]
Liuweidihuang Pill (Decoction)	Shu Di Huang (*Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. & C.A.Mey.) DC), Shan Zhu Yu (C*ornus officinalis* Sieb. et Zucc.), Shan Yao (*Dioscorea polystachya* Turcz.), Mu Dan Pi (*Paeonia suffruticosa* Andr.), Fu Ling (*Poria*), Ze Xie (*Alisma orientale* (Sam.) Juzep.)	DR	The treatment group exhibited markedly reduced DR incidence compared to controls ($P < 0.05$).	[67]
Mingmu Wuzi Decoction	Jue Ming Zi (*Cassia tora L.*), Qing Xiang Zi (*Celosia argentea* L.), Che Qian Zi (*Plantago asiatica* L.), Man Jing Zi (*Vitex trifolia* L.), Chi Shao (*Paeonia lactiflora* Pall.), Tu Si Zi (*Cuscuta chinensis* Lam.), Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Tao Ren (*Prunus persica* (L.) Batsch), Zhi Zi (*Gardenia jasminoides* Ellis), Hong Hua (*Carthamus tinctorius* L.), Pu Huang (*Typha angustifolia* L.)	DR	The intervention group demonstrated superior outcomes compared to the comparison group ($P < 0.01$).	[68]
Heying Qingre formula	Jin Yin Hua (*Lonicera japonica* Thunb.), Dang Gui (*Angelica sinensis* Oliv.), Xuan Shen (*Scrophularia ningpoensi* Hemsl.), Sheng Di (*Rehmannia glutinosa* Libosch), Gou Qi Zi (*Lycium barbarum* L.), Pu Gong Ying (*Taraxacum mongolicum* Hand.), Huang Jing (*Polygonatum sibiricum* F. (Rhizome))	NPDR	The experimental group yielded notably superior outcomes over the comparative group regarding ocular health, funduscopic findings, and TCM manifestations ($P < 0.05$).	[69]
Jiawei Buyanghuanwu Decoction	Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Chi Shao (*Paeonia lactiflora* Pall.), Hong Hua (*Carthamus tinctorius* L.), Tao Ren (*Prunus persica* (L.) Batsch), Chuan Xiong (*Chuanxiong Rhizoma*), Sheng Di (*Rehmannia glutinosa*), Xuan Shen (*Scrophularia ningpoensi* Hemsl.), Shan Yao (*Dioscorea polystachya* Turcz.), Fu Ling (*Poria*), Cang Zhu (*Atractylodes lancea* (Thunb.) DC.)	NPDR	Reduced plasma ET-1 levels in patients with NPDR. The experimental group showed significantly better results than the control group ($P < 0.05$).	[70]
Compound Danshen Dripping Pill	Dang Shen (*Salvia miltiorrhiza* Bge.), San Qi (*Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow), Bing Pian (*Borneolum Syntheticum*)	NPDR	The experimental cohort demonstrated markedly superior effectiveness *vs.* the comparison cohort ($P < 0.001$).	[71]
TangWang Prescription	Huang Qi (*Astragalus membranaceus* (Fisch.) Bge.), Dang Shen (*Salvia miltiorrhiza* Bge.), Pu Huang (*Typha angustifolia* L.), Jue Ming Zi (*Cassia tora L.*), Mi Meng Hua (*Flos Buddlejae*)	NPDR	The experimental group yielded notably superior outcomes compared to the control group.	[72]

ARCT: Arm-to-retinal circulation time; DR: Diabetic retinopathy; ET-1: Endothelin-1; NPDR: Non-proliferative DR; TCM: Traditional Chinese Medicine.

Components of TCM

TCM components are singular active ingredients in Chinese herbal medicines and are characterized by clear chemical structures and diverse pharmacological activities, including antioxidant, antitumor, and antibacterial properties. They have the advantages of being both TCM and chemical drugs. Research indicates that TCM components such as flavonoids, polyphenols, polysaccharides, and saponins exhibit potential effects on DR. The mechanisms are detailed in Table 4.

Flavonoids

Flavonoids are natural compounds widely distributed in plants. Evidence highlights their multifaceted biological properties, including antioxidant, anti-inflammatory, and glucose-lowering actions, among others[94]. Given

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Table 3

Effects of Chinese herbs on DR

Name	Model	Mechanism of action	Refs.
Typha angustifolia L. (Pu Huang)	Rat	Anti-inflammatory and improved blood circulation.	[73]
Dendrobium Chrysotoxum Lindl. (Gu Chui Shi Hu)	Rat	Anti-inflammation and anti-angiogenesis.	[84]
Astragalus membranaceus (Fisch.) Bunge (Huang Qi)	Rat	Diminished high blood sugar-induced VEGF upregulation in retinal Müller cells.	[87]
Zingiber zerumbetmagnum Elmer (Hong Qiu Jiang)	Rat	Inhibited the ERK1/2 and NF-κB signaling pathways.	[89]
Scutellaria barbata D. Don (Ban Zhi Lian)	Mouse	Enhanced the manifestation of retinal tight junction proteins claudin-1 and claudin-19.	[90]
Polygonum cuspidatum var. spectabile Noter (Hu Zhang)	Rat	Suppressed HMGB1-RAGE-NF-κB signaling cascade activation.	[91]
Lonicera japonica Thunb.(Jin Yin Hua)	Mouse	Inhibited retinal angiogenesis.	[92]
Arctium lappa L. (Niu Bang Zi)	Rat	Inhibited PKC activation and blocked VEGF elevation.	[93]

DR: Diabetic retinopathy; ERK: Extracellular signal-regulated kinase; HMGB1: High mobility group box 1; NF-κB: Nuclear factor κB; PKC: Protein kinase C; RAGE: Receptors for advanced glycation end products; VEGF: Vascular endothelial growth factor.

the intimate connection between DR and oxidative stress as well as the inflammatory reactions induced by prolonged hyperglycemia, flavonoids, with their antioxidant and anti-inflammatory properties, may offer relief. Furthermore, studies suggest that flavonoids ameliorate vascular damage and edema associated with DR by enhancing microcirculation and safeguarding vascular endothelial function[95].

Quercetin is a natural constituent that is widely found in plants and belongs to the flavonoid family. Quercetin has been shown to have a variety of biological activities, including antioxidant, anti-inflammatory, anticancer, cardiovascular, and ocular protection[96]. Furthermore, it suppressed abnormal blood vessel formation in the choroid and retina[97]. Ola et al.[98] demonstrated that quercetin administration to diabetic rats suppressed retinal cytochrome c and caspase-3 levels. The levels of neurotrophic factors and Bcl-2 protein were increased, which helped protect against diabetic retinal neurodegeneration[98]. Neurotrophic factors are crucial for neuronal viability, synaptic plasticity, and repair. Retinal brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are important members of the neurotrophic factor family that play potential roles in diabetic retinal neuroprotection[99]. Quercetin supports the function of retinal neurons by regulating the synthesis, release, and receptor signaling pathways of various neurotrophic factors[100]. Research has indicated decreased BDNF and NGF levels in diabetic rat retinas, with quercetin therapy notably enhancing these neurotransmitter levels[98]. This further indicates that quercetin stimulates the production and release of neurotrophic substances within glial cells and the brain[101]. BDNF activates intracellular signaling pathways and exerts neuroprotective effects by binding to its receptor, tropomyosin receptor

Table 4

Effects of active components of TCM on DR

Active components	Herb	Model	Mechanism of action	Refs.
Quercetin	*Ginkgo biloba* L.	Rat	Inhibited the levels of cytochrome c and caspase-3, elevated expression of neurotrophic factors, and the anti-apoptotic protein Bcl-2.	[98]
Puerarin	Pueraria lobate (Willd.) Ohwi	Rat	Regulated expressions of VEGF and HIF-1a stimulated by STZ.	[106]
Curcumin	*Curcuma longa* L.	Rat	The hypoglycemic, antioxidant, VEGF-downregulating, and neuroprotective properties.	[115]
Lycium barbarum polysaccharides	*Lycium barbarum* L.	Rat	Decreased GFAP expression and decreased Müller cell protrusion hypertrophy.	[119]
Polygonati sibiricum polysaccharide	*Polygonatum sibiricum* Delar. ex Redoute	Rat	Reduced hyperglycemia, suppressed abnormal vascular growth, and suppressed apoptosis.	[120]
ginsenoside Rb1	*Panax ginseng* C.A. Mey.	Rat	Inhibited MDA elevation and GSH reduction.	[123]
ginsenoside Rg1	*Panax ginseng* C.A. Mey.	Mouse	Reduced apoptosis in GCL and INL cells.	[124]
ginsenoside Rk1	*Panax notoginseng*	Mouse	Inhibited VEGF and AGE-mediated retinal vascular leakiness.	[125]
Astragaloside IV	*Astragalus membranaceus* (Fisch.) Bge.	Mouse	Inhibited the activation of NFjB and various cytokines, and downregulated the expression of aldose reductase.	[126]

AGE: Advanced glycation end product; GCL: Ganglion cell layer; GFAP: Glial fibrillary acidic protein; GSH: Glutathione; HIF-1a: Hypoxia inducible factor 1 subunit alpha; INL: Inner nuclear layer; MDA: Malondialdehyde; NFjB: Nuclear factor kappa B; STZ: Streptozotocin; VEGF: Vascular endothelial growth factor.

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kinase B (TrkB)[102]. Studies have shown that quercetin upregulates BDNF expression, promotes its binding to the TrkB receptor, activates the downstream PI3K/Akt pathway, and inhibits neuronal apoptosis. Kumar et al.[103] used quercetin to treat streptozotocin (STZ)-induced diabetic rats. The results show that quercetin treatment is effective in slowing the progression of DR through multi-targeted mechanisms such as restoring retinal antioxidant enzyme activity, ameliorating neuroinflammation, and combating neural apoptosis[103]. Therefore, it can be concluded that quercetin can be proven to be a clinically suitable drug for the prevention of DR, with its mechanism of action shown in Figure 3.

Puerarin (7,4'-dihydroxy-8-C-glucosylisoflavone) is a flavonoid extracted from TCM and serves as the primary active constituent in TCM's Pueraria lobata extract. Studies have shown that puerarin is widely used for diabetes and diabetic complications, and exerts protective effects against inflammation, hyperlipidemia, and oxidative damage[104]. Chen et al.[105] reported that puerarin could delay and improve diabetes and its complications, such as DR, and could potentially serve as an adjunct therapy for diabetic conditions and their associated complications in clinical practice. Teng et al.[106] demonstrated that puerarin effectively decreases STZ-induced DR by modulating VEGF and hypoxia-inducible factor-1α (HIF-1α) levels. Thus, puerarin has the potential to be an effective therapeutic agent for DR.

Naringenin (4', 5, 7-trihydroxyl flavone) is a citrine-derived flavonoid with antioxidant, antidiabetic, and anti-inflammatory activities, which is widely found in the peels of citrus plants[107]. Al-Dosari et al.[108] demonstrated through experiments that oral naringenin has the potential to improve DR. Treatment with naringenin provided neurotrophic support and improved levels of apoptotic proteins[108]. Xue et al.[109] evaluated the effects of naringin on HG-induced retinal endothelial cell injury induced by high glucose (HG). The results of this study suggested that naringenin regulates the GTP cyclohydrolase 1/endothelial nitric oxide synthase (GTPCH1/eNOS) axis, thus ameliorating HREC damage[109].

Phenolic compounds

Phenolic compounds have antioxidant, antibacterial, anti-inflammatory, and other pharmacological activities[110–111]. Curcumin, a yellow powder extracted from the tubers of turmeric plants, is a naturally occurring polyphenol with antioxidant, anti-inflammatory effects[112]. Studies have shown that curcumin can reduce retinal damage in the early stages of diabetes through its antioxidant effects[113]. Yao et al.[114] conducted an experimental study demonstrating that curcumin may mitigate the inflammation and oxidative stress induced by diabetes within the vitreous microenvironment of rats. Furthermore, curcumin attenuated the elevation of VEGF levels in the vitreous bodies of diabetic rats. This study suggests that curcumin may serve as an effective treatment for DR[114]. Yang et al.[115] discovered that curcumin possesses significant therapeutic potential for curing DR, which may be related to its hypoglycemic properties, antioxidant activity, VEGF downregulation, and neuroprotective properties. Therefore, curcumin may have a promising potential for ameliorating DR pathophysiology.

Resveratrol is a polyphenol compound derived from plants that is recognized for its antioxidant, hypoglycemic, and vascular protective effects[116]. Animal studies have shown that resveratrol alleviates DR by targeting oxidative stress, NF-κB, and apoptosis pathways[117]. In a series of experiments, Chen et al.[118] demonstrated that

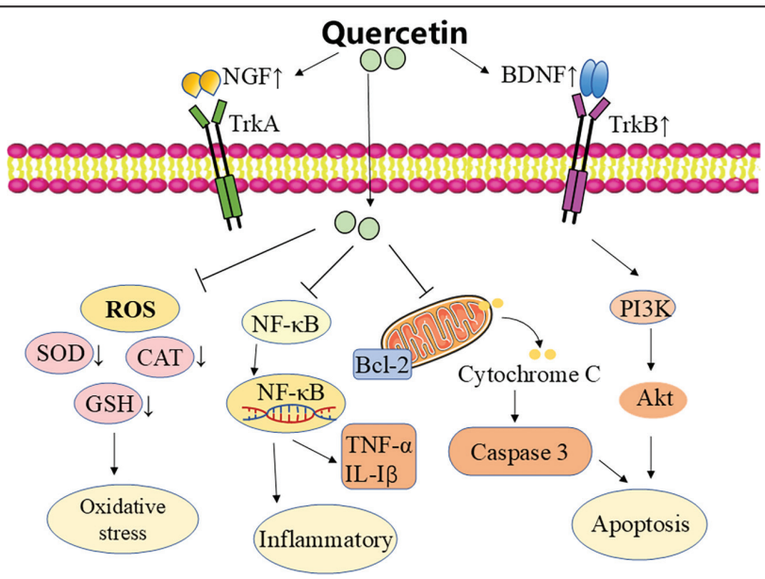


Figure 3. Main mechanisms of quercetin against DR. BDNF: Brain-derived neurotrophic factor: Akt: Protein kinase B; CAT: Catalase; DR: Diabetic retinopathy; GSH: Glutathione; IL: Interleukin; NF-κB: Nuclear factor κB; NGF: Nerve growth factor; PI3K: Phosphatidylinositol-3 kinase; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TNF: Tumor necrosis factor; TrkB: Tropomyosin receptor kinase B.

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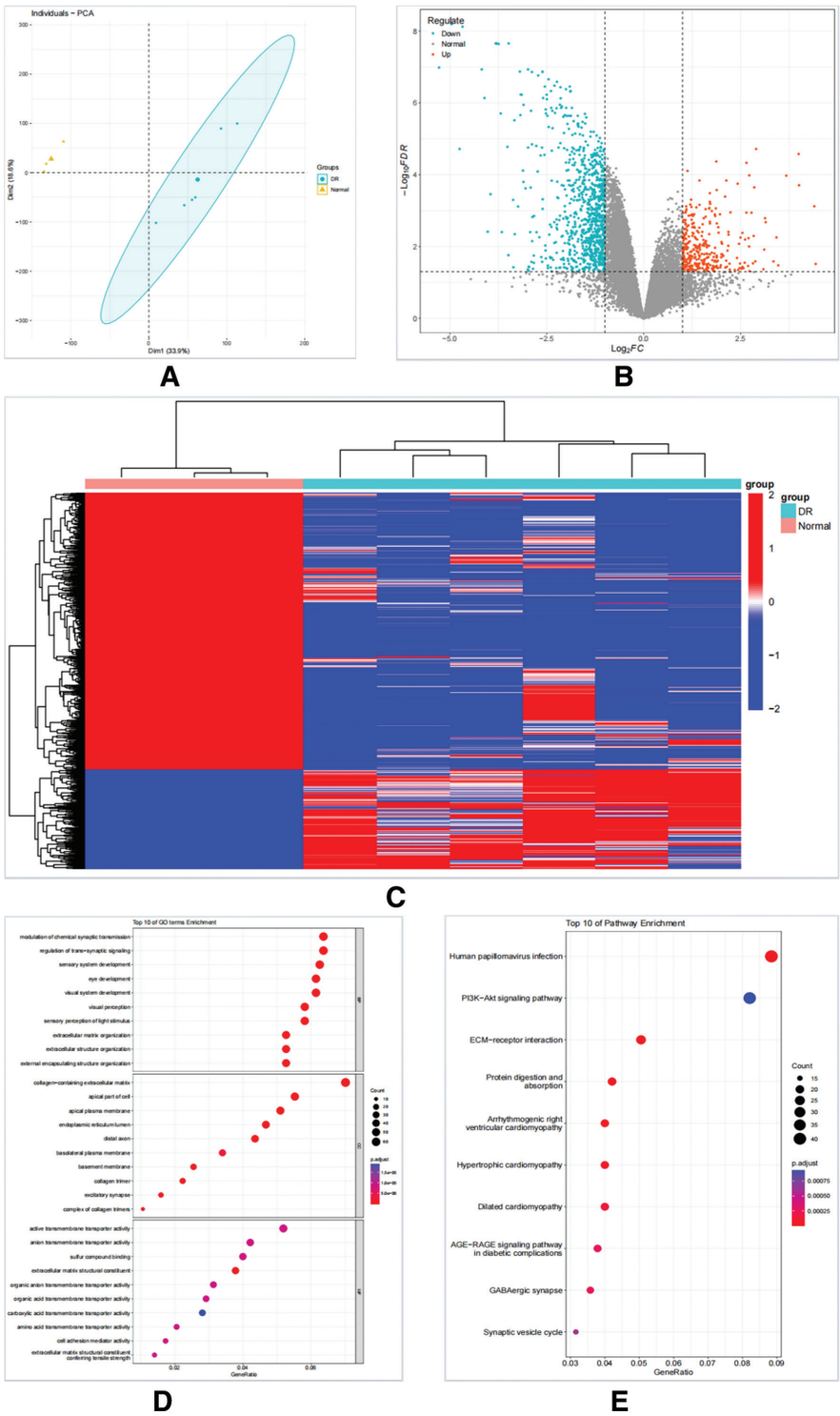


Figure 4. Differentially expressed gene analysis and bioinformatics results for DR based on the GEO database. (A) PCA for GSE60436. Yellow: normal; blue: DR. (B) Volcano plot of differentially expressed genes (n = 1,216). Blue represents downregulated genes; red represents upregulated genes. (C) Retinal transcriptome differential gene expression profiles in DR patients *vs.* healthy subjects (blue represents downregulated genes; red represents upregulated genes). (D) GO enrichment analysis. (E) KEGG pathway enrichment analysis. AGE: Advanced glycation end product; Akt: Protein kinase B; DR: Diabetic retinopathy; ECM: Extracellular matrix; GABA: Gamma- aminobutyric acid; GEO: Gene Expression Omnibus; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; PCA: Principal component analysis; PI3K: Phosphatidylinositol 3-kinase; RAGE: Receptors for advanced glycation end products.

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resveratrol reduced retinal inflammation and DR damage *via* PON1. The results showed that Resveratrol decreases Ox-DLD, inflammatory cytokines, and retinal damage in STZ diabetic rats. In addition, apoptosis of Ox-DLD and RREC cells is decreased by increasing PON1 activity *in vitro*.

Polysaccharides

Polysaccharides exhibit significant therapeutic benefits in DR. Yang et al.[119] revealed that retinas treated with *Lycium barbarum* polysaccharides were effective in attenuating ischemia-induced retinal hypoplasia. Wang et al.[120] demonstrated the potential preventive effects of *Polygonati sibiricum* polysaccharides (PSP) on retinal damage in diabetic rats using *in vivo* experiments. Their findings revealed that PSP effectively safeguards against diabetes-related damage to the retina by regulating a variety of signaling pathways[120]. In summary, polysaccharides offer a promising therapeutic strategy for DR. Hua et al.[121] demonstrated that resveratrol prevents retinal neovascularization by modulating retinal VEGF expression.

Ginsenosides

In addition to polyphenols, polysaccharides, and flavonoids, ginsenosides have demonstrated promising efficacy against DR. Ginsenosides can weaken oxidative stress reactions in the retinas of mice, inhibit endoplasmic reticulum stress, and alleviate apoptosis of retinal endothelial cells, significantly reducing damage to the retinal barrier caused by exposure to high blood sugar levels[122]. Dong et al.[123] found that the ginsenoside Rb1 effectively improved retinopathy in diabetic rats by enhancing the antioxidant defense functions of the retina. Gao et al.[124] used experimental data to show that ginsenoside Rg1 inhibits DR alterations by diminishing apoptosis in ganglion cell layer (GCL) and inner nuclear layer (INL) cells. A study has shown that ginsenoside Rk1 effectively inhibits vascular hyperpermeability induced by a variety of disease-causing factors and thus protects *xue* vessels, the results suggesting that ginsenoside Rk1 has the potential to be a therapeutic compound for the treatment of diseases characterized by vascular leakage[125]. Recent research revealed that astragaloside IV offers a multifaceted defense mechanism in mouse models of DR by inhibiting the inflammatory response and downregulating the expression of aldose reductase, a key player in the polyol pathway[126].

Acupuncture

Acupuncture consists of "needle acupuncture" and "moxibustion" and is an important part of TCM, which can relieve a variety of diseases[127]. Acupuncture and moxibustion function by clearing the meridians to harmonize *yin* and *yang* energies and regulate the flow of *qi* and *xue* within the body. Acupuncture for the treatment of eye diseases was recorded as early as in Neijing, and current clinical and experimental studies have proven that acupuncture can be an effective method for treating eye diseases. Prevention and treatment of DR with acupuncture may be carried out through the synthetic effects of enhancing the retinal capillary condition, boosting microcirculation, decreasing clot formation, increasing the transformation capacity of erythrocytes, and decreasing blood sugar[128–129]. Dr. Zhang Ren believes that DR is closely related to *qi* and *yin*. Acupuncture stimulates acupoints and meridians to enhance *xue* circulation and eliminate *xue* stasis, thereby preventing and treating DR[130]. Ang et al.[131] found that acupuncture offers therapeutic advantages to patients with DR. Their findings indicated that whether used as a standalone treatment or in conjunction with conventional pharmaceuticals, acupuncture appeared to outperform standard medicines alone in the treatment of DR[131]. Therefore, the combination of acupuncture with drugs to treat DR may yield superior results.

Potential therapeutic targets for DR

Bioinformatics analysis

To further our understanding of DR, bioinformatics analyses were used to identify potential mechanisms and therapeutic targets for DR. We used publicly available microarray data (GSE60436) to analyze targets associated with DR. The GSE60436 microarray dataset was procured from the Gene Expression Omnibus (GEO) database at this on-line location: https://www.ncbi.nlm.nih.gov/geo/. This dataset encompassed genetic information from seven DR retinal tissues and four normal retinal tissues. PCA of the dataset GSE60436 showed that the DR group was significantly separated from the normal control group, and the sample points were clustered within the group (Figure 4A). As shown in Figure 4B, the volcano plot visualizes the differentially expressed gene profiles of the DR group and the blank control group. Based on the set threshold ($P < 0.05$, |log2FC| > 1), we identified 1,216 significantly differentially expressed genes. Among them, 321 genes were significantly upregulated and 895 genes were significantly downregulated. Heat maps illustrating the genes with altered expression levels were created for graphical representation, and the outcomes are detailed in Figure 4C. We used Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses for functional annotation and pathway localization of target gene sets to systematically elucidate their potential biological significance. GO enrichment analysis revealed significant overrepresentation of genes involved in synaptic transmission and transmembrane transporter activity (Figure 4D). Concurrently, the KEGG analysis yielded substantially enriched metabolic pathways (Figure 4E). KEGG pathway analysis indicated that this might be related to the PI3K-Akt, AGE-RAGE, and other signaling pathways.

Cutting-edge targets and strategies

In recent years, research on DR treatment has progressed rapidly, particularly in terms of exploring cellular and

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molecular mechanisms, and many breakthroughs have been achieved. Cheng et al.[132] revealed that the angiogenic factor AGGF1 promotes cell cycle protein expression through the activation of the TNFSF12/FN14 pathway and is a key mechanism driving pathological retinal angiogenesis. Targeted inhibition of AGGF1 effectively attenuates ischemia-induced pathological retinal neovascularization, providing a potential new target for DR treatment[132]. Tang et al.[133] reported that ginsenoside Rd or other agonists targeting the GPR30 receptor promote AMPK-mediated fatty acid oxidation (FAO), which may provide a feasible treatment strategy for DR. Chen et al.[134] revealed that lactate modification promotes vascular abnormalities in DR through the FTO-CDK2 axis, which is important for regulating EC function and retinal homeostasis and provides new potential targets and therapeutic strategies for the treatment of DR. Shao et al.[135] indicated that the gamma-aminobutyric acid system is a potential therapeutic target for alleviating early DR. A deeper understanding of the pathological mechanisms of DR is fundamental to the development of new therapeutic strategies. Based on our understanding of these mechanisms, many novel treatment strategies and drug delivery technologies are currently being explored. Improving treatment delivery strategies and developing long-acting, minimally invasive, or non-invasive drug delivery methods can optimize the therapeutic outcomes for DR[136]. Exploring cutting-edge targets for DR treatment interventions, innovating delivery technologies and mechanisms, and integrating TCM with modern medical advancements in target identification and mechanism innovation may provide innovative strategies for TCM-based DR treatments. Novel delivery systems can enhance the targeting and bioavailability of herbal medicines. Furthermore, combining TCM with modern medical advancements in target identification and mechanism innovation enables precise and multitarget interventions to address the progression of DR.

Conclusions and prospects

TCM has demonstrated significant efficacy in treating complex diseases through its holistic and syndrome differentiation approaches. To prevent the onset and progression of DR, this article summarizes the use of classic Chinese herbal formulae, Chinese herbs, and active components of TCM. Bioinformatics analysis of DR by the GEO database microarray showed that the pathogenesis of DR may be associated with signaling cascades, such as PI3K-Akt and AGEs-RAGE, as revealed by KEGG pathway analysis, which provides a reference for subsequent in-depth investigation of the pathogenesis of this disease (Figure 5). The correct use of TCM may become a key link in the prevention and treatment of diabetic complications, and is of great value for reducing their occurrence and progression. Thus, efforts should focus on expediting the clinical application of TCM and

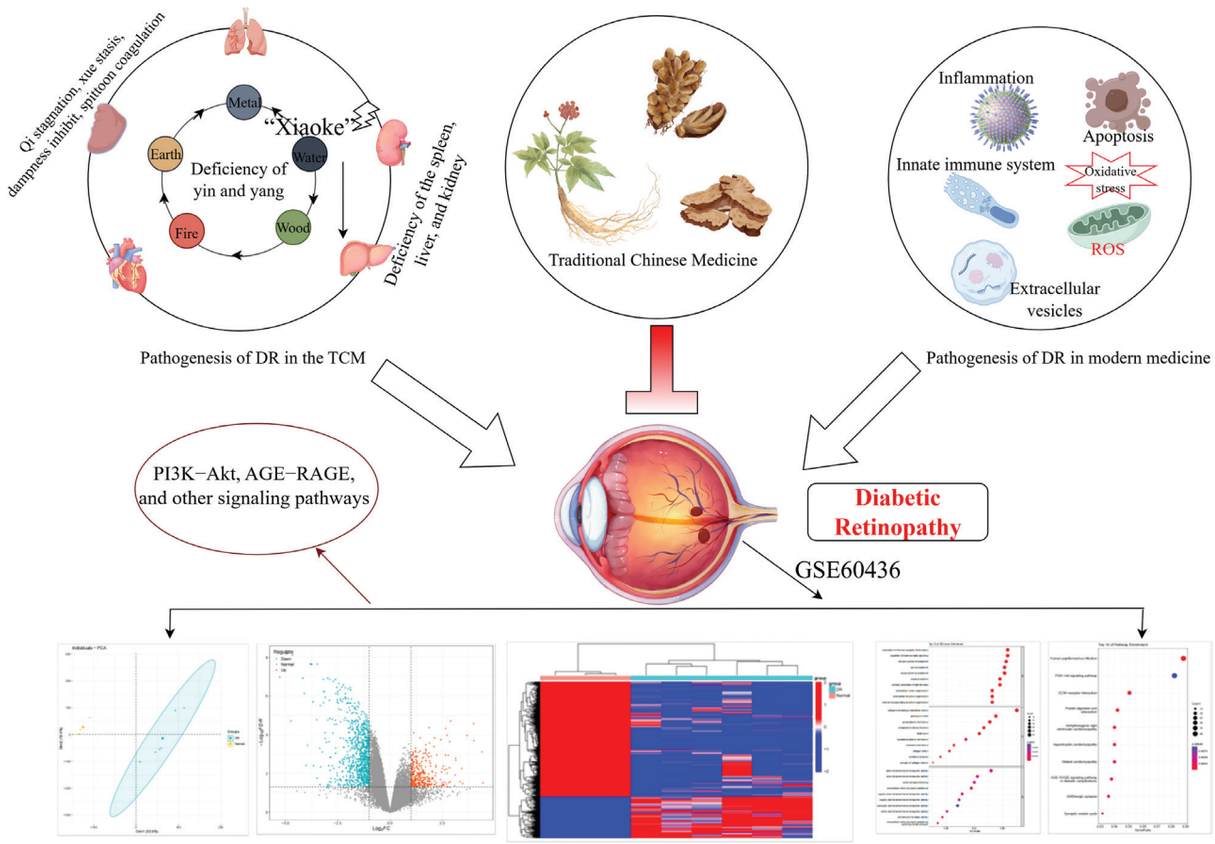


Figure 5. Schematic overview of the potential effects of TCM on DR. AGE: Advanced glycation end product; DR: Diabetic retinopathy; ECM: Extracellular matrix; RAGE: Receptors for advanced glycation end products; PCA: Principal component analysis; PI3K: Phosphatidylinositol 3-kinase; ROS: Reactive oxygen species; TCM: Traditional Chinese Medicine.

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providing safer treatment options for patients with DR. Although TCM shows promising prospects in the treatment of DR, several challenges and future directions remain. For instance, the underlying mechanisms require further in-depth investigation, and the level of clinical evidence needs to be improved. Therefore, future efforts should be driven by evidence-based medicine and multidisciplinary integration to accelerate the transformation of TCM from empirical medicine to precision medicine, thereby providing safer and more effective treatment options for patients with DR.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Tao Lin contributed to conceptualization, methodology, data curation, writing—original draft. Chen Chen contributed to conceptualization, formal analysis, project administration. Hongyan Zhu contributed to conceptualization, writing—review and editing. Lichun Zhao contributed to investigation, formal analysis, project administration. Wei Li contributed to conceptualization, writing—review and editing, supervision, funding acquisition. All authors have read and agreed to the published version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

Data availability

All data generated or analyzed during this study are included in this published article.

Declaration of Generative AI in Scientific Writing

The authors declare that no generative artificial intelligence (AI) technologies were used in the conception, drafting, or revision of this manuscript. All work was performed solely by the authors.

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