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Erigeron breviscapus: A Promising Medication for Protecting the Optic Nerve in Glaucoma

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ABSTRACT

Glaucoma is a common eye condition characterized by the loss of retinal ganglion cells and their axons, optic nerve damage, and visual field defects, which seriously affect a patient's quality of life. The pathogenesis of glaucoma is still unclear at present. It presents as damage to retinal ganglion cells, and the main treatment is primarily to reduce intraocular pressure by surgery or taking medication. However, even with well-controlled intraocular pressure, retinal ganglion cells still undergo degeneration, progressive apoptosis, and axonal loss. Therefore, protecting the optic nerve and inhibiting the apoptosis of retinal ganglion cells are the current hot topic for prevention and treatment of glaucoma. Recently, *Erigeron breviscapus*, originating from Yunnan province in China, has been shown to be a promising herb with neuroprotective effects to treat glaucoma. Therefore, the traditional usage, botanical characteristics, and phytochemical composition of *E. breviscapus* were explored through a literature review. Furthermore, we have summarized the pharmacological mechanisms of *E. breviscapus* and its active components in inhibiting the apoptosis of retinal ganglion cells. These research findings can not only provide guidance and recommendations for the protection of retinal ganglion cells but also further explore the potential of *E. breviscapus* in the treatment of glaucoma.

Introduction

Glaucoma is a group of irreversible blinding optic nerve degenerative diseases caused by multiple factors, with visual field defects, decreased visual acuity, and eventually complete loss of vision in one or both eyes as the main clinical features [1]. Glaucoma is one of the leading causes of vision impairment worldwide [2]. As the population ages, the prevalence of glaucoma is likely to increase [3,4]. In 2020, there were 4.13 million people aged 50 and older who suffered moderate to severe vision impairment due to glaucoma, and 3.6 million were blind because of it. The prevalence of glaucoma is rising in various countries and regions [5]. It is projected that by 2040, the global number of people with glaucoma will reach 111.8 million [6]. Glaucoma causes irreversible damage to the optic nerve, and the consequences of blindness are extremely severe. Elevated intraocular pressure (IOP) has long been considered the main factor leading to damage of retinal ganglion cells (RGCs) [7]. According to clinical research reports, even if the IOP of glaucoma patients is well controlled, degeneration, apoptosis, progressive loss, and axonal loss of RGCs still persist [8]. Numerous studies have shown that various risk factors such as elevated IOP, impaired blood flow dynamics, oxidative stress, de-

ficiency of neurotrophic factors, inflammatory responses, and excitotoxicity caused by glutamate (Glu) can all lead to apoptosis of RGCs [9, 10]. Therefore, preventing or slowing down RGC apoptosis and optic nerve degeneration, known as optic nerve protection, has become a hot and challenging topic in the prevention and treatment of glaucoma. It is equally important as reducing IOP in the treatment of glaucoma [11].

The primary treatment for glaucoma focuses on lowering IOP. Antiglaucoma eye drops, which work by reducing the production of aqueous humor or increasing its outflow [12], are effective in lowering IOP. However, these drops often contain the preservative benzalkonium chloride (BAK), which is cytotoxic and can damage conjunctival and corneal epithelial cells, leading to symptoms such as dry eyes, redness, and allergic reactions [13]. Other treatment methods, including glaucoma surgery, can also effectively control IOP but cannot completely prevent the apoptosis of RGCs. Additionally, these methods are costly and carry significant risks [14]. In contrast, natural products, with their antioxidant, anti-inflammatory, and antiapoptotic properties, are considered low-cost and safe neuroprotective agents. They offer significant therapeutic potential for ischemic retinal diseases, particularly glaucoma [15, 16].

In recent years, traditional Chinese medicine (TCM) has been continuously developing and making progress in the fundamental research of protecting RGCs, becoming an indispensable part of the global medical field. For example, the main component of *Lycium barbarum* extract, *Lycium barbarum* polysaccharides (LBPs), and *Ginkgo biloba* extract have shown antioxidant and neuroprotective effects. They can promote the survival of damaged neurons and prevent apoptosis and damage caused by hypoxia [17–19].

Erigeron breviscapus (Vant.) Hand-Mazz. (EBHM), which belongs to the *Erigeron* genus, is a chrysanthemum plant primarily distributed in Yunnan province, China. It thrives in warm and humid environments. The main active components of EBHM are scutellarin and baicalin, which have been proven to have various effects, such as inhibiting apoptosis of neuronal cells, anti-inflammatory properties, scavenging oxygen free radicals, and improving microcirculation and perfusion [20].

However, the mechanisms by which EBHM and its active components protect against glaucomatous optic neuropathy remain unclear. This study conducted searches of PubMed, Web of Science, China National Knowledge Infrastructure, and Scopus databases using the search terms "*Erigeron breviscapus* (Vant.) Hand-Mazz.," "*Erigeron breviscapus*," "Dengzhan," and "glaucoma" to identify components related to optic nerve protection. Subsequently, the search terms "scutellarin," "breviscapine," "quercetin," "baicalin," and "retinal ganglion cells" were used to explore the specific mechanisms of these components. The research primarily focused on the period from 2014 to 2023; however, if highly relevant literature was not found, earlier published papers are also included. We reviewed the traditional uses, botany, and phytochemistry of EBHM and further investigated its pharmacological mechanisms in protecting against glaucomatous optic neuropathy. This aims to develop new therapeutic strategies for glaucomatous optic nerve protection and potentially foster the clinical application of EBHM.

Traditional Usages

EBHM, also known as "Dengzhan Asarum", possesses extensive biological activities and pharmacological effects, with a long history of medicinal use. Its earliest record can be traced back to the Ming Dynasty's South Yunnan Materia Medica. EBHM has a pungent and slightly bitter flavor, warm nature, and enters the Heart and Liver meridians, with the efficacy of invigorating blood circulation, unblocking collaterals, relieving pain, dispelling wind, and dissipating cold [21]. In the 1960 s, as a commonly used medicine among minority groups in Yunnan, EBHM was mainly used to treat cardiovascular and cerebrovascular diseases such as cerebral palsy, stroke, and hemiplegia [22]. According to the development strategy of TCM in China, the whole raw material of EBHM has been excavated through empirical formulas and verified by clinical trials, drug development, and production. It has been successfully developed into various TCM preparations and has been widely used in clinical practice [23–25]. This smooth progress has enabled EBHM to play an important role in the field of TCM. In 1994, EBHM (Dengzhan Asarum) was included in the National Torch Plan as a high-tech product. It is also one of the essential Chinese patent medicines in emergency departments of TCM hospitals nationwide and was listed as a protected species of national TCM and prescription medicine in 2000 [26]. In addition, it is included in the 2020 edition of the Pharmacopoeia of the People's Republic of China [22].

As a medicinal and edible plant with a history of over 500 years, EBHM is widely used for consumption and cooking in folk applications. The traditional method involves drying the entire plant in the sun, removing impurities, and then using it as herbal medicine [21]. Modern pharmacological studies have shown that EBHM possesses various biological activities, including improving cerebral ischemia, scavenging oxygen free radicals, anti-inflammatory, anticancer, and neuroprotective effects [22]. It is primarily used in the treatment of cardiovascular and cerebrovascular diseases, diabetes complications, Alzheimer's disease, glaucoma, and other conditions [27, 28]. Currently, in clinical practice, various formulations of Dengzhan flower extract have been developed, including Dengzhan Asarum injection, oral capsules, and tablets [29].

In the preparations made from EBHM, oral and intravenous injection are currently the mainstream of preparation research. Among them, DZXX injection, a sterilized aqueous solution extracted from EBHM, is the most widely used preparation in clinical practice, and multiple randomized controlled trials have shown that it has effects such as protecting nerves and improving the prognosis of patients with cerebral ischemia and cerebral infarction [30–32]. The main components of DZXX injection are flavonoids and caffeic acid esters, among which the flavonoid components mainly include scutellarin and apigenin, while the caffeic acid ester components mainly include di-caffeic acid esters [33, 34].

Research has shown that DZXX injection exhibits neuroprotective effects in a rat model of cerebral ischemia/reperfusion (I/R) injury. The specific mechanisms involve the enhancement of superoxide dismutase (SOD) activity, reduction of malondialdehyde (MDA) accumulation as an indicator of lipid peroxidation and oxygen free radical levels, and modulation of mitochondrial

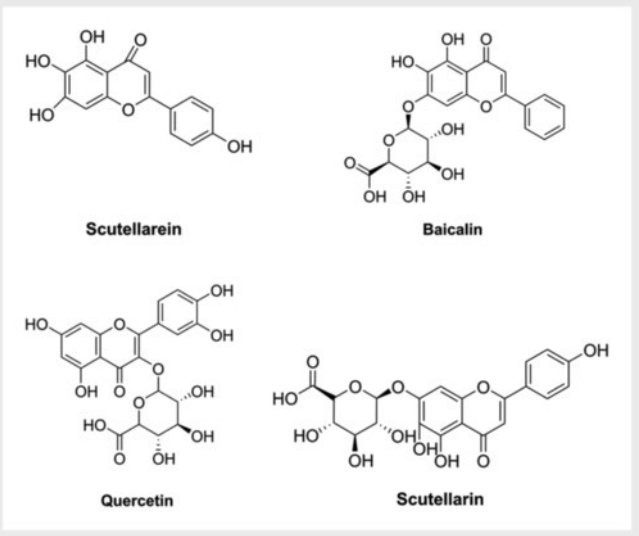
autophagy and reduction of neuronal apoptosis. SOD plays a crucial role in scavenging intracellular oxygen free radicals. The decrease in MDA levels reflects a reduction in lipid peroxidation and oxygen free radical generation. Additionally, DZXX injection regulates mitochondrial autophagy and reduces neuronal apoptosis, further protecting brain cells from cerebral I/R injury [35].

The development of oral preparations is another important direction for the research and development of EBHM in addition to its topical application. It has unique advantages in ocular diseases such as diabetic retinopathy, where traditional intravitreal injection of anti-vascular endothelial growth factor (VEGF) and laser photocoagulation may lead to irreversible retinal damage and neuronal loss [36]. The EBHM oral preparation has the advantages of high safety and low toxicity, and its main active ingredient, baicalin, has been proven to have antiangiogenic effects [37]. This means that EBHM has the potential to replace an intravitreal injection with an oral medication for the treatment of new blood vessel growth in diabetic retinopathy [38]. In addition, recent studies have also demonstrated that oral EBHM plays a role in ischemic diseases through multitarget pathways such as antioxidant and anti-inflammatory pathways, and improvement of mitochondrial function [39, 40].

Botany

EBHM is a plant primarily found in the southwestern region of China, especially in Yunnan province. It is a traditional herb among ethnic minorities such as Miao and Yi. This plant thrives in high mountain environments and typically grows at elevations between 1500 and 2400 meters, preferring an average annual temperature range of 14–20 °C. It usually reaches a height of 20–30 centimeters and has cylindrical stems with a diameter ranging from 0.1 to 0.2 centimeters. The stems are yellow green or light brown in color, with slender longitudinal lines and covered in white short hairs. The stems are brittle and may have a yellow white cross-section, with the possibility of containing a pith or being hollow. EBHM has mostly basal leaves that emerge from the base of the plant, is spoon shaped or reverse lanceolate, with lengths of 5–20 centimeters and widths of 1.0–3.0 centimeters. The leaves are green and covered in short white hairs, lacking distinct petioles, and the leaf base may be purple or green. The stem leaves are alternate, spoon shaped, and reverse lanceolate. The flowers are purple or pale purple, with the corolla tube opening being a pale yellow color [41, 42].

Due to its high economic and medicinal value, the cultivation of EBHM has become an important pillar industry for increasing income and alleviating poverty. Yunnan province is the main distribution area for wild EBHM resources and also the primary province for its cultivation, processing, and development. A complete industry chain encompassing cultivation, extraction, and formulation production has been established. EBHM has become one of the representative varieties in transforming Yunnan's advantageous traditional Chinese medicinal resources into economic value and has been listed as one of the "Five Natural Series" medicines for focused development in Yunnan province. Currently, the industry has achieved an annual output value of approximately 3 billion yuan [43].



▶ **Fig. 1** The main chemical structure of EBHM.

Plant Chemistry

The compounds isolated from EBHM mainly include 46 types of caffeic acid esters, 25 flavones and their glycosides, and 78 volatile oil components [44–46]. Among them, flavones and their glycosides, including flavone, flavonol, dihydroflavone, flavonol glycoside, and flavone glycoside, with scutellarin, scutellarein, quercetin, and baicalin as representative components, are the main active ingredients related to the treatment of glaucoma (▶ **Fig. 1**) [47].

In addition to the active ingredients related to glaucoma, EBHM also contains other compounds. Caffeoyl compounds primarily include caffeoylquinic acid (CQA), 2,7-anhydro-3-deoxy-2-octylpyrrolidone acid (CDOA), 2,7-anhydro-2-octylpyrrolidone acid (COA), and 1-(2′-γ-pyrone) [48, 49]. Furthermore, a small amount of caffeic acid derivatives have been isolated and identified [50]. Additionally, EBHM contains a large number of volatile oil components, predominantly long-chain fatty acids, cyclic compounds, and long-chain alkanes [45]. Moreover, it has been found to contain various components such as coumarin, pentacyclic triterpenes, aromatic acids, plant sterols, and oxygenated anthraquinones [51]. The diverse range of compounds provides multiple supports for the medicinal effects of EBHM, and also offers broad prospects for exploring its pharmacological effects further and developing new drugs.

Clinical Applications

As of June 5, 2024, a comprehensive search using the key words "*Erigeron breviscapus*", "breviscapine", and "Deng zhan" on the clinical trial website http://clinicaltrial.gov/and the Chinese Clinical Trial Registry (ChiCTR) website https://clinicaltrials.gov/identified a total of seven clinical trials related to EBHM. One completed study evaluated the prognosis of 537 patients with acute ischemic stroke treated with *E. breviscapus* injection. The results demon-

strated that the medication significantly ameliorated neurological deficits and enhanced daily living activities in these patients, underscoring its potential efficacy as a therapeutic intervention for acute ischemic stroke. Another study reported that the TCM DZSM (Dengzhan Shengmai) capsule, primarily composed of EBHM, exhibited notable efficacy in 3143 patients with acute ischemic stroke. This study highlights the potential benefits of integrating EBHM into the treatment regimen for ischemic stroke patients. Several additional studies are ongoing or unpublished. These studies aim to enroll patients with ischemic stroke, coronary heart disease, and angina pectoris to assess the broader clinical effects of EBHM-related preparations. Specifically, they will evaluate the safety and adverse reactions associated with breviscapine powder injection. Furthermore, some studies are recruiting healthy volunteers to investigate potential drug interactions between breviscapine and cytochrome P450 enzymes as well as P-glycoprotein (refer to ▶ **Table 1**).

Erigeron breviscapus (Vant.) Hand-Mazz.'s mechanism of action in protecting the optic nerve in glaucoma

Previous studies have shown that EBHM extract has a protective effect on the optic nerve. In a study conducted by Zhong et al., where the study subjects were patients with primary open-angle glaucoma, it was observed that treatment with EBHM extract resulted in a significant reduction in the mean defect of visual field and a significant increase in mean sensitivity, with no reported adverse reactions, indicating good safety [52]. However, the specific mechanisms by which EBHM and its active components protect the optic nerve are not yet fully understood. Therefore, we will summarize the potential mechanisms of action of EBHM extract and its active components on optic nerve protection, including neuronal apoptosis, oxidative stress, neuroinflammatory response, and excitotoxicity of Glu, based on the underlying mechanisms of glaucoma pathogenesis (refer to ▶ **Table 2**). This will provide a basis for further research on optic nerve protection in glaucoma.

Antiapoptotic effect

RGCs are neurons located in the innermost layer of the retina. Their axons form the optic nerve and are responsible for receiving input from light-sensitive cells, converting visual signals into neural electrical signals, and transmitting these signals through the axons to the visual centers of the brain [53, 54]. Just like other neurons, RGCs cannot divide or regenerate, and once damaged, they are unable to repair themselves. The dysfunction or degeneration of RGC axons is closely associated with glaucoma [55, 56]. The specific mechanism of RGC cell apoptosis is currently unclear, but research has shown that the damage process mainly involves axonal transport inhibition, excitotoxicity of Glu, inflammatory cascade reaction, and oxidative stress [57–59]. These factors can all serve as signals that regulate apoptosis and initiate apoptotic pathways, leading to RGC cell death. Therefore, adopting a multitarget intervention to inhibit RGC cell apoptosis is currently one of the important strategies for protecting RGCs.

Scutellarin, the main active ingredient of *E. breviscapus*, exerts its inhibitory effect on RGC apoptosis mainly by restoring axoplasmic flow transport and reducing the inflammation response [60]. In an experimental model of high IOP in rats, Zhu et al. [61] retrogradely labeled RGCs using horseradish peroxidase (HRP) injected into the superior colliculus of the left hemisphere. Through this study, it was found that an injection of *E. breviscapus* extract, with scutellarin as the main component, helped the dying RGCs to restore their axoplasmic transport function. Specifically, scutellarin facilitated the smooth delivery of neurotrophic signals from target cells in the brain or neurotrophic factors from target tissues to the cell bodies of RGCs, thereby preventing the death of some RGCs.

Quercetin is a natural polyphenol that exerts biological effects such as antioxidant, antiapoptotic, and regulation of intracellular calcium levels through multiple pathways. In the rat model of retinal I/R injury, quercetin can significantly reduce RGC apoptosis [62], while in the chronic high IOP rat model, quercetin also showed a preventive effect on RGC apoptosis. This effect involves multiple signaling pathways, such as regulating the expression of Bcl-2 and inhibiting the cleavage of caspase-3 [63].

Anti-oxidative stress

Oxidative stress refers to the imbalance between oxidative and antioxidative processes in the body, leading to the production of reactive oxygen species (ROS) levels that exceed the body's antioxidant capacity. This can cause a large accumulation of ROS in cells and lead to oxidative damage of macromolecules such as DNA, proteins, and lipids, ultimately resulting in irreversible cell and tissue damage. This process is closely related to the pathogenesis of optic nerve damage in glaucoma [64]. The optic nerve is one of the tissues in the body with the highest energy demand and oxygen consumption rate, requiring a significant amount of adenosine triphosphate (ATP) for an efficient energy supply [65]. The electron transport chain in the mitochondria produces a large amount of ROS during the energy generation process. Antioxidants such as SOD and catalase (CAT) exist in ocular tissues to maintain an oxidative balance. However, when the electron transport chain or mitochondrial function is impaired, it leads to the accumulation of ROS, damaging cellular structures and triggering oxidative stress injury [66]. Flavonoid compounds found in plants are believed to possess antioxidant capabilities, making them potential protectants that can be used to prevent and alleviate oxidative stress-induced damage caused by glaucoma, reduce the risk of optic nerve damage, and have a positive impact on the pathogenesis of glaucoma.

Baicalin has shown strong antioxidant capabilities in both *in vivo* and *in vitro* experiments [67]. In a rat model of retinal I/R, baicalin can reduce the decrease in neurofilament protein NF-L, Thy-1, and tubulin protein in RGCs. GFAP (Glial Fibrillary Acidic Protein) is a specific protein present in Müller cells and astrocytes. Retinal I/R injury can activate Müller cells and astrocytes, leading to an upregulation of GFAP expression. Baicalin can inhibit the upregulation of GFAP and apoptosis-related protein PARP-1 expression. Furthermore, according to research findings, baicalin at a concentration of 15 µM has been shown to reduce oxidative stress-induced damage to human trabecular meshwork (hTM) cells. Specifically, baicalin can inhibit the production of inflammatory factors IL-1α and ELAM-1, decrease the activity of the aging marker SA-β-gal, and lower the levels of protein carbonylation products [68].

▶ **Table 1** Summary of clinical trial registrations for EBHM.

Trial identifier	Study title	Condition/disease	Study type	Intervention	Registration status	Registration site
NCT00351806	AISTCM-The Pathological Pattern Differentiation and Outcome Measurement of Acute Ischemic Stroke Treated With Traditional Chinese Medicine	Cerebral infarction	Interventional	Erigeron breviscapus injection	Completed	ClinicalTrials.gov
NCT00548223	The Secondary Prevention Trial for Ischemic Stroke With DengzhanShengmai Capsule (SPIRITDZSM1)	Stroke	Interventional	Dengzhan Shengmai capsule	Completed	ClinicalTrials.gov
NCT02559960	Post-marketing Safety Surveillance of Breviscapine Powder-Injection: a Registry Study	Adverse drug reaction	Observational	Drug: breviscapine powder – injection	Suspended	ClinicalTrials.gov
ChiCTR2300067750	A randomized, double-blind, double-simulation, positive parallel control, multicenter clinical study to evaluate the efficacy and safety of breviscapine dripping pills in the treatment of ischemic stroke (stroke meridians and collaterals) with blood stasis	Ischemic stroke	Interventional	Breviscapine dripping pills	Prospective registration	China Clinical Trial Registry (ChiCTR)
ChiCTR-IPC-16010161	The effect of breviscapine on the viable myocardium and left ventricular remodeling after revascularization of coronary chronic total occlusion	Cardiovascular disease	Interventional	Breviscapine	Prospective registration	China Clinical Trial Registry (ChiCTR)
ChiCTR-IPR-16009366	To study the effects and mechanism of breviscapine on cytochrome P450 enzymes and drug protein transporter activity	Healthy	Interventional	Breviscapine	Prospective registration	China Clinical Trial Registry (ChiCTR)
ChiCTR2300072852	Evaluate the efficacy and safety of Dengzhan Shengmai Capsule in patients with coronary heart disease complicated with heart failure with preserved ejection fraction: a multicenter, randomized, double-blind, placebo-controlled clinical trial	Coronary heart disease complicated with heart failure with preserved ejection fraction	Interventional	Dengzhan Shengmai capsule	Prospective registration	China Clinical Trial Registry (ChiCTR)

▶ **Table 2** The pharmacology and possible mechanisms of EBHM in protecting the optic nerve in glaucoma.

Active ingredients	Model	Administration	Pharmacological	Test index	Possible mechanism	References
Scutellarin	HIOP model rats	15 mg/100 g i. p.	Some of the RGCs that are on the verge of death regain their axoplasmic transport, allowing the smooth delivery of neurotrophic signals from target cells in the brain or neurotrophic factors secreted by target tissues to the cell bodies of RGCs, thereby preventing the death of some RGCs	Anterior chamber perfusion method	Restore axoplasmic transport	[61]
Scutellarin	HIOP model rats	50 mg/kg p. o.	Inhibition of NLRP3 expression resulted in a decrease in the upregulation of ASC, caspase-1, IL-18, and IL-1β	Anterior chamber perfusion method	Targeting oxidative stress, neuroinflammation	[82]
Scutellarin	Chronic EIOP; mice	300 mg/kg p. o.	Reduces the expression of NLRP3 inflammasome-associated proteins and inflammatory factors	Intracameral hydrogel or PBS injection	Targeting neuroinflammation	[83]
Baicalin	Cultured RGC-5 retinal ganglion cells	1/5/10 μM	Reduces the damaging effect of H2O2 on RGC-5 cells, and inhibits the apoptosis of RGC-5 cells	–	Targeted oxidative stress and anti-apoptotic effects	[68]
Baicalin	I/R rats	12.5 mg/kg	Reduces the extent of decrease in retinal ganglion cell-related proteins NF-L, Thy-1, and tubulin, and inhibits the upregulation of GFAP and PARP-1 expression	Anterior chamber perfusion method	Targeted oxidative stress, neuroprotective, and antiapoptotic effects	[68]
Baicalin	hTM	10/15 μM	Inhibits the production of IL-1α and ELAM-1, decreases the activity of SA-β-gal, and lowers the levels of protein carbonylation products	–	Targeted oxidative stress and neuroprotective effects	[69]
Baicalin	Chronic EIOP; mice	50 mg/kg i. p.	Inhibits autophagy-related proteins (LC3-II, Beclin-1, and ATG5) and modulating the PI3K/AKT signaling pathway protects the survival of RGCs	Episcleral venous occlusion with cauterization	Targeted anti-autophagy and oxidative stress	[88]
Baicalin	NMDA (150 μmol/L)-exposed RGC-5 cells	10 μmol/L	Inhibits the expression of autophagy-related proteins (LC3-II, Beclin-1, and ATG5) and increases the levels of PI3K/AKT signaling pathway-related proteins (p-AKT and p-PI3K)	–	Targeted anti-autophagy and oxidative stress	[88]
Quercetin	I/R rats	20 mg/kg i. p.	Inhibits caspase-3 and regulates calpain	Anterior chamber perfusion method	Targeted oxidative stress, neuroprotective, and antiapoptotic effects	[62]
Quercetin	Chronic EIOP; rat	10 μM/2 μL intravitreal injection	Enhances the inhibitory effect of the GABA neurotransmitter and reduces glutamate excitotoxicity	Episcleral venous occlusion with cauterization	Targeted oxidative stress	[63]
Quercetin	Primary cultured RGC	100 nM/1 μM	Inhibits calcium influx, scavenges ROS, and reduces the release of glutamate	–	Targeted oxidative stress and antiapoptotic	[70]

continued next page

▶ **Table 1** *Continued*

Active ingredients	Model	Administration	Pharmacological	Test index	Possible mechanism	References
Quercetin	Chronic EIOP; rat	10 μM/2 μL intravitreal injection	Increases the expression of Bcl-2 and decreases the cleavage of caspase-3	Microbead injection	Targeted neuroprotective, and antiapoptotic effects	[73]
Quercetin	Primary cultured RGCs	20 μM	Reduces the loss of mitochondrial membrane potenzial (ΔΨm) and clears the generation of ROS	–	Targeted oxidative stress and antiapoptotic effects	[73]
Quercetin	Cultured retinal precursor R28 cells	20 μM	Upregulates the SIRT1/FOXO3A pathway and inhibits p38 activation	OGD	Targeted oxidative stress	[72]
Quercetin	I/R rats	20 μM	Upregulates the SIRT1/FOXO3A pathway, inhibits the upregulation of IBA1 and GFAP, and reduces the secretion of TNF-α and IL-1β	Anterior chamber perfusion method	Targeted oxidative stress, neuroprotective, and antiapoptotic effects.	[72]
Quercetin	NTM5	1 μM	Activates the Nrf2/NRF1 transcription pathway, regulates the expression of antioxidant peroxiredoxin proteins PRDX3 and PRDX5	–	Targeted oxidative stress	[75]
DSX	RGCs	0.1/0.2/0.5 g/L	Inhibits peak current and steady-state current	–	Inhibited outward potassium ion channel currents	[93]

HIOP: high intraocular pressure; i.p.: intraperitoneal; RGCs: retinal ganglion cells; p.o.: per os; EIOP: elevated intraocular pressure; I/R: ischemia/reperfusion; hTM: human trabecular meshwork; NMDA: N-methyl-D-aspartate; GABA: gamma-aminobutyric acid; ROS: reactive oxygen species; OG: oxygen-glucose deprivation; NTM5: normal trabecular meshwork-5

Quercetin has been shown to have a protective effect on primary cultured rat RGCs under conditions of hypoxia, Glu excitotoxicity, and oxidative stress. It can improve the survival rate of RGCs [69]. Mitochondria play a crucial role in oxidative stress and cell apoptosis. Protecting mitochondrial function can effectively alleviate cell damage caused by oxidative stress [70]. In addition, *in vitro* cellular experiments have shown that quercetin dose-dependently inhibits the loss of mitochondrial membrane potential (ΔΨm), improves mitochondrial function, thereby eliminating the generation of ROS, and prevents mitochondria-mediated cell apoptosis, thus increasing the survival rate of primary cultured RGCs under hypoxic conditions *in vitro* [71].

In a study by Zhao et al., quercetin was loaded into ROS-responsive mitochondria-targeted liposomes that were targeted to the mitochondria, called Que@TPP-ROS-Lips, to increase its effective delivery to the retina [72]. In *in vitro* cell experiments induced by oxygen-glucose deprivation (OGD), R28 cells were pretreated with Que@TPP-ROS-Lips, which significantly reduced the levels of ROS induced by OGD and increased the levels of glutathione (GSH) and the GSH/GSSG (Glutathione disulfide) ratio inside the cells. Furthermore, Que@TPP-ROS-Lips attenuated OGD-induced mitochondrial depolarization, improved mitochondrial function, and helped combat oxidative stress. These improvements may be achieved by reversing the decrease in FOXO3A, SIRT1, and SOD1 expression induced by OGD, reducing the cleaved form of caspase-3 induced by OGD, increasing the expression of antiapoptotic protein BCL2, and reducing the level of proapoptotic protein BAX. Overall, Que@TPP-ROS-Lips inhibited the activation of p38 *in vitro* OGD via upregulating the SIRT1/FOXO3A pathway.

In a rat model of I/R injury, similar conclusions were drawn. Intravitreous injection of Que@TPP-ROS-Lips effectively reduced the accumulation of ROS and the decrease in ΔΨm. Additionally, there was an improvement in the levels of β-III-tubulin, a marker of RGCs [73]. Furthermore, Que@TPP-ROS-Lips successfully inhibited the upregulation of inflammatory cell markers IBA1 and GFAP and reduced the secretion of inflammatory cytokines TNF-α and interleukin (IL)-1β. These effects were also achieved by activating the FOXO3A antioxidant stress signaling pathway and inhibiting the p38 signaling pathway. In addition, quercetin can regulate the expression of antioxidant peroxiredoxins PRDX3 and PRDX5 through activating the Nrf2/NRF1 transcription pathway to inhibit oxidative stress damage in the retina [74].

Anti-neuroinflammatory

The mechanism of neuroinflammation is a key factor in the progression of neurodegenerative diseases and plays an important role in the pathogenesis of glaucoma [75, 76]. In patients with glaucoma and in rat models of high IOP, inflammatory factors are elevated in the aqueous humor and retina, leading to the degeneration of RGCs [77]. Three types of neural glial cells, including microglia, Müller cells, and astrocytes, are widely present in the retina and jointly support and maintain tissue homeostasis. However, under conditions of sustained damage, microglia become activated, promoting the expression of M1 polarization-related genes, stimulating peripheral macrophages to engulf neurons, and exacerbating RGC apoptosis in the retina [78]. In addition, activated astrocytes migrate from the lamina cribrosa to the axon bundles of neurons and release toxic mediators that cause RGC damage [79]. Moreover, abnormal proliferation of Müller cells can lead to disturbances in retinal homeostasis, resulting in increased RGC apoptosis [80]. In summary, controlling neuroinflammation and regulating the activity of neural glial cells are key factors in protecting RGC function.

The inflammasome is a complex of multiple proteins within the cytoplasm of immune cells that mediates the activation of caspase-1 (cysteine aspartic protease 1) following activation of immune cells. It subsequently mediates the cleavage and maturation of proinflammatory cytokines IL-1β and IL-18, while also mediating pyroptosis, a form of cell death. The study of the NLRP3 inflammasome, which is composed of NLRP3, apoptosis-associated speck-like protein (ASC), and pro-caspase-1, has been the most in-depth, and its mediated inflammatory response is closely related to RGCs apoptosis, making inhibiting its activation a potential direction for optic nerve protection [81]. In acute high IOP rat models and hypoxia models, scutellarin inhibits the expression of both intracellular and extracellular NLRP3 inflammasomes, which then downregulates caspase-1 activity and reduces the release of inflammatory mediators such as IL-18 and IL-1β [82]. Further experiments have also shown that scutellarin (300 mg/kg) can intervene in the NLRP3 inflammasome pathway of chronic high IOP mice, reduce retinal thinning, and improve visual functional defects [83].

Anti-excitotoxicity of glutamate

Glu is an excitatory neurotransmitter that is widely distributed in the retina. It mediates excitatory synaptic transmission by binding to ionotropic Glu receptors on the postsynaptic neuronal cell membrane, including N-methyl-D-aspartate (NMDA), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and kainate receptors. It can also activate metabotropic Glu receptors, which are coupled to intracellular G proteins and regulate second messenger signaling systems. In addition, Glu transporters are distributed on neuronal and glial cell membranes, which can timely clear excess Glu and regulate its concentration in the synaptic cleft. However, under stress conditions, such as ischemia and hypoxia, Glu may accumulate excessively in the synaptic cleft due to excessive release or inadequate clearance. This will continuously activate ion channels, causing a large amount of calcium ions to enter the cells, leading to a calcium overload in postsynaptic neurons [84]. This in turn activates nucleases, proteases, and phospholipase signaling pathways, producing ROS and other intermediate substances. These substances can cause nitrosylation and fragmentation of DNA, ultimately leading to neuronal apoptosis [85]. Multiple studies have found that changes in the expression and channel activity of NMDA receptor subunits are an important mechanism underlying the damage to RGCs in glaucoma. NMDA receptor antagonists have been shown to reduce RGC apoptosis [86, 87]. Therefore, the development of drugs that can block NMDA receptors is considered a potential neuroprotective strategy that could be used to prevent retinal damage caused by excitotoxicity.

EBHM is believed to have a similar effect to NMDA receptor antagonists. Based on previous research results, baicalin has been found to have the ability to reduce apoptosis of RGCs. In an *in vitro*

glaucoma model induced by NMDA, baicalin was found to counteract the autophagic process induced by NMDA by inhibiting autophagy-related proteins (LC3-II, Beclin-1, and ATG5) and modulating the PI3K/AKT signaling pathway, thereby reducing the adverse effects of NMDA on RGCs [88]. In an established chronic glaucoma mouse model, it was observed that baicalin could activate the PI3K/AKT signaling pathway, participate in the inhibition of autophagy, and effectively slow down the decrease in RGC density.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that is synthesized from Glu by the catalysis of glutamine synthetase (GS) in neurons and then converted into glutamine (Gln) and released into the extracellular space [89]. The GABA is then taken up by Gln and converted to GABA by the catalysis of glutamic acid decarboxylase (GAD) and taken up by astrocytes. In astrocytes, GABA is reconverted to Gln and Glu, which maintains the balance of Glu-GABA content in the body through the tricarboxylic acid cycle [90]. When GABA function is disrupted or inhibited, the excitatory effect of Glu is enhanced. Quercetin can enhance the inhibitory effect of GABA neurotransmitters, inhibit the excitatory effect of Glu neurotransmitters, and reduce the excitotoxicity of Glu, thus directly protecting RGCs [91].

Other mechanisms

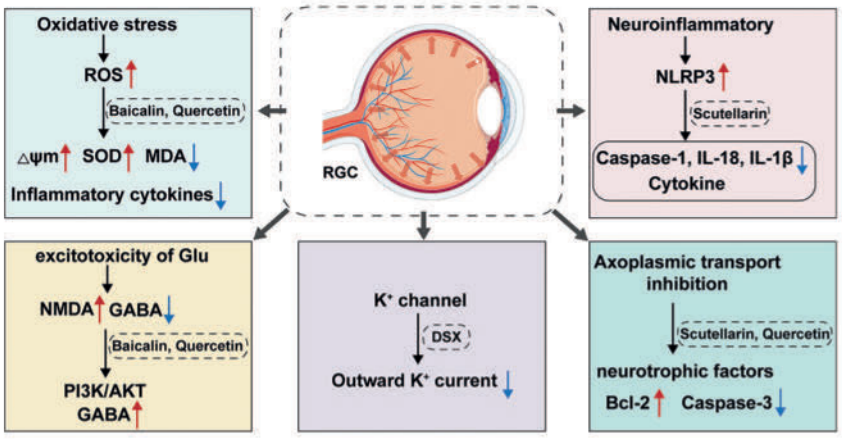
EBHM has been found to have additional mechanisms in protecting the optic nerve in glaucoma. K^+ channels on RGCs play a crucial role in maintaining cellular resting potential and regulating cell excitability [92]. The extract DSX from EBHM has been shown to reduce I/R injury, enhance axoplasmic flow, and reversibly and dose-dependently inhibit outward K^+ currents in rat RGCs, preventing vision loss and RGC damage caused by glaucoma [93]. These effects may be due to DSX binding to extracellular sites and altering channel gating properties, entering the cytoplasm to inhibit K^+ channels, or modulating intracellular signaling pathways to stimulate release of blockers and inhibit K^+ channel function through various mechanisms [94]. The discovery of the glymphatic system in the eye has provided a new direction for optic nerve protection in glaucoma. Under normal physiological conditions, the production and clearance of toxic substances such as Aβ are in balance. However, under high IOP conditions, glial cell proliferation leads to the accumulation of toxic products like Aβ in the retina, which may activate microglia-mediated neuroinflammatory responses and induce RGC apoptosis [95, 96]. Some studies have found that EBHM and its active components can inhibit Aβ deposition and reduce Aβ levels [97–99]. However, current research on the mechanism of EBHM's effect on Aβ in glaucoma RGC protection mainly focuses on central neurodegenerative diseases such as Alzheimer's disease and vascular dementia. Therefore, further experimental validation is needed to explore the role of EBHM and its active components in Aβ clearance and its related mechanisms in glaucoma RGC protection. In the future, this field of research can serve as a potential direction for optic nerve protection.

Recent studies have found that changes in the composition of gut microbiota are closely related to the occurrence and progression of glaucoma. Specific microbiota may trigger or sustain neurodegenerative T cell responses, promoting neuronal loss in glaucoma. Moreover, the gut microbiota of glaucoma patients differs significantly from that of healthy individuals, and these differences may affect the health of the optic nerve [100]. One study showed that scutellarin significantly improved Aβ pathology and cognitive deficits in APP/PS1 mice by modulating gut microbiota, increasing its diversity and activity. Scutellarin regulates microglia and reduces neuroinflammation through the cAMP-PKA-CREB-HDAC3 signaling pathway, while also inhibiting SCFAs (Short-Chain Fatty Acids) downstream signaling pathways, reducing the association between acetylated histone 3 and the IL-1β promoter, thereby further alleviating neuroinflammation. Thus, scutellarin may have potential neuroprotective properties by modulating gut microbiota and its anti-inflammatory effects. Although there are currently no studies on the effects of scutellarin on gut microbiota in glaucoma, its role in protecting the optic nerve in glaucoma warrants further investigation [101]. Tau protein plays a crucial role in RGC damage in glaucoma, characterized by its abnormal accumulation, phosphorylation, and mislocalization under IOP [102]. Studies have found that quercetin significantly reduces the hyperphosphorylation of Tau protein in okadaic acid-induced HT22 cells by inhibiting the Ca2+-calpain-p25-CDK5 signaling pathway, thereby reducing the conversion of p35 to p25 and the expression of calpain, improving cell morphology and increasing cell numbers. Additionally, quercetin blocks the okadaic acid-induced increase in p35 mRNA and intracellular Ca2+ levels, demonstrating potential neuroprotective effects [103]. However, the quercetin used in the study was not specifically sourced from EBHM. Therefore, further research is needed to clarify the specific role of quercetin extracted from EBHM in reducing Tau protein accumulation and protecting the optic nerve in glaucoma.

Conclusion

Previous studies have shown that optic nerve damage in glaucoma can be caused by multiple risk factors, including high IOP, transport dysfunction of axoplasm, oxidative stress, inflammatory reactions, and excitotoxicity of Glu. These factors interact with each other and lead to RGC damage. Therefore, developing drugs that target multiple pathways is a promising approach for protecting the optic nerve in glaucoma. The natural product EBHM contains multiple effective components, including baicalin, scutellarin, quercetin, which can synergistically exert their effects by inhibiting RGCs apoptosis, suppressing oxidative stress, anti-neuroinflammatory, anti-Glu excitotoxicity, and other mechanisms (▶ **Fig. 2**).

However, EBHM still has limitations. Oral EBHM preparations exhibit low solubility, a short half-life, and low bioavailability *in vivo*, which limits its efficacy in clinical applications. Currently, research on the mechanism of EBHM for protecting the optic nerve focuses on multiple targets or pathways. These targets and pathways overlap and need to form a systematic mechanism network to explain the interrelationships between them. In addition, there are still insufficient pharmacokinetic studies on EBHM and the lack of research on its mechanism of action in combination with other drugs. Secondly, the research on the protective mechanism of EBHM on the optic nerve mainly focuses on animal models, and there are a few clinical trials with small sample sizes, lack of long-



▶ **Fig. 2** The mechanism of EBHM in protecting the optic nerve in glaucoma.

term follow-up observations, standardization, and other issues. Although extensive research focuses on single components like baicalin, scutellarin, and quercetin, extrapolating these results to the whole extract of EBHM has limitations. The components within the extract may interact synergistically or antagonistically, altering the effects of single components. The complex constituents of the whole extract affect pharmacokinetics and pharmacodynamics, making it difficult to accurately predict the overall effect based on single components. Additionally, the bioavailability and metabolic pathways of the components in the extract may differ. Therefore, more research on the whole extract of EBHM is needed to fully understand its bioactivity and therapeutic potential. Furthermore, the protective effects of some components of EBHM, such as caffeoylquinic acid, on the optic nerve in glaucoma remain unclear, and there is a lack of relevant experimental evidence, highlighting the limitations in this area. These problems still need to be addressed in the future.

Therefore, investigating the systematic mechanism network of EBHM in protecting the optic nerve in glaucoma and synthesizing new EBHM derivatives through chemical modification of its structure to improve its bioavailability and therapeutic efficacy constitutes a pivotal trajectory in the development of innovative neuroprotective agents for glaucoma.

Contributors' Statement

YC: Conceptualization, Writing–original draft, Writing–review and editing. XC, GZ, NL, YS, SL, YL: Writing–review and editing. XL: Writing–original draft, writing, Reviewing final draft.

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Conflict of Interest

The authors declare that they have no conflict of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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