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Research Progress in the Application of Lycium Barbarum Polysaccharide in Ophthalmic Diseases

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Abstract: Lycium barbarum polysaccharides (LBP) are widely used in age-related macular degeneration, glaucoma, diabetic retinopathy, and other eye diseases. With further studies on the pharmacological action of Lycium barbarum polysaccharides in recent years, researchers have found that Lycium barbarum polysaccharides (LBP) play a protective role in the treatment of various eye diseases through anti-oxidation, scavenging oxygen free radicals, and inhibiting inflammatory reaction as well as cell senescence. This paper reviews the application of Lycium barbarum polysaccharides in ophthalmology.

Keywords: Medlar; Lycium barbarum polysaccharide; Ophthalmic diseases; Research progress

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1. Introduction

Wolfberry, also known as citrate thorn, beet, day essence, Digu Dixian, etc., is a commonly used yin-tonic drug, which was first recorded in Shennong Materia Medica. Its nature and taste are "calming" and "sweet," respectively. It belongs to the liver and kidney channels and have the effect of nourishing both the liver and kidney, clarifying eyes, nourishing essence, relieving cough, moistening the lungs, delaying aging, and can be used as both medicine and food [1,2]. Modern pharmacological studies have shown that Lycium bararum polysaccharides (LBP) can scavenge oxygen free radicals, improve microvascular circulation, and increase the activity of superoxide dismutase. It also enhances immune function, lowers blood glucose and lipids, eliminates inflammation, and has anti-tumor, analgesic, as well as neuroprotective properties [2]. In recent years, Lycium barbarum polysaccharide (LBP) has been widely used in ophthalmic diseases, especially in age-related macular degeneration, glaucoma, and diabetic retinopathy.

2. Composition of wolfberry

Lycium barbarum has a complex chemical composition. The leaves, fruits, and bark of Lycium barbarum are rich in polysaccharides, carotenoids, flavonoids, alkaloids, amide compounds, lignin compounds, anthocyanins, essential oils, and sugar lipids, among which the highest content is Lycium barbarum polysaccharide (LBP). It participates in the physiological protective mechanisms of various diseases, such as immune regulation, anti-tumor, antioxidant performance, metabolic effect, neurodegenerative changes, etc. [3-7].

3. Pharmacological effects related to ophthalmology

3.1. Neuroprotection

LBP plays a role in protecting neurons. A study showed that LBP can promote the increase of dendrites and improve the morphology of neurons as well as the density of dendritic spines in elderly rats [8]; the study also found that aging and atrophic neurons still have plasticity, thus delaying the evolution of neural degeneration. It has been suggested that Lycium barbarum not only promotes the proliferation of rat sciatic nerve cells but also the differentiation of glial cells and neurons [9]. These are sufficient to indicate that LBP plays a certain role in nerve regeneration and functional reconstruction and is widely used in various diseases, such as functional injury of the nervous system, which can change tissues and surrounding microcirculation as well as promote the proliferation and division of nerve cells in the damaged area [10,11].

3.2. Antioxidant

Oxidative stress is a phenomenon that damages molecules, cells, and organisms by increasing the production or reducing the clearance of reactive oxygen species (ROS) that accumulates in the body. LBP also has a good antioxidant effect. Zhang Na and another researcher studied the protective effect and mechanism of LBP on diabetic kidney injury [12]; they found that LBP can reduce the level of malondialdehyde (MDA) and increase the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx), so as to alleviate the oxidative stress damage to the kidney of diabetic rats.

4. Application of Lycium barbarum polysaccharide in ophthalmic diseases

4.1. Retinal ischemia-reperfusion injury

Retinal ischemia-reperfusion injury (RIRI) is a common clinical pathology. Factors such as ischemic optic neuropathy, glaucoma, and retinal vascular obstruction can all lead to varying degrees of retinal ischemia, resulting in varying degrees of visual impairment. Several researchers conducted an experimental study on retinal RIRI rat model induced by elevated intraocular pressure and found that LBP has a certain protective effect on the survival of RIRI retinal ganglion cells and non-secretory cells [13]; they also evaluated the protective effect of LBP by detecting retinal cell apoptosis. Studies have confirmed that LBP plays a therapeutic role in the oxidative stress process of retinal ischemia-reperfusion injury model. LBP directly inhibits the production of ROS after RIRI and enhances the activation of Nrf2/HO-1 pathway in RIRI retina through its antioxidant effect, thus inhibiting the apoptosis of retinal ganglion cells and alleviating the damage from oxidative stress. It protects against nerve cell apoptosis and vascular degeneration in retinal ischemic injury.

4.2. Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most serious fundus lesions that can cause blindness. High glucose levels thicken the basement membrane of retinal capillaries and increases the permeability of blood vessels, resulting in the damage of blood-retinal barrier and the death of retinal ganglion cells. Although diabetes can induce cell apoptosis through various mechanisms, the mitochondrial pathway still plays an important role. High glucose levels lead to the generation of a large number of reactive oxygen species in cells, which causes changes in mitochondrial permeability, mitochondrial edema, and dissipation of mitochondrial membrane potential, eventually resulting in cell apoptosis. Through intraperitoneal injection of STZ to establish a diabetic retinal rat model, the study found that LBP can effectively remove reactive oxygen species generated in high glucose states and inhibit retinal cell apoptosis induced by high glucose by regulating the expression of retinal-cell-apoptosis-related proteins – caspase-3, Bax, and Bcl-2 [14]. Several researchers observed the ultrastructure of the retina of SD rat DR model after treatment with LBP and found that LBP can improve the disorder of internal and external segments of photoreceptors, reduce the number of pyretic nuclei, improve Muller cell dysfunction induced by high glucose and GFAP overexpression, upregulate cell mitochondrial membrane potential, as well as alleviate mitochondrial edema changes [15]. It can be concluded that LBP can largely relieve the pathological changes of mitochondria and inhibit neuronal apoptosis by exerting its antioxidant effect [16]. In another study [16], Pan Hong used LBP to detect the expression of body weight, blood glucose, ROS, Nrf2, and HO-1 in a treated rat DR model and found that LBP not only promotes the increase in body weight, but also the decrease in blood glucose levels and the increase in RGCs as well as the number of non-long process cells in rats; in addition, ROS expression can also be reduced by stimulating Nrf2/HO-1 signaling pathway [17]. In short, LBP can regulate the ROS state of diabetic mice's retina, and it is expected to be applied in the early stages of DR in the future, laying the groundwork for the treatment of DR using Lycium barbarum drugs.

4.3. Retinitis pigmentosa

Retinitis pigmentosa (RP) is a clinically inherited optic neuropathy characterized by retinal photoreceptor cell injury and osteocellular pigmentation. Patients with this condition have reduced visual field and night blindness. Its pathogenesis is still unclear. Clinical trials have reported the therapeutic effect of LBP on the cones of RP patients over 12 months, indicating that LBP has a neuroprotective effect on the retina and can delay or reduce the degeneration of RP cones [18]. Zeaxanthin palmitate (ZD) is the main composition of carotenoids in wolfberry. Liu used ZD in a RP mice model and found that it improved the visual behavior of rd10 mice and delayed retinal photoreceptor degeneration; the study also found that ZD improved the light responses of photoreceptors, bipolar cells, and light reaction of retinal ganglion cells; in addition, ZD inhibited STAT3, CCL2, and MAPK pathways, further decreased the activation of signal transduction and transcription activator 3 and chemokine (C-C motif) ligand 2, downregulated the expression of inflammatory factor GFAP, and inhibited the expression of extracellular signal-regulated protein kinase, suggesting that LBP can inhibit the inflammation of rd10 mice and delay RP, with a protective effect on retinal neurons [19]. In a study, the apoptosis and damage of central retinal photoreceptor cells occurred in rats 7 days after intraperitoneal injection of N-methyl-N-nitrosourea (MNU); LBP upregulated the expression levels of PARP and cleaved PARP in retina and downregulated the expression levels of caspase-9, -7, and -3 [20]. These results indicate that LBP can inhibit photoreceptor cell apoptosis and protect retinal damage induced by MNU. Lutein and zeaxanthin are two well-known carotenoids found in Lycium berries. Foreign researchers used lutein and zeaxanthin to intervene in the oxidative damage of human retinal pigment epithelial cells induced by hydrogen peroxide (H_2O_2). The results showed that MMP-2 and TIMP-1 of ARPE-19 cells significantly increased in the H_2O_2 damaged group, suggesting that H_2O_2 can inhibit cell proliferation. After treating with lutein and zeaxanthin, the decrease of MMP-2 and TIMP-1 reversed the inhibition of H_2O_2 on cell viability. These results indicate that lutein and zeaxanthin can restore the inhibited cell activity of ARPE-19 cells under H_2O_2-induced oxidative stress as well as regulate the MMP/TIMP system to protect the retinal pigment epithelium [21].

4.4. Age-related macular degeneration

Age-related macular degeneration (AMD) commonly occurs in middle-aged and elderly people over 60 years old. Clinically, it is a retinal disease, characterized as damage to the macular area of the retina, which eventually leads to the gradual loss of central vision. It is one of the important causes of visual damage. The early features are vitreous warts and changes in retinal pigment epithelial cells. In a study, the ARPE-19 cell line induced by hydrogen peroxide was treated with LBP, and a significant decrease in pro-apoptotic Bax and caspase-3 was detected, along with a significant increase in anti-apoptotic protein Bcl-2, and the activation of Nrf2/HO-1 pathway, thus protecting ARPE-19 cells from H_2O_2-induced damage [22]. These results suggest that LBP-pretreated ARPE-19 cells can reduce oxidative damage and inhibit apoptosis as well as reduce the risk of AMD-related retinal diseases. Gao Yuanyuan irradiated cells with cold light for up to 12 hours to establish a light-damaged human RPE cell line (ARPE-19) model in vitro [23]. After treating with LBP, it was found that the levels of Akt and mTOR were upregulated, and the PI3K/Akt/mTOR signaling pathway was also activated, thus inhibiting autophagy. It is suggested that LBP can protect retinal epithelial cells in the establishment of photoinduced injury model.

4.5. Other eye diseases

Lycium barbarum is one of the important traditional Chinese medicines in China, which is widely used in eye diseases. Lycium barbarum polysaccharide extract has a good protective effect on various eye diseases. It has been found that the treatment of LBP on a diabetic rat cataract model established by intraperitoneal injection of streptozotocin (STZ) upregulated Sirt1 and Bcl-2, inhibited p53, Caspase3, FOXO1, Bax, and P27 cell death genes, as well as prevented diabetes-related cataract in animals; in addition, it can reduce the body weight and blood sugar levels in diabetic animals [24]. Other research progress has been made in the treatment of corneal xerosis [25,26] and chronic ocular hypertension [27].

5. Conclusion

In conclusion, LBP has the effects of anti-oxidation, inhibiting neuronal apoptosis, and improving retinal inflammation. In recent years, with the deepening of pharmacological research on LBP, it has been known that the drug has multiple biological and pharmacodynamic effects. LBP also has anti-tumor, anti-oxidation, anti-aging, and other biological effects, with good therapeutic effect on various ophthalmic diseases (retinal ischemic disease, glaucoma, diabetic retinopathy, and retinitis pigmentosa). The disadvantage is that these research achievements are basically stalled at the level of animal experiments or cell experiments. Therefore, further research on the clinical application of LBP in ophthalmic diseases and other diseases is still necessitated to ensure LBP plays a greater role in the field of ophthalmology.

Disclosure statement

The authors declare no conflict of interest.

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