• Review

Research advances on the usage of traditional Chinese medicine for neuroprotection in glaucoma

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ABSTRACT: Progressive loss of retinal ganglion cells (RGCs) and their axons is the main pathogenesis of glaucoma. The cause of glaucoma is not fully understood, but the neurodegeneration of glaucoma involves many mechanisms such as oxidative stress, glutamate toxicity and ischemia/reperfusion insult. In order to target these mechanisms, multiple neuroprotective interventions have been investigated to prevent the death of RGCs. Of note are some tonic herbs from the traditional Chinese medicine (TCM) pharmacopeia that have shown neuroprotective effects in glaucoma. TCM differs from Western medicine in that TCM exhibits complicated bioactive components, triggering many signaling pathways and extensive actions on vital organs. Modern scientific approaches have demonstrated some of their underlying mechanisms. In this review, we used Lycium barbarum and Ginkgo biloba as examples to elaborate the characteristics of TCM and their potential applications in neuroprotection in glaucoma.

KEYWORDS: neuroprotection; neuroprotective agents; traditional Chinese medicine; glaucoma; review

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1 Introduction

Glaucoma is the leading cause of irreversible blindness throughout the world[1] and one of the most prevalent age-related diseases among people over age 40[2]. Currently, lowering intraocular pressure (IOP) is the primary proven therapeutic strategy, and treatments for such include laser trabecuoplasty, glaucoma filtration surgery and antiglaucoma medications. However, it is difficult or impossible to completely stop the progression of glaucoma, and many glaucoma patients experience progressive neurodegeneration[3].

A potential area in the treatment of glaucoma is neuroprotection, which aims to slow or prevent the death of retinal ganglion cells (RGCs) and loss of their axons. Neuroprotection in glaucoma is similar in concept to the treatment of central nervous system (CNS) diseases including trauma, stroke, Parkinson’s disease, and Alzheimer’s disease[4]. Some traditional Chinese medicines (TCMs), with a long history of usage as tonics in China and other Asian countries, have been shown by modern science to have neuroprotective effects in glaucoma. This article will summarize the current research into these TCM, their neuroprotective properties in glaucoma, and the possible mechanisms.

2 Mechanisms of degeneration in RGCs

Progressive loss of RGCs and their axons is the key neuropathology of glaucoma. IOP plays a dominant role in the primary mechanical damage of RGCs, but there are many...
other destructive factors involved in the neurodegeneration of glaucoma, such as oxidative stress, glutamate toxicity and ischemia/reperfusion insult. Thus, several hypotheses were established to investigate the mechanisms of RGC neurodegeneration. These include blocked transportation of neurotrophic factors, neurotoxicity, oxidation, and the intracellular activities resulting in the death of RGCs, such as the signaling pathways for apoptosis, necrosis or autophagy[5-7].

2.1 Neurotrophic insufficiency

Neurotrophic factors, such as neurotrophins, cytokines, fibroblast growth factor (FGF) family and growth-derived neurotrophic factor (GDNF) can promote the growth, differentiation and survival of neurons. Neurotrophic insufficiency can induce the degeneration of RGCs[8-12]. Experiments have shown that intravitreous injection of brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-4, NT-3 and NT-4/5 can help promote RGC survival that is otherwise threatened by chronic ocular hypertension and optic nerve transection[13].

2.2 Cytotoxicity accumulation

Glutamate is both a neurotransmitter and a neurocytotoxic substance. In ocular ischemic insult, retinal tissue overloads with the accumulation of glutamate plus the up-regulation of glutamate receptors on neurons, and high levels of glutamate have also been detected in the vitreous body[14]. One possible source of the elevated levels of glutamate may be from neuronal death or impaired Ca\(^{2+}\) influx. In normal conditions, low glutamate levels can be removed by retinal astrocytes and Müller cells[15]. However, in the pathological processes of ischemia or glaucoma, excessive production of glutamate cannot be counterbalanced by its proper elimination, which results in glutamate accumulation in the retina and vitreous body, leading to RGC death by cytotoxicity[16]. Up-regulation of the glutamate receptors, such as N-methyl-D-aspartate (NMDA), can stimulate the production of superoxide anion (O\(_{2}^-\)) from mitochondria and trigger oxidative damage, leading to neuronal apoptosis[17]. Experiments have shown that intraperitoneal injection of NMDA antagonists enhances RGC survival in ocular hypertensive rats[18].

2.3 Oxidative damage

Nitric oxide (NO), a neurotoxin, is involved in the degeneration of neurons[19]. Excessive NO damages retinal tissues through the mechanism of free radical oxidative damage[20]. In glaucoma patients, increased production of NO has been found in the aqueous humor[21]. NO integrates with O\(_{2}^-\), which is produced from activated NMDA, to form oxidant peroxynitrite anion (ONOO\(^{-}\)). ONOO\(^{-}\) then dissociates into hydroxyl free radical (OH\(_{\cdot}\)), which is an oxidizing agent that damages RGCs, resulting in apoptosis or necrosis.

Nitric oxide synthase (NOS), a group of enzymes, plays an important role in the generation of NO[22]. There are three isoforms of NOS including NOS-1 (or neuronal NOS), NOS-2 (or inducible NOS) and NOS-3 (or constitutive NOS)[23]. NOS-1 and NOS-3 are constitutively expressed in normal retinal tissue, and act as vasodilators or neurotransmitters. NOS-2, on the other hand, contributes to RGC neurotoxicity[24]. Up-regulation of NOS-2 has been observed in hypertensive eyes[25] due to cytokine secretion by the activation of astrocytes, such as interferon and tumor necrosis factor (TNF[26]). Other experiments have shown that antioxidants that inhibit NOS-2 or NMDA have neuroprotective effects via reducing oxidative damage[26].

3 Current medical treatment for neuroprotection in glaucoma

3.1 Mechanisms of protection for RGCs

Experiments into the neuroprotective mechanisms and RGC survival in different animal models provide opportunities to investigate new therapeutic interventions against neurodegeneration in glaucoma. Targeting the mechanisms of protection for RGCs and their axons are the main role of neuroprotectants. The current literature summarizes investigations into recent neuroprotective agents[27, 28]. These studies into neuroprotective agents vary widely among animal models used, delivery approaches, time frames, and disease endpoints. However, to each potential neuroprotectant, there would be more than one research group to prove its neuroprotective effects.

The main possible mechanisms and the representative agents from the published literature are summarized as: (1) anti-excitotoxicity, such as memantine targeting to glutamate toxicity; (2) mitochondrial dysfunction, such as erythropoietin targeting PI3-Akt and nuclear factor-κB signaling pathway; (3) protein misfolding, such as anti-amyloid-β; (4) oxidative stress, such as Ginkgo biloba, braziliiz green propolis targeting NOS and ROS; (5) inflammation and immunological mechanisms, such as Cop-1 targeting myelin basic protein; (6) neurotrophic withdrawal, such as the application of trophic factors including cilary neurotrophic factor and BDNF; (7) gene therapy, such as aiming to deliver specific neurotrophic factors via viral vectors; (8) multiple mechanisms if there is more than one target.

3.2 Clinical trials for neuroprotection in glaucoma

Until recently, IOP-lowering treatment aiming to enhance the aqueous drainage through conventional pathways of the trabecular meshwork and Schlemm’s canal was the most common method of glaucoma treatment. Some IOP-lowering drugs have also been reported to provide degrees of neuroprotection in glaucoma. Recent results from preclinical and clinical studies suggest that brimonidine may protect RGCs and their projections from damage and death independently of its effects on...
IOP\textsuperscript{[29]}. Memantine is an approved drug by Food and Drug Administration (FDA) of the United States to treat Alzheimer’s disease and has so far completed a phase III clinical trial as a neuroprotective agent in patients with open angle glaucoma\textsuperscript{[30]}. However, other neuroprotectant drug candidates have not advanced as far in clinical trials. One main problem is that the animal models cannot fully mimic the course of human disease; furthermore, the higher disease variability in human patients as compared to in laboratory animals makes the models difficult to compare.

4 General profiles of TCM tonics

In many Asian countries, there is widespread acceptance that some tonic herbs can promote general health and reduce the effects of aging. The traditional understanding is that the effects of the tonic herbs are mediated via qi and blood. The exploration of modern medical science into TCM’s mechanisms has found that tonic herbs have neuroprotective effects\textsuperscript{[31]}. As glaucoma has come to be understood as an age-related neurodegenerative disease\textsuperscript{[45]}, the neuroprotective effect demonstrated by some TCM tonics has become of increasing interest to researchers.

TCM’s mechanisms of action differ greatly from that of Western medicine. Whereas Western medicine employs purified molecules that exert a concentrated, single-target effect, the effects of TCM are generally regarded as multi-functional and non-specific. These effects are due to the complex formulation of herbal medicinals that exert global effects on multiple organ systems or targets. Adopted by modern method, TCM is extracted by single ingredient approach, standardized extracted approach and fixed herbal formula approach. Each approach has its own pros and cons. As we know, herb contains many active components\textsuperscript{[32]}. Thus, in many cases, using a general or crude extract that contains multiple active components is more biologically powerful than a purified extraction containing only one or a few active components\textsuperscript{[33]}. The modern approach of using standardized extracts and herbal formulas can offer a high degree of quality control and standardization for crude extract of TCM when they are used in research of herbal bioeffects, thus preserving the multi-system targets for neuroprotection that is possible from TCM tonics.

5 The effects of tonic TCM in neuroprotection of glaucoma

In order to further explore the potential mechanisms of TCM, \textit{Lycium barbarum} and \textit{Ginkgo biloba} are used as two examples on the neuroprotective roles of tonic herbs in glaucoma.

5.1 \textit{Lycium barbarum}

5.1.1 Neuroprotective roles of polysaccharides of \textit{L. barbarum}

Known as \textit{Fructus Lycii}, or Wolfberry in the West, \textit{L. barbarum} is called “Gouqizi” in China. It is a traditional herbal medicine with tonic effects, which has long been incorporated into \textit{Pharmacopoeia of the People’s Republic of China}\textsuperscript{[32]}. The TCM properties of \textit{L. barbarum} are to modulate qi and tonify yin in our body, and nourish vital organs such as the liver and eyes. In Asia, it is taken not only as a medicinal food but is also used as a part of therapeutic prescriptions in TCM. Modern science has shown that it has multiple biological effects, especially in its protective effects to neurons\textsuperscript{[32,33]}. \textit{L. barbarum} has many bioactive components, such as polysaccharides, carotenoids, flavonoids, amino acids, trace elements, fatty acids and vitamins\textsuperscript{[34]}. In our laboratory, \textit{L. barbarum} was prepared as a standardized water extract\textsuperscript{[35]}. Amongst the various components, polysaccharides constituted the highest percentage, at around 45\%\textsuperscript{[32]}. Many researchers believe that the polysaccharides of \textit{L. barbarum} (LBPs) play a major role in neuroprotection. Recently, the potential neuroprotective effects of LBPs on neurons in the CNS have been demonstrated in many studies from different groups\textsuperscript{[35,36]}.

In the eyes, our previous studies have reported the neuroprotective effects of LBPs on the survival of RGCs in an experimental chronic ocular hypertension (COH) model of glaucoma\textsuperscript{[37,38]} and in a model of middle cerebral artery occlusion (MCAO)-induced ischemic retinopathy\textsuperscript{[39]}. Generally, these studies showed that LBPs protect neurons via several targets using multiple mechanisms. Chang et al\textsuperscript{[32]} have summarized the direct cellular effects and indirect modulation effects of LBPs. The direct cellular effects show LBPs to be neuroprotective against amyloid-β neurotoxicity\textsuperscript{[40]} and glutamate excitotoxicity\textsuperscript{[36]}, e.g., in the COH model, LBP can up-regulate the expression of β-B2-crystallin, insulin-like growth factor-1 (IGF-1) and interleukin-10 receptor (IL-10R) on RGCs, which are helpful to the survival of RGCs\textsuperscript{[39]}. Another study demonstrated that one possible mechanism for RGC protection of LBPs is immune modulation, which is an indirect effect; LBPs were shown to activate microglia in a “semi-activation” status to be beneficial to the survival of neurons\textsuperscript{[41]}.

5.1.2 The possible mechanisms of LBPs in neuroprotection

5.1.2.1 Global immune modulation

Many studies have demonstrated evidence that abnormal immune responses are involved in the development of glaucoma\textsuperscript{[42,43]}. Studies involving T cells have shown that in optic nerve crush animals, T cell aggregation was observed only in the area of crush\textsuperscript{[44]}. Autoreactive T cells can induce neurotrophin production and microglia infiltration to protect injured rat optic nerve\textsuperscript{[45]}. Microglia are one main type of immunoactive cells in the CNS. A recent study showed the activation of microglia in the retina using DBA/2J mice with experimental chronic ocular hypertension (COH) model of glaucoma\textsuperscript{[46,47]}. The TCM active component LBPs can induce microglia’s activation and in turn protect RGCs in the COH model, and the global immune modulation effect is demonstrated by the up-regulation of the expression of β-B2-crystallin, IGF-1 and IL-10R on RGCs. As a result, LBPs can protect RGCs via an immune modulation effect in the COH model of glaucoma. Further studies are needed to understand the underlying mechanisms of neuroprotection. This study showed the possible mechanisms of LBPs in neuroprotection and suggested that LBPs may be beneficial in the treatment of glaucoma.

5.1.2.2 Other possible mechanisms

Studies on the neuroprotective effects of LBPs in neuroprotection of glaucoma have been demonstrated in many studies from different groups\textsuperscript{[35,36]}. Generally, these studies showed that LBPs protect neurons via several targets using multiple mechanisms. Chang et al\textsuperscript{[32]} have summarized the direct cellular effects and indirect modulation effects of LBPs. The direct cellular effects show LBPs to be neuroprotective against amyloid-β neurotoxicity\textsuperscript{[40]} and glutamate excitotoxicity\textsuperscript{[36]}, e.g., in the COH model, LBP can up-regulate the expression of β-B2-crystallin, insulin-like growth factor-1 (IGF-1) and interleukin-10 receptor (IL-10R) on RGCs, which are helpful to the survival of RGCs\textsuperscript{[39]}. Another study demonstrated that one possible mechanism for RGC protection of LBPs is immune modulation, which is an indirect effect; LBPs were shown to activate microglia in a “semi-activation” status to be beneficial to the survival of neurons\textsuperscript{[41]}.

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glaucoma mice. \textsuperscript{[46]} TCM is known for its immune system-modulating effects. LBPs can increase the proliferation of cytotoxicity of natural killer (NK) cells in the spleen. In human peripheral blood mononuclear cells, LBPs were shown to increase expression of mRNA for interleukin-2 (IL-2) and TNF-α. These studies suggest the immunestimulatory effects of LBPs. Our recent study reported that LBPs can activate retinal microglia in response to high ocular pressure insult, which is protective to RGCs.\textsuperscript{[48]}

5.1.2.2 Direct protective effects to neurons

\textit{In-vitro} data from our lab have shown that LBPs can protect cortical neurons from β-amyloid neurotoxicity\textsuperscript{[35]}, glutamate excitotoxicity\textsuperscript{[36]}, and homocysteine-induced toxicity\textsuperscript{[42,43]}. LBPs have been shown to protect neurons on their organelle, such as the endoplasmic reticulum\textsuperscript{[48]}. In an \textit{in-vivo} rat model, feeding animals on LBPs solution up-regulated the expression of β-B2-crystallin on RGCs, which is helpful to neural survival from high pressure insult\textsuperscript{[37]}, as β-B2-crystallin has been shown to be protective to retinal neurons. Similarly, endothelin-1 (ET-1), another damage marker, was found to induce apoptosis of the RGC-5 cell line\textsuperscript{[49]}, and kill RGCs \textit{in-vivo} animal models. In one of our studies, over-expression of ET-1 was observed on RGCs in a glaucoma model, but feeding LBPs to rats daily down-regulated the expression of ET-1.\textsuperscript{[50]}

5.1.2.3 Effects on other cells around neurons

Microenvironment changes, such as astrocytic proliferation, or breaking down of blood vessel endothelial cells, are risk factors that threaten the survival of neurons. In a MCAO model, LBPs have shown a beneficial effect on retinal astocytes and Müller cells, resulting in the stabilization of the microenvironment that supports the survival of neurons in the retina and brain. In an acute ocular hypertension model, LBPs have demonstrated a protective effect on retinal blood vessels, such as decreasing damage on blood-retinal barriers (BRBs) and protecting the survival of endothelial cells and pericytes.\textsuperscript{[51]}

By using LBPs as an example, we have demonstrated that a TCM tonic herb can provide neuroprotective benefits via multiple mechanisms: it may affect the neurons directly, and also alter their microenvironment as well as the global environment of the body. A previous study has summarized that neurodegeneration in RGCs goes through two phases: direct damage to RGC and axons, and secondary damage by responses of non-neuronal cells. This secondary degeneration is considered the major cause of RGC loss in glaucoma\textsuperscript{[52]}. The term neurovascular unit is a collection of different cells around blood vessels, including neurons, glia cells and vascular cells, which come together to form a structural and functional integrated unit that maintains the balance of the microenvironment outside the cells. External risk factors, such as aging, ischemia and oxidative stress, may affect blood vessels and provoke damage to their function as a barrier system. When these barriers are broken, toxic factors may freely pass through blood vessel to the microenvironment, resulting in the activation of glial cells and affecting neurons directly. Using the theory of neurovascular dysregulation, we demonstrated the mode of neuroprotective function of LBPs in an acute ocular hypertension model.\textsuperscript{[51]} LBPs protect the integrity of BRBs, inhibiting the pass of ET-1 and amyloid-β (Aβ), two neuro-damaging markers that may induce RGC degeneration directly. It regulates the activation of retinal glial cells, such as astrocytes and Müller cells to maintain the structure of the retina to support neurons with a relatively normalized microenvironment, inhibiting secondary damage to the neurons. The pharmacokinetiks of LBPs are still currently unclear, nor do we know whether and how it can pass the BRB to protect the retinal cells directly; however, the blood vessel-protective effects of LBPs provided a possible functional mode to investigate its neuroprotective mechanisms (Figure 1).

5.1.3 Other components in \textit{L. barbarum} and their neuroprotective effects

As mentioned above, other than polysaccharides, there are some other bioactive components found in \textit{L. barbarum}. Carotenoids, including β-carotene, zeaxanthin and lutein, were reported to be about 0.03%-0.5% in \textit{L. barbarum}. Zeaxanthin has been reported as an antioxidant that protects the macular region in the retina by maintaining pigment density. Betaine, which is used by the liver to produce choline, is one of the components (0.7%-1.2%) of \textit{L. barbarum}. Dietary supplementation of betaine may be a promising anti-oxidizing agent for the liver or red blood cells, and has been shown to inhibit glutamate-induced neurotoxicity. Other components, such as cerebroside, β-sitosterol and vitamin C are also antioxidants. Since oxidative stress and glutamate toxicity are two main degenerative factors to the neurons, effects of these components in \textit{L. barbarum} should not be neglected.

5.2 \textit{Ginkgo biloba}

\textit{Ginkgo biloba} is another well-known TCM tonic. The leaves of \textit{Ginkgo biloba} have been used to treat asthma and bronchitis in China for thousands of years. Nowadays, the extract from the leaves of \textit{Ginkgo biloba} is also marketed as a natural supplement in Western countries. The extract from \textit{Ginkgo biloba} contains more than 60 bioactive compounds, such as kaempferol, quercetin and isorhamnetin, many of which have been shown to have neuroprotective effects. Standardized extract from the dried leaves of \textit{Ginkgo biloba}, named as \textit{Ginkgo biloba} extract 761 (EGb761), is often used in clinical research for cognitive impairment and dementia.\textsuperscript{[56]} EGb761 contains 24% ginkgo flavone glycosides (flavonoids), 6% terpene lactones (ginkgolides and bilobalides) and approximately 7%...
proanthocyanidines and other uncharacterized compounds. EGB761 has been successfully used to treat dementia in a study with humans. However, in a randomized controlled trial, usage of EGB761 did not significantly reduce the incidence of dementia. In a normal tension glaucoma study, Ginkgo biloba extract (GBE) administration was reported to improve visual field progression and visual function in patients. Although the data for GBE’s neuroprotective effects in clinical trials is inconclusive, there is still ample evidence for its mechanisms in neuronal survival. GBE has an effect on increasing ocular blood flow in glaucoma patients. GBE can induce the expression of glial cell line-derived neurotrophic factor GDNF and vascular endothelial growth factor, which is beneficial to the growth of motor neurons. As an effective scavenger of peroxy and superoxide, GBE has antioxidant activity. Research has shown it to be related with heme oxygenase 1 (HO1) induction of the collapsin response mediator protein 2 pathway. GBE has been reported to reduce glutamate neurotoxicity in ischemic animal and motor neuron culture. GBE has been shown to exhibit immunomodulatory activity by reducing the activation of glial cells in ischemia of the brain to suppress their phagocytic activity and inflammatory cytokine secretion. In a cerebral ischemic experiment, GBE exhibits anti-apoptotic properties by preventing the interaction of genes Bad and Bcl-XL. Furthermore, in a cell culture model, a DNA microarray assay study indicated that GBE can modulate the transcription of multiple apoptosis-related genes by either up- or down-regulating them in cells. Taken together, the above evidence demonstrates that the ability of GBE to treat glaucoma patients remains an open issue. In a chronic glaucoma rat model, GBE was shown to protect the survival of RGCs. Many researchers still believe that GBE has the potential to be a complementary therapeutic agent for glaucoma patients.

In summary, GBE provides protection against neurodegeneration in glaucoma and several CNS disease models. Similar to L. barbarum, GBE activates multiple neuroprotective mechanisms, such as anti-oxidation, anti-glutamate excitation, vasoregulation and anti-apoptosis. GBE differs from L. barbarum in that GBE has already been standardized with a well-defined procedure for extraction in different countries, such as EGb761 and LI1370. This standardization will most likely be helpful to promote the quality and consistency of TCM.

Figure 1  Neurovascular dysregulation and neuroprotective mechanisms of LBP
When challenged by external stress or insult, LBP protected RGCs directly by reducing the cytotoxicity on RGCs (ET-1 and Aβ), and indirectly by inhibiting the damage of BRB and modulating retinal gliosis. LBP: polysaccharide of Lycium barbarum; RGCs: retinal ganglion cells; ET-1: endothelin-1; Aβ: amyloid-β; BRB: blood retinal barriers.
6 Summary

Using L. barbarum and Ginkgo biloba as examples, we demonstrated the neuroprotective effects and the underlying mechanisms of TCM tonic herbs in protecting RGCs against degeneration in glaucoma. By using modern scientific tools, some mechanisms have been elucidated, but many more properties need to be further investigated in the future. We also found a possible mode of function of these herbal medicinals: acting through a neurovascular unit where many molecules and cells may partake in the multiple mechanisms of neuroprotection steered by the TCM. Clinical trials will be the final step when investigating the TCM as potential therapeutic interventions. Important areas such as searching for reliable biomarkers to evaluate the effectiveness of the TCM, and how to balance a personalized medicine approach with the use of standardized herbal extracts should be explored in future experiments.

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8 Competing interests

The authors declare that they have no competing of interests.

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