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Research Progress on Protective Effect and Mechanism of Puerarin on Diabetic Retinopathy

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Abstract: ***Diabetic retinopathy (DR) is one of the many complications of diabetes. The mechanism of the occurrence and development of diabetic retinopathy in modern medicine has not been fully elucidated. Its physiology and pathology are complex, and various mechanisms are inseparable. At present, it is believed that it is related to oxidative stress, abnormal enhancement of inflammatory response, up-regulation of vascular endothelial growth factor (VEGF) induced neovascularization, hemodynamic changes and ferroptosis. DR is often treated with retinal photocoagulation, vitrectomy and intravitreal injection. However, these treatments have many adverse reactions, such as: intravitreal injection requires repeated injections, and there is a risk of infection with endophthalmitis. Laser therapy will leave scars in the fundus retina, thus affecting vision. In recent years, a large number of research data have been accumulated on the prevention and treatment of DR by various traditional Chinese medicine monomers. Puerarin has good anti-inflammatory, anti-oxidation and anti-apoptosis properties, which has attracted the attention of researchers. This article reviews the application of puerarin in the treatment of DR and discusses its mechanism of action, hoping to provide new ideas and directions for the treatment of DR and drug development.***

Keywords: Diabetic retinopathy, DR, Puerarin, Chinese medicine monomer, Research progress.

1. Introduction

DR is one of the many complications of diabetes, and it is also the main cause of visual loss in working-age workers around the world [1]. Therefore, exploring the pathogenesis of diabetic retinopathy and finding effective treatment is one of the challenges faced by diabetic patients. At present, the treatment of DR mainly includes retinal laser photocoagulation, vitrectomy and intravitreal injection. Although laser treatment and vitrectomy are currently effective ways to reduce the blindness rate of DR, laser treatment will leave permanent scars in the fundus. Intravitreal injection requires multiple injections of anti-VEGF or steroids or other drugs into the vitreous to achieve the effect of relieving the disease. Intravitreal injection is a risky operation, which has the risk of infection with endophthalmitis and the possibility of promoting glaucoma and cataract [2]. More and more studies have shown that Chinese patent medicines and traditional Chinese medicine monomers can act on DR through a variety of mechanisms to reduce the degree of retinal damage, effectively slow down the development of the disease, and improve its clinical symptoms. This article will review the research on the protective effect and mechanism of puerarin, the main active ingredient of pueraria, on DR.

2. Diabetic Retinopathy

Diabetic retinopathy is one of the most prominent manifestations of diabetic microangiopathy. It is a fundus lesion with specific changes caused by diabetes. The early basic pathological manifestations of DR include thickening of the basement membrane, increased vascular permeability, and loss of retinal capillary pericytes. The late basic pathological manifestations include new capillaries, vitreous hemorrhage, fiber proliferation, and traction retinal detachment, which seriously affects vision. The occurrence of DR is related to a variety of factors, including increased levels of oxidative stress, non-enzymatic glycosylation of proteins, activation of polyol pathways, glycated hemoglobin, hexosamine bypass, cytokines, protein kinase C bypass, and neurovascular unit damage. In addition, there is also a view that epigenetic modification, metabolic memory and its molecular mechanism, nitration stress and matrix metalloproteinases are involved in the pathogenesis of DR [3]. Although the occurrence and development of DR are associated with many factors, a large number of in vivo and in vitro studies and clinical studies have shown that hyperglycemia is the ' trigger key ' of DR [4]. It is known that the degree of DR injury is directly related to the degree of hyperglycemia in patients. Continuous and good control of blood glucose, blood pressure and blood lipids is the basis for reducing the risk of DR development, which has become the consensus of retinal experts [5]. Hyperglycemia induces increased oxidative stress, excessive expression of inflammatory factors and VEGF, changes in retinal hemodynamics, damage to the blood-retinal barrier, damage to neurotrophic factor receptors and their signaling pathways, and damage to retinal blood vessels, neurons, and glial cells. These pathogenic mechanisms involve retinal microangiopathy and early neuropathy, which gradually lead to retinal structural disorders, eventually leading to irreversible visual loss and total blindness [6-8]. Therefore, it is particularly urgent to find multi-channel drugs that can act on DR.

3. Puerarin

3.1 Introduction of Puerarin

Puerarin, its chemical name is 4,7-dihydroxy-8-β-D glucosyl isoflavone, which comes from the legume Pueraria. Its main components can be summarized into three categories: (1) isoflavones, such as daidzein, daidzein, puerarin and so on; (2) Puerarin glycosides, such as puerarin glycosides A, B and C (derivatives of three dihydrochalcones); (3) Triterpenoid saponins, such as seven new saponins, sophordiol, soyasaponin A, soyasaponin a, soyasaponin b, soyasaponin c, alkaloids and other similar derivatives. Puerarin is the most

important active ingredient of Pueraria lobata. The pharmacological effects of puerarin include improving metabolic dysfunction, anti-oxidation, reducing apoptosis, protecting nerves, improving microvascular circulation, improving ischemia and hypoxia, anti-arrhythmia, improving cardiovascular and cerebrovascular diseases, enhancing lung function, preventing osteoporosis, enhancing immunity and protecting liver and liver, showing a therapeutic effect that cannot be ignored in many diseases [9-11]. In recent years, more studies have applied puerarin to ophthalmic diseases.

3.2 The Clinical Application of Puerarin in Eye Diseases

The role of puerarin in the treatment of ophthalmic diseases has been confirmed, (1) reducing retinal oxidative stress and inhibiting retinal neovascularization and occurrence [12]; (2) Reduce blood viscosity, inhibit platelet aggregation and adhesion, and increase blood fluidity; (3) Dilate retinal blood vessels, supply enough blood and oxygen, relieve vasospasm caused by ischemia, improve blood flow status, shorten retinal circulation time, and reduce the generation of non-perfusion areas. Therefore, puerarin is mainly used in glaucoma, ischemic retina, optic neuropathy, choroidal lesions, DR and other diseases in ophthalmology. Wei et al. [13] suggested that puerarin significantly reduced the expression of inflammatory factors interleukin-1 (IL-1), IL-17A and tumor necrosis factor-α (TNF-α) in neovascular glaucoma, alleviated the damage of inflammatory factors to the retina, and had a good effect on the treatment of glaucoma and improved its prognosis. Zhao et al. [14] studied that puerarin can control intraocular pressure by β-receptor blocking and reducing serum catecholamine levels, indicating that puerarin plays a role in the clinical treatment of glaucoma and can alleviate the progression of glaucoma, with significant clinical efficacy. In addition, puerarin can greatly improve the blood flow velocity of the central retinal vein and the average peak systolic blood flow velocity of the central retinal artery, effectively reduce the damage to the retina caused by ischemia, and protect the effective vision of patients with central retinal vein occlusion. This study suggests that puerarin has a positive effect on central retinal vein occlusion [15]. In addition, puerarin can protect the optic nerve by preventing apoptosis induced by n-methyl-d-aspartate induced by JNK/p38MAPK signaling pathway, alleviating the damage of inflammatory factors, malondialdehyde (MDA) and reactive oxygen species (ROS) to retinal ganglion cells [16]. Another study found that puerarin is an effective drug to increase choroidal blood flow. Xuan et al [17] measured choroidal blood flow in an ischemic model induced by high intraocular pressure, and measured retinal function using the B-wave amplitude of the electroretinogram. Before treatment with puerarin, the amplitude of B wave only recovered to 39 %. After treatment with puerarin, the B wave recovered to 84 %, and the choroidal blood flow increased. The difference was statistically significant, suggesting that puerarin has a therapeutic effect on ischemic retinal diseases. Because of its ability to reduce retinal oxidative stress damage, inhibit retinal neovascularization, and improve retinal microcirculation, puerarin has also been widely used and studied in DR.

4. The Mechanism of Puerarin on Diabetic Retinopathy

The single active ingredient of traditional Chinese medicine is the meaning of traditional Chinese medicine monomer. Its chemical structure is clear and has a variety of pharmacological activities, which is an important source of new drug research and development. Traditional Chinese medicine monomer has two advantages of both traditional Chinese medicine and chemical drugs. On the one hand, traditional Chinese medicine monomer has the characteristics of safety, high efficiency, multi-target and multi-channel of traditional Chinese medicine. On the other hand, traditional Chinese medicine monomer has the advantages of clear structure of chemical drugs, which has significant advantages in the prevention and treatment of DR. The research on traditional Chinese medicine monomer has attracted more attention.

4.1 Anti-Inflammatory Effect

Puerarin can be used as an effective immunomodulator, which can affect the activity of many inflammatory factors, such as IL-1, IL-6, TNF-α and iNOS [18]. Studies have shown that the Nrf-2/ERK signaling pathway plays a unique role in the development of DR, especially its mediated inflammatory response [19]. NF-κB (Nuclear factor-kappa B, NF-κB) is a redox-sensitive nuclear transcription factor, which plays an important role in the inflammatory response [20]. Puerarin can exert anti-inflammatory effects by inhibiting the activity of NF-κB and down-regulating the expression of ICAM-1 and MCP-1 induced by TNF-α. Studies have shown that puerarin can effectively reduce the level of protein non-enzymatic glycosylation and inhibit the activity of NF-κB. Puerarin inhibits the expression of AGE and AGE receptors, the activation of NF-κB is hindered, and the expression of downstream cytokines caused by NF-κB is interrupted, thereby effectively reducing the release of retinal VEGF, thereby protecting the retina of diabetic rats [21-22]. Despite current reports, the anti-inflammatory effects of puerarin, especially in DR, appear to require further study. Future work should focus on further elucidating the possible potential mechanisms of action and finding more effective potential targets for the treatment of DR.

4.2 Antioxidant Effect

Hyperglycemia leads to increased oxidative stress in the retina, which is an important cause of DR. Over the years, many clinical trials have shown that antioxidant has a crucial protective effect on the occurrence and development of diseases[23]. The increase of reactive oxygen species (ROS) will greatly increase the level of oxidative stress. When the body 's antioxidant capacity is exceeded, a variety of cells will have oxidative damage. Therefore, antioxidants are considered to be the basis for DR treatment. Malondialdehyde (MDA) is the final product of lipid peroxidation and one of the markers of oxidative stress. Superoxide dismutase (SOD) activation can scavenge superoxide free radicals and has antioxidant damage ability. SOD activity reflects the antioxidant capacity of tissues. Oxidative stress increased the content of MDA and decreased the activity of SOD and catalase. Studies have shown that puerarin enhances the SOD activity of retinal tissue in a streptozotocin or N-methyl-D-aspartate-induced retinopathy model [24-25]. The activity and expression of SOD were also increased in retinal ganglion

cells after puerarin intervention and mouse retinal pigment epithelial cells treated with peroxynitrite [26]. AGE is one of the sources of ROS under hyperglycemia and plays a key role in the pathogenesis of DR [27]. AGE-mediated damage is produced by the interaction between AGEs and RAGEs, thereby activating the ROS-producing enzyme of NAPDH oxidase, thereby increasing the formation of intracellular ROS [28]. Some studies have reported that under the intervention of puerarin, the production of ROS in retinal tissue has been weakened in both in vivo and in vitro models [29-30]. The antioxidant effect of puerarin can inhibit the oxidative stress reaction caused by hyperglycemia to a certain extent, delay the progress of DR, and reduce the damage of oxidative stress to the retina, so as to achieve the purpose of protecting the retina.

4.3 Anti-Apoptotic Effect

The expression of apoptosis-related genes B-cell lymphoma-2 (Bcl-2) and Bcl2-associated X protein (Bax) in retinal blood vessels and nerve cells of early DM rats changed with the course of disease. Both of them play an important role in retinal cell apoptosis in diabetic rats. Caspase-3 is one of the major cysteine proteases in the caspase family. It plays a key role in regulating apoptosis and is considered to be an important mediator of apoptosis [31]. Studies have found that puerarin exerts its anti-apoptotic effect by increasing the expression of Bcl-2 and reducing the expression of pro-apoptotic factors such as Bax and caspase-3 [32-33]. It has been confirmed that NF-κB is the main target of hyperglycemia and oxidative stress in DR state. It has been confirmed that NF-κB is the main target of hyperglycemia and oxidative stress in DR state. NF-κB in the retina of diabetic patients is activated during the development of retinopathy and plays an important role in the development of the disease. Studies have found that NF-κB initiates the pro-apoptotic process of retinal pericytes under high glucose conditions, which may explain the early pericyte death of DR [34]. Chen et al [35] found that the protective effect of puerarin on the neuroretina of DM rats may be due to the inhibition of the activation of NF-κB in the retina caused by DM, and the production of oxygen free radicals in the retina of DM rats is related to the activation of NF-κB. Puerarin can inhibit the activation of NF-κB, reduce the production of oxygen free radicals, reduce oxidative stress, inhibit the apoptosis of retinal nerve cells and play a role in protecting the omentum.

3.4 Anti-Vascular Endothelial Growth Factor Effect

VEGF is induced during ischemia or hypoxia, and many types of retinal cells can produce VEGF, including retinal pigment epithelial cells, astrocytes, Muller cells, vascular endothelial cells, pericytes, and ganglion cells [36-39]. A large number of preclinical studies have shown that VEGF plays a very important role in all stages of DR, and may be an important factor in the development of DR. For example, VEGF changes retinal capillary permeability by increasing the phosphorylation of proteins related to tight junctions [40]. Under the action of hyperglycemia toxicity, ROS activity increases, leading to phosphorylation of JAK2/STAT3 in retinal capillary endothelial cells, thereby increasing the expression of VEGF and leading to DR [41]. Cai et al [24] found that puerarin can effectively inhibit the phosphorylation of JAK2/STAT3, thereby reducing the expression of VEGF, reducing the inflammatory response, and having a therapeutic effect on DR. Another study has pointed out that AGEs can significantly increase the expression of VEGF mRNA, and VEGF is positively correlated with AGEs, which further suggests that puerarin may reduce the expression of VEGF by blocking the combination of AGE-RAGE, and play a protective role in DR injury [42].

4.5 Other Effects

Ferroptosis is a newly discovered iron-dependent programmed cell death in recent years. It is essentially different from traditional apoptosis, necrosis and autophagy. This death mechanism is regulated by specific genes. In addition, death is also different from common cell death in morphology, which can induce mitochondrial membrane shrinkage and increase mitochondrial membrane density [43]. The main characteristics of ferroptosis are as follows: (1) increased lipid peroxides and reactive oxygen species; (2) Excessive iron accumulation accelerates cell death; (3) Antioxidant glutathione levels decreased [44]. Studies have shown that oxidative stress caused by increased intraocular iron content is an important factor leading to retinal damage [45]. Retina is a highly oxygen-consuming tissue. Under high glucose conditions, the expression of pro-oxidation protein TXNIP in cells is increased, and antioxidants such as glutathione are consumed in large quantities, resulting in mitochondrial dysfunction in retinal cells, leading to cell ferroptosis [46-47]. Song et al [48] found that puerarin reduced serum and retinal iron content, reduced retinal iron deposition, and inhibited oxidative stress caused by iron overload. Puerarin can enhance the activity of antioxidant such as catalase, SOD and glutathione-Px, and reduce the content of MDA. It can effectively enhance the antioxidant capacity of iron overload mice, maintain the activity of retinal cells under iron overload conditions, and protect cells from high glucose-induced ferroptosis, which plays an effective protective role in DR injury. However, the role of puerarin in ferroptosis requires further research to determine its molecular mechanism. Therefore, this also provides a new direction for puerarin research.

5. Summary

The antioxidant, anti-inflammatory and anti-apoptotic properties of puerarin make it a potential adjuvant drug for the prevention and treatment of DR. In this review, we summarized the therapeutic effects of puerarin on DR through several different pathways. In future studies, more experiments are needed to determine the specific mechanism of puerarin in ocular tissues, and more potential therapeutic targets remain to be discovered. In addition, puerarin also has a good application prospect in the treatment of other eye diseases, not only limited to DR, but also can be applied to glaucoma, retinal vein occlusion and other eye diseases. In conclusion, puerarin is a promising new method for the treatment of diabetes and its complications, and it is necessary to further study this topic.

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