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Advances in Lycium Barbarum Polysaccharide in the Prevention and Treatment of Ophthalmic Diseases

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Abstract: ***Lycium barbarum is the dried mature fruit of Ningxia wolfberry, family Solanaceae. Chinese medicine believes that wolfberry has the effect of nourishing the liver and kidney, benefiting the essence and brightening the eyes. Lycium barbarum polysaccharide (LBP) is a proteoglycan isolated from Chinese medicine goji berry, which is the most important active ingredient in goji berry extract, with antioxidant, anti-inflammatory, anti-aging, anti-tumor, protection of the nervous system, protection of the retina, hypoglycemia, hypolipidemia, enhancement of immunity and other effects. In recent years, research results about LBP in the prevention and treatment of ophthalmic diseases have been emerging, such as cataract, glaucoma, diabetic retinopathy, macular degeneration has a certain preventive and therapeutic effects. This paper analyzes and reviews the relevant literature on LBP in the prevention and treatment of ophthalmic diseases.***

Keywords: Lycium barbarum polysaccharide, Ophthalmic diseases, Cataract, Glaucoma, Diabetic retinopathy**.**

1. Introduction

Goji berry is a deciduous shrub in the family of Solanaceae, first recorded in "Shennong Ben Cao Jing", and is classified as a top quality medicine. Wolfberry is also a good daily health care product. In the Compendium of Materia Medica, it is recorded that wolfberry has the effect of tonifying the liver and kidney and brightening the eyes. With the advancement of molecular biology technology, a variety of active ingredients in Lycium barbarum have been isolated, such as Lycium barbarum polysaccharides (LBP), carotenoids, and free amino acids. Among them, Lycium barbarum polysaccharides have high biological activity and have been gradually recognized [1]. LBP is a kind of natural macromolecule water-soluble polysaccharide, which is a polymer of aldose or ketose connected by glycosidic bond [2]. LBP has the effects of anti-inflammatory, antioxidant, anti-aging, anti-tumor, protection of the nervous system, protection of the retina, lowering of blood glucose, lowering of blood lipids, and enhancement of immunity, etc. [3-4]. In this paper, we mainly review the latest research on the role of LBP in the prevention and treatment of ophthalmic diseases at home and abroad. The purpose is to provide new ideas for future research on LBP in the prevention and treatment of ophthalmic diseases and to provide the corresponding theoretical basis for the early clinical application of LBP.

2. LBP and Ophthalmic Diseases

2.1 Preventive Improvement of Cataract with LBP

Cataract is a visually disabling disease due to clouding of the lens, which manifests as painless progressive vision loss [5]. Diabetic cataract (DC) is a common complication of diabetes mellitus and one of the main causes of blindness in diabetic patients [6]. The pathogenesis of diabetic cataract is quite complex, in which apoptosis of lens epithelial cells (LEC) plays an important role in the development of the disease [7]. The basis of its pathology is the elevated concentration of glucose due to abnormal glucose metabolism in the lens. And high glucose concentration is able to induce lens epithelial cell damage [8]. When the cellular damage fails to activate the body's normal repair mechanism, it will cause metabolic disorders in the lens epithelial cells, increase the permeability of the cells, and disrupt the redox state of the lens, until it directly damages the lens proteins, such as cross-linking, aggregation, and precipitation of the proteins. This ultimately leads to turbidity of the lens and subsequent cataract formation [9].

Zhou Yue investigated the effects of LBP on high glucose-induced apoptosis and expression of silent information regulator 1 (SIRT1) in human lens epithelial cells (SRA01/04) [10]. It was concluded that LBP may protect the lens epithelial cells by regulating the expression of SIRT1 and its related cytokines, inhibit the apoptosis of human lens epithelial cells under high glucose environment, and increase their cellular activity to delay the occurrence and development of diabetic cataract. It has also been shown that LBP can reduce the damage of human lens epithelial (HLEB3) cells in high glucose environment, increase cell proliferation activity, and reduce the occurrence of intracellular nuclear condensation and nuclear fragmentation. It also up-regulated the expression levels of Silent Information Regulator 1 (SIRT1) and Silent Information Regulator 6 (SIRT6) proteins in HLEB3 cells damaged in high glucose environment [11]. In diabetic cataract rats, it was concluded that LBP may reduce lens opacity in diabetic cataract rats by increasing the antioxidant effect of the lens and promoting the expression of heat shock protein 27 (HSP27) in lens epithelial cells, as well as improve body weight loss and hyperglycemia [12]. The beneficial effect of LBP on diabetic cataract was associated with the supression of p53, caspase 3, FOXO1, BAX, p27 and elevation of SIRT1 and Bcl-2, which were consistent with the in vitro findings [13]. This provides new research ideas to improve the prevention of cataracts in the clinic.

2.2 Preventive Improvement of Glaucoma with LBP

Globally, glaucoma is the leading cause of irreversible blindness and is second only to cataract as a blinding eye disease [14]. Clinical manifestations include optic papillary atrophy and depression, visual field defects, and decreased visual acuity. It is characterized by progressive degeneration of retinal ganglion cells (RGCs) and their axons, which progressively causes irreversible vision loss. Elevated intraocular pressure (IOP) is a major risk factor for the pathologic progression of the disease [15] and a major contributor to further damage to RGCs. By studying the effect of LBP on the electrophysiological properties of pressurization-induced apoptotic retinal ganglion cells, Zhao Ying concluded that LBP may protect RGCs by inhibiting potassium currents and thereby protecting them [16]. In the disease treatment of glaucoma, this idea could potentially be a new breakthrough, providing new ideas and methods for future research on the therapeutic correlation between LBP and glaucoma disease.

Oxidative stress is an important part of the pathogenesis of glaucoma. Excessive accumulation of reactive oxygen species (ROS) in the body during oxidative stress damages the structure and function of mitochondrial and trabecular meshwork tissues, obstructs aqueous humor outflow, and causes an increase in intraocular pressure (IOP), which leads to neural axonal degeneration and the demobilization of retinal ganglion cells (RGCs) [17]. It has been suggested in the literature [18] that LBP may protect RGCs in patients with glaucoma by regulating oxidative stress-related pathways such as phosphatidyl inositol 3-kinase (PI3K)/Akt, nuclear factor-kB (NF-kB), mitogen- activatedproteinkinase (MAPK), and Keap1/Nrf2/ARE to protect RGCs in glaucoma patients.

Jiang Zhaorong established a chronic glaucoma model to study the ameliorative effect of LBP on retinal ganglion cell damage and its mechanism in chronic glaucoma rats [19]. It was concluded that LBP protects RGCs and attenuates the damage of RGCs after oxidative stress by inhibiting the RHOA/ROCK1 pathway, PI3K/AKT pathway, and regulating the level of HIF-1α, which in turn reduces the apoptosis of RGCs. Meanwhile, LBP can also make the intraocular pressure of chronic glaucoma disease well controlled, which has a certain therapeutic effect on chronic glaucoma. LBP can inhibit NF-kB pathway activation, reduce p-NF-kBp65 and p-Ik Bα protein expression, enhance SOD activity, reduce ROS and malondialdehyde MDA, and protect H_2O_2-induced PC12 pull injury in neuronal cells, and protect neuronal cells [20]. Keap1 was highly expressed and Nrf2 and ARE were low expressed in the trabecular meshwork tissues of patients with age-related glaucoma, and the ability to activate the Keap1/Nrf2/ARE pathway could improve the mitochondrial function of the trabecular meshwork tissues, inhibit oxidative stress, and reduce intraocular pressure [21]. It has been reported in the literature that LBP can activate Nrf2 expression, increase heme oxygenase-1 levels, reduce ROS production, and attenuate oxidative damage and apoptosis in RGCs. Therefore, LBP can enhance antioxidant capacity and attenuate optic nerve damage through Keap1/Nrf2/ARE signaling pathway [22].

2.3 The Preventive Effect of LBP on Diabetic Retinopathy

Diabetic retinopathy (DR), as the most common microvascular complication in diabetic patients, is a multifactorial-mediated pathologic and physiologic disease [23]. DR is also a common blinding ophthalmic disease in clinical practice. According to researchers, more than one-third of the diabetic population suffers from DR worldwide, with nearly one-tenth of the diabetic population suffering from vision-endangering DR [24]. DR is known as Xiaoke eye disease in Chinese medicine, and the therapeutic effect of wolfberry on Xiaoke eye disease has been documented as early as in the Materia Medica Tongxuan [25]. Oxidative stress is intricately related to the multiple pathogenesis of DR. Currently, it is thought to be related to the abnormalities of various metabolic pathways caused by hyperglycemia, such as the protein kinase C pathway, polyol pathway, and late glycosylation end product pathway. Activation of these pathways can produce reactive oxygen species, resulting in an imbalance between the production and elimination of reactive oxygen species SOD, which can increase the level of oxidative stress in the body. This causes apoptosis and abnormal retinal cell structure and function [26].

When studying the effect of LBP on the ultrastructure of the retina in diabetic rats, Guo Jian found that LBP could protect the mitochondrial damage induced by hyperglycemic state through antioxidant and thus improve DR [27]. Subsequently, the experimental rats with successful modeling were randomly divided into experimental and model groups. The rats in the experimental group were gavaged with 6% lycium barbarum polysaccharide solution 0.5 m L for 24 weeks. It was found that compared with the model group, the retinal SOD level of the experimental group increased, the MDA level decreased significantly, and the vascular endothelial growth factor m RNA level also decreased significantly [28]. Zhang Huixi found that LBP can significantly reduce the expression of MDA and 8-OHd G in the retinal tissue of rats with diabetic retinopathy. This suggests that LBP can reduce the level of oxidative stress in the retina, thus delaying the progression of diabetic retinopathy [29].

In a hyperglycemic environment it leads to accelerated apoptosis in RGCs. Meanwhile, the Nrf-2 antioxidant pathway in RGCs can be activated compensatorily. It was found that LBP increases the Nrf-2 antioxidant pathway, which in turn enhances the antioxidant capacity of RGCs and inhibits apoptosis of RGCs. This provides new ideas and methods for the clinical treatment of LBP in DR [30]. Pan Hong used streptozotocin STZ to establish a diabetic rat model. Using LBP intervention, it was found that LBP was able to significantly improve the oxidative stress status of the retina in diabetic rats by decreasing the retinal reactive oxygen species content, increasing the number of RGCs, and promoting retinal Nrf2 expression to protect retinal nerve cells [31]. Wang Haibin showed that LBP could effectively prevent and control diabetic retinopathy by elevating the expression level of retinal Bcl-2 mRNA and protein, decreasing the expression level of retinal caspase-3 and Bax mRNA and protein, and decreasing the apoptosis of RGCs [32], which provides a theoretical basis for clinical application.

2.4 The Preventive Effect of LBP on Age-related Macular

Degeneration

Aging and degeneration are important factors in age-related macular de-generation (AMD), which is mainly related to the degeneration of retinal pigment epithelial (RPE). AMD is an age-related disease that is characterized by a decline in the phagocytic function of RPE cells, a decrease in the proliferative capacity of RPE cells, and a gradual increase in the amount of lipofuscin in RPE cells, which results in irreversible loss of vision, and it is a blinding ophthalmopathy that severely affects the eyesight of the elderly [33]. Therefore, to prevent the occurrence of AMD, it is necessary to search for drugs that can have a protective effect on human RPE cells.

It has been indicated that purified black fruit LBP polysaccharides can improve the antioxidant capacity of retinal pigment epithelial ARPE-19 cells. And it may inhibit ARPE-19 cell pyroptosis by down-regulating the protein expression of NLRP3, Caspase-1 and IL-1β [34]. In H2O2-induced ARPE-19 cells, LBP had a protective effect on RPE under oxidative stress by inhibiting the expression of miR-181, decreasing ROS levels, and increasing cell viability, as well as affecting the Bcl-2/Beclin1 autophagy signaling pathway and decreasing the rate of apoptosis [35]. The survival rate of human retinal pigment epithelial (ARPE-19) cells was significantly increased in the intervention group with different concentrations of LBP.LBP can inhibit apoptosis by down-regulating Bax, Caspase-3, Caspase-9 protein expression, up-regulating Bcl-2 protein expression, Bcl-2/Bax ratio. And the protective effect was more significant with the increase of LBP purity [36]. LBP can protect human retinal pigment epithelial cells induced by oxidative stress. In particular, the number of apoptotic cells was significantly reduced after pre-intervention with 500 μg/mL concentration of LBP [37]. Another study was to culture hRPE cell line in vitro to establish a porcine porcine baroreceptor outer segment POS-induced human RPE lipofuscin model. The growth of the hRPE cell line was observed in the experiment, again with the intervention of different concentrations of LBP.The final study showed that LBP could enhance the phagocytosis function of RPE cells, improve the proliferation ability of RPE cells, reduce the lipofuscin in RPE cells, and promote the anti-aging effect of RPE cells, which could further prevent and treat the age-related disease AMD [34].

Lipofuscin is a non-degradable pigment with fluorescent properties and is highly sensitive to blue light. Blue light, in an aerobic environment, stimulates the retina to initiate photo-oxidation, generating a large amount of singlet oxygen, hydrogen peroxide and hydroxyl radicals, which will trigger oxidative damage to the cells, disrupting the normal cellular redox reaction, leading to retinal pigment epithelial cell damage or even necrosis. The experimental results suggest that LBP may reduce the oxidative stress damage of blue light on APRE-19 cells by inhibiting the excessive production of lipofuscin [38]. An experimental model of RPE cell injury was established using blue light induction. Different concentrations of LBP were used in the experiment to detect the morphology, apoptosis and other indicators of human RPE cells. The results showed that LBP could stabilize the mitochondrial membrane potential of cells and maintain the level of reactive oxygen species in mitochondria, thus protecting the viability of human RPE cells and reducing the number of apoptotic cells caused by light damage. Moreover, the higher the concentration of LBP within a certain range, the stronger the protective effect on human RPE cells, with a concentration-dependent effect [39]. LBP may also inhibit light-induced apoptosis of ARPE-19 cells by up-regulating miRNA-21-5p and down-regulating PTEN mRNA expression, thereby activating the PI3K/Akt/mTOR signaling pathway, and enhancing the protection of RPE cells against photodamage in a concentration-dependent manner [40]. The above study suggests that the protective effect of LBP on RPE cells may be closely related to the mitochondria-mediated apoptosis signaling pathway, which provides a new idea to improve the utilization of LBP in clinical applications.

3. Summarization and Prospect

In China, wolfberry is a medicinal herb. At present, compounded remedies based on Lycium barbarum are used for the treatment of dimness of the eyes, dryness and pain in the eyes, and cloudiness covering the eyes. For the active extract LBP of Lycium barbarum in the treatment of eye diseases, are also found in animal or in vitro cultured cell experiments have a significant effect, especially to protect the lens, optic nerve and retinal structure function. By studying from the molecular level and various signaling pathways, it has provided a lot of data support and innovative ideas for the prevention and improvement of cataract, glaucoma, diabetic retinopathy and age-related macular degeneration. However, most of the studies on the mechanism of LBP and ophthalmic diseases are based on the establishment of experimental models with animals, and it is difficult to implement the experiments in human beings, coupled with the fact that animals and human beings possess a certain degree of variability, the conditions are limited, and the sample size is not large enough, so the extrapolation of the conclusions is not sufficiently strong and persuasive. Therefore, in the future research, it is necessary to further explore the mechanism of LBP on ophthalmic diseases, in order to pave the way for the early clinical application of LBP.

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