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Chapter One - Effects of *Lycium barbarum* on the Visual System

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Abstract

Lycium barbarum (wolfberry, gogi berry, *gouqizi*, 枸杞) is one of the most widely used Chinese herbal medicines (CHMs) and is also one of the most scientifically studied. Indeed, the polysaccharide component of this berry (LBP) has been shown to have antioxidant, antiinflammatory, antiexcitotoxic, and antiapoptotic properties. These properties make it a particularly useful treatment option for the ocular environment. Although there are a handful of studies investigating the use of LBP to treat diseases affecting the lens, the vast majority of the published literature investigating LBP in the visual system focus on the retina. In this chapter, we have described what is currently understood concerning the effects of LBP treatment on various retinal diseases, including glaucoma, ischemia/reperfusion, age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy. We then describe the functions attributed to LBP using other cellular contexts to elucidate the full mechanisms this CHM utilizes in the retina. By making connections between what is known about the function of LBP in a variety of tissues and its function as a therapy for retinal degenerative diseases, we hope to further emphasize the continued use of this CHM in clinical medicine in addition to providing a platform for additional study.

Introduction

Treatment with Chinese herbal medicines (CHMs) is a common aspect of the healthcare system in many Asian countries and traditionally focuses on the concept of balancing a person's yin and yang. When applied to the physiological functions and pathological changes in the human body, this theory utilizes a holistic approach, whereby various herbal supplements are administered to synergistically treat a disease. This model is in contrast to that of single synthetic drugs, which are often used in Western cultures. In fact, as the study and use of CHMs becomes increasingly accepted, more herbal treatments are being used, alone or in combination with classical drugs, to treat diseases worldwide. This has also lead to further scientific analysis, discovery, and quality control of various CHMs.

Lycium barbarum, a reddish-orange berry (Fig. 1) also known as wolfberry, gogi berry, or *gouqizi* (枸杞) in Chinese, has been used as a preventative and curative agent in various forms for thousands of years (Wang et al., 2015). In fact, *L. barbarum* has been consumed as an herbal supplement in a number of forms, from tea to concentrated capsule, and has been linked to enhanced protection and nourishment of the kidney, liver, and eye (Junlin & Aicheng, 2002). It is also currently one of the most widely scientifically studied CHMs. Various active compounds have been isolated from *L. barbarum*, including various polyphenols/flavonoids and carotenoids (reviewed in Wang et al., 2015). Indeed, Zhou et al. (2016) recently identified 15 new compounds that appear to be dicaffeoylspermidine derivatives that also make up a significant portion of the active constituents in *L. barbarum*. However, the most well-studied functional moiety involved in the observed *L. barbarum*-mediated health benefits appears to be the polysaccharide (LBP) component. This group of water-soluble glycoconjugates includes rhamnose, xylose, glucose, mannose, arabinose, and galactose (Benlloch et al., 2015, Liu et al., 2012).

The health benefits of LBPs have been classically linked to their antioxidative properties (Cheng and Kong, 2011, Cui et al., 2011, He et al., 2012, Li, 2007, Shan et al., 2011, Xiao et al., 2012, Zhang, Chen, et al., 2016, Zhou et al., 2016). LBPs have also been demonstrated to influence proliferation, cell cycle arrest, and apoptosis during carcinogenesis (Jin et al., 2013, Mao et al., 2011, Zhang et al., 2005). Other protective mechanisms related to *L. barbarum* include antiexcitotoxicity (Ho et al., 2009), antiinflammation (Chen, Soo, et al., 2009, Xiao et al., 2012), and antiapoptosis (Ho et al., 2010, Li et al., 2011, Song et al., 2012). This CHM was also previously shown to play a neuroprotective role and help protect cells against amyloid-β neurotoxicity (Yu et al., 2007, Yu et al., 2005) and enhance cognitive function (Zhang, Du, et al., 2013, Zhou et al., 2016) in Alzheimer's disease-related neurodegeneration.

While the function of LBPs appears to be multifaceted, the underlying mechanisms involved may differ to a degree depending on physiological context and the specific cell type affected. In the current review, we have focused on the mechanism of LBPs in the visual system in addition to detailing their therapeutic use to treat various vision-related diseases.

Notably, the visual system is exceedingly sensitive to change, including increased oxidative stress (Kruk, Kubasik-Kladna, & Aboul-Enein, 2015), altered blood flow (Flammer et al., 2013), inflammation (Perez, Saeed, Tan, Urbieta, & Cruz-Guilloty, 2013), etc., implying that the mechanisms of LBPs in this cellular context may be similar to those demonstrated systemically or in other tissues. The eye is derived from three types of tissue during embryogenesis: the surface ectoderm, which generates the lens; the mesoderm, from which the cornea and sclera are produced; and the neural ectoderm, which gives rise to the retina and retinal pigmented epithelium (RPE) (for an excellent review of general ocular development, please see Heavner & Pevny, 2012). During development, signals between the surface ectoderm and the optic vesicle, an outgrowth from the developing central nervous system that will later become the optic nerve, initiate lens placode formation, invagination, and creation of the bilayered optic cup. These tissues will then differentiate into a number of specialized cell types that are essential for vision. Although some recent work has been conducted concerning the therapeutic effects of LBPs on both the formation of senile cataracts in the human lens (Kee et al., 2013 (clinicaltrials.gov identifier: NCT01142960)) and oxidatively damaged lens epithelial cells in culture (Qi et al., 2014), the majority of published literature concerning LBPs in the visual system focus on the retina.

The cells in the outer and inner layers of the optic cup formed during development will specifically differentiate into the RPE and neural retina, respectively (Fig. 2) (reviewed in Heavner & Pevny, 2012). The latter includes various cells types and is organized into three layers: the outer nuclear layer, composed of the rod and cone photoreceptors; the inner nuclear layer, containing the amacrine, horizontal, and bipolar cells as well as Müller glia; and the ganglion cell layer, which is composed of the retinal ganglion cells (RGCs). During vision, the dense layer of posteriorly located photoreceptors converts the incoming light into electrochemical signals involving a phototransduction cascade in the outer segment of the cell and downstream changes in cation channels (reviewed in Sung & Chuang, 2010). This hyperpolarization of the light-stimulated photoreceptor then causes altered neurotransmitter release that initiates an action potential-mediated chain reaction through the cells in the inner nuclear layer to the RGCs, which then transmit the signal to the brain via the optic nerve (reviewed in Baccus, 2007). Alternatively, the outer layer-derived RPE is a monolayer of cells that forms the blood–retinal barrier (BRB) and supports the photoreceptor cells via the phagocytosis of the outer segments and secretion of various trophic factors (Heavner & Pevny, 2012). Finally, the Müller and retinal microglial cells are the resident immune cells in this tissue and eliminate foreign substances as well as dead/dying cells.

Under normal conditions, the retina internally balances the levels of reactive oxygen species (ROS) and inflammatory molecules, while limiting aberrant apoptosis and interference from the surrounding vasculature in order to process light signals properly for vision. Unfortunately, in a diseased state, these mechanisms may be inactive or dysfunctional leading to further problems. Thus, while some drugs or herbal supplements, including LBPs, may not have an effect on the visual system under normal conditions, they may have significant therapeutic benefits on retinal function under stress or after trauma-/diseased-induced retinal cell death or dysfunction.

Section snippets

Effect of *L. barbarum* Polysaccharide Treatment in Animal Models of Retinal Disease

The loss of retinal neurons, including the RGCs and photoreceptors, either directly or as a secondary effect, can lead to significant deficits in visual acuity that have been associated with a number of retinal diseases, including glaucoma, ischemia/reperfusion (I/R), age-related macular degeneration (AMD), retinitis pigmentosa (RP), and diabetic retinopathy (DR). Although a number of clinical/preclinical studies have been performed in healthy humans (Amagase and Nance, 2008, Amagase, Sun, et…

Underlying Mechanisms of *L. barbarum* Polysaccharides in the Retina

The retinal diseases described in the previous sections, while different in genetics, phenotype, and prevalence, all share some common variables, namely, changes in the local retinal neurons, inflammation, and altered vascular function in addition to the overall increase in oxidative stress in the eye/retina. While the mechanistic effects of LBP treatment on these pathogenic processes could be dependent on the unique retinal microenvironment, it is also likely that some signaling pathway…

L. barbarum Polysaccharide as a Treatment and Preventative Medicine: Future Perspectives and Conclusions

In Chinese medicine, a disease is traditionally treated as an issue of balance in the entire body. While the use of homeopathic compounds is becoming more mainstream worldwide, further scientific analysis is required in order to determine the mechanisms underlying the associated health benefits as well as to evaluate any detrimental side effects. As one of the most well-studied CHMs, *L. barbarum* has been used to treat a variety of diseases, including those of the retina, and a vast amount of…

Acknowledgments

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Immune activities of polysaccharides isolated from Lycium barbarum L. What do we know so far?
2022, Pharmacology and Therapeutics

Citation Excerpt :
…Among these chemical constituents, carbohydrates are significant components in L. barbarum (approximately 51%), and polysaccharides are the main component, which make up 5% - 8% of the dried fruits. Lycium barbarum polysaccharides (LBPs) contribute most significantly to the multiple pharmacological activities of L. barbarum, which includes the traditional belief that β-carotene is efficacious in nourishing the eyes (Manthey, Chiu, & So, 2017). Indeed, LBPs have now been demonstrated to play an indispensable role in healing vision-related diseases that affect the lens and retina, including glaucoma (H. C. Chan et al., 2007; Mi, Zhong, Chang, & So, 2013), proliferative vascular retinopathy (Mi et al., 2012; Tian et al., 2013), ischemia/reperfusion (He et al., 2014; S. Y. Li et al., 2011; Yang, So, & Lo, 2017), and retinitis pigmentosa (H. L. Chan et al., 2019).…

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Lycium barbarum polysaccharides improve hepatic injury through NFkappa-B and NLRP3/6 pathways in a methionine choline deficient diet steatohepatitis mouse model
2018, International Journal of Biological Macromolecules

Citation Excerpt :
…LBP is composed of arabinose, glucose, galactose, mannose, xylose and rhamnose [6]. Damage of retina, brain, and neuronal systems is shown to be safely ameliorated by the supplementation with LBP [7–10]. Moreover, LBP exhibits hypolipidemic, cardioprotective, antiviral, and anti-inflammatory activities [6].…

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Lycium barbarum glycopeptide (wolfberry extract) slows N-methyl-N-nitrosourea-induced degradation of photoreceptors
2024, Neural Regeneration Research

Integrative transcriptome and metabolome analysis reveals the discrepancy in the accumulation of active ingredients between Lycium barbarum cultivars
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2024, Current Drug Therapy

Complementary Approaches to Retinal Health Focusing on Diabetic Retinopathy
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