

REVIEW

Neuroprotective effects of resveratrol on retinal ganglion cells in glaucoma in rodents: A narrative review

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Abstract

Glaucoma, an irreversible optic neuropathy, primarily affects retinal ganglion cells (RGC) and causes vision loss and blindness. The damage to RGCs in glaucoma occurs by various mechanisms, including elevated intraocular pressure, oxidative stress, inflammation, and other neurodegenerative processes. As the disease progresses, the loss of RGCs leads to vision loss. Therefore, protecting RGCs from damage and promoting their survival are important goals in managing glaucoma. In this regard, resveratrol (RES), a polyphenolic phytoalexin, exerts antioxidant effects and slows down the evolution and progression of glaucoma. The present review shows that RES plays a protective role in RGCs in cases of ischemic injury and hypoxia as well as in ErbB2 protein expression in the retina. Additionally, RES plays protective roles in RGCs by promoting cell growth, reducing apoptosis, and decreasing oxidative stress in H₂O₂-exposed RGCs. RES was also found to inhibit oxidative stress damage in RGCs and suppress the activation of mitogen-activated protein kinase signaling pathways. RES could alleviate retinal function impairment by suppressing the hypoxia-inducible

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factor-1 alpha/vascular endothelial growth factor and p38/p53 axes while stimulating the PI3K/Akt pathway. Therefore, RES might exert potential therapeutic effects for managing glaucoma by protecting RGCs from damage and promoting their survival.

KEYWORDS

glaucoma, ischemic-reperfusion injury, oxidative stress, resveratrol, retinal ganglion cells

1 | INTRODUCTION

Glaucoma, a primary cause of blindness worldwide, is a neurodegenerative disease.¹ Early diagnosis and proper management are important to prevent visual impairment.² According to the study by the World Health Organization, approximately 3% of the global population aged 40–80 years, equivalent to about 76 million people, are expected to be affected by glaucoma.³ Regular eye examinations and early detection are essential in managing glaucoma and preventing visual impairment.⁴ Glaucoma has two fundamental types: primary open-angle glaucoma (POAG) and angle-closure glaucoma (ACG).^{5,6} POAG, the most common type, often has an unknown cause but is associated with hereditary factors, age-related changes in the eye, and increased intraocular pressure (IOP) due to reduced aqueous humor outflow.^{7,8} On the contrary, ACG occurs when there is a blockage in the drainage angle connecting the iris and the cornea, leading to a sudden increase in IOP.⁹

One main cause of glaucoma is oxidative stress, which significantly contributes to the progression of glaucoma and damages the retinal ganglion cells (RGC).¹⁰

RGCs are neurons located in the innermost layer of the retina, known as the ganglion cell layer (GCL).¹¹ These cells are responsible for transmitting visual information from the retina to the brain through the optic nerve.¹² RGCs play an important role in the visual processing system, as they collect visual input from other retinal cells and send signals to the brain for interpretation and processing.¹³ The death of RGCs can be caused by the formation of reactive oxygen species (ROS), particularly hydrogen peroxide (H₂O₂).¹⁴ This apoptosis is one of the main reasons for the progression of glaucoma.¹⁵ Oxidative stress can also affect the activity of antioxidant enzymes, which reduces their ability to neutralize ROS and protect against oxidative damage. This further contributes to the degeneration of RGCs and the development of glaucoma.^{16,17} Furthermore, oxidative stress can trigger various signaling pathways, including those associated with apoptosis and mitogen-activated protein kinases (MAPK), which are implicated in cell death and inflammation-related cascades. These pathways lead to the death of RGCs and the development of glaucoma. Therefore, protecting RGCs from ROS-induced apoptosis could be an effective strategy to mitigate or prevent glaucoma.¹⁸

The choice of treatment for glaucoma depends on various factors such as the patients' overall health, the type and stage of glaucoma, and their adherence to therapy.^{19,20} Regular monitoring and follow-up are necessary to determine the success rates of treatment

and prevent further visual loss.²¹ Medical therapy is typically the primary treatment option, involving the use of eye drops or oral medications to reduce IOP.²² Selective laser trabeculoplasty is a laser treatment intended to lower IOP in individuals with glaucoma.²³ Surgical procedures, such as trabeculectomy or microinvasive glaucoma surgery (MIGS), are typically reserved for patients who are unresponsive to or unable to receive medication or laser treatment.²⁴ Moreover, natural substances like antioxidants have shown potential for treating glaucoma.²⁵ Antioxidants play an important role in combating oxidative stress.²⁶ Studies have shown that antioxidants like resveratrol (RES), curcumin, and vitamins C and E, as well as carotenoids such as lutein and zeaxanthin, have protective effects on RGCs and the optic nerve.^{27–31} RES is found in cereals, fruits, vegetables, and red wine.^{32,33} It has been shown to possess antioxidant, anti-inflammatory, and antiapoptotic activities. These properties are beneficial in protecting RGCs against oxidative stress and inflammation.^{31,34} Additionally, RES inhibits hypoxia-induced death of RGCs by downregulating apoptosis and promoting the production of ErbB2.³⁵

ErbB2, also known as HER2 (human epidermal growth factor receptor 2), is a gene that encodes a 185-kDa transmembrane glycoprotein belonging to the epidermal growth factor receptor family. It is a receptor tyrosine kinase with intrinsic tyrosine kinase activity.³⁶

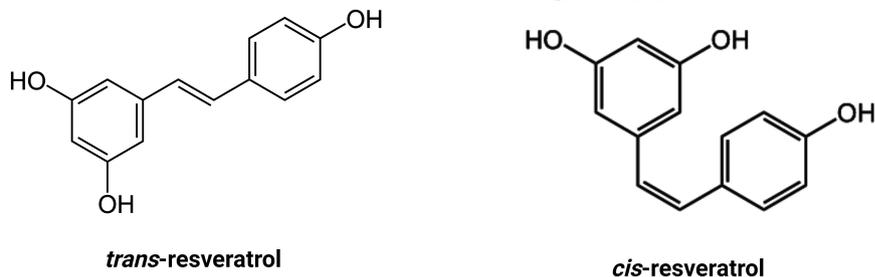
This review article focuses on in vitro experimental studies that illustrate the efficiency of RES in protecting RGCs from injury. The review also provides insights into the cellular and molecular mechanisms of action of RES and its potential as an adjuvant treatment for glaucoma. The antioxidant and antiapoptotic properties of RES contribute to its therapeutic potential in alleviating the signs and symptoms of glaucoma.

2 | OVERVIEW OF RES

2.1 | Chemistry of RES

RES was discovered by Takaoka in 1939, who isolated the compound from the root of *Veratrum grandiflorum*.³⁷ RES is a natural polyphenol with the chemical formula C₁₄H₁₂O₃. It consists of a stilbene backbone, which is a double-bonded phenyl group connected to another phenyl group by a double bond.^{38,39} RES has three hydroxyl groups (–OH) attached to the phenyl rings, located at positions 3, 5, and 4'.⁴⁰ The structure of RES enables it to exist

FIGURE 1 Structures of *trans*- and *cis*-RES (resveratrol).⁴⁶



in different geometric arrangements, including *cis* and *trans* isomers (Figure 1).⁴¹ RES is abundant in grapes, particularly in their skins and kernels, with red grapes having a higher level of RES than green grapes.^{42,43} Moreover, red wine contains RES due to the presence of grape skins during the fermentation process.⁴⁴ RES is also present in peanuts and peanut products like peanut butter, although the amounts may vary based on the processing and roasting procedures.⁴⁵

2.2 | RES metabolism

RES has a high absorption rate in the small intestine, likely due to its small, nonpolar shape. When it is administered orally, about 75% of the dose of *trans*-RES is efficiently absorbed by the human body, and the absorption can be further maximized by consuming dietary fat.⁴⁷⁻⁴⁹ However, its bioavailability is limited due to its quick metabolism, which leads to the production of different metabolites such as RES glucuronides and RES sulfates.⁵⁰ Once absorbed, RES and its metabolites enter the systemic circulation and are distributed to peripheral tissues, including adipose tissue.⁵¹ The absorption of RES occurs through a quick process of passive diffusion, as demonstrated in Caco-2 cells. Transepithelial diffusion is responsible for approximately 70%–75% of the absorption of RES.^{52,53} The absorption of RES can be greatly enhanced, resulting in about a fourfold increase in plasma concentration, when it is in the micronized form.^{54,55} Micronized RES has been proven to have a considerably enhanced absorption rate compared to non-micronized RES.⁵⁶ Extensive phase II metabolism occurs in both the gut and liver after oral administration of RES, leading to the generation of different metabolites. The primary metabolites of RES include RES-3-O-glucuronide, RES-3-O-sulfate, and RES-4'-O-glucuronide. Additional metabolites such as RES diglucuronide, RES sulfoglucuronide isomers, RES glucuronide isomers, and RES sulfate have also been found in some studies.⁵⁷⁻⁵⁹

2.3 | RES biological properties

RES exhibits antioxidant effects by scavenging free radicals and decreasing oxidative damage to cells and tissues. It demonstrates a defensive impact against lipid peroxidation in cellular membranes and DNA harm induced by ROS.^{53,60} Additionally, RES upregulates the activity of several antioxidant enzymes such as superoxide

dismutase (SOD) and catalase (CAT).³² In RGCs, RES increases the levels of SOD, CAT, and glutathione.¹⁸ Moreover, RES exhibits anti-inflammatory characteristics by inhibiting the synthesis of pro-inflammatory molecules and altering inflammatory signaling pathways.⁶¹ This can help reduce inflammation and improve overall wellness. Furthermore, RES has metabolic regulatory effects such as enhancing mitochondrial function and energy metabolism. It can improve nutrient usage and metabolic efficiency, leading to enhanced growth performance and general metabolic health.^{62,63} According to a thorough assessment of experimental *in vivo* and *in vitro* models of Parkinson's disease (PD), RES can cross the blood–brain barrier and prevent the development of the disease. Therefore, RES may have neuroprotective benefits by reducing oxidative stress and inflammation in the brain, which are significant factors in the development and progression of PD.⁶⁴

2.4 | Toxicological studies

The recommended daily intake of RES has not been determined by the U.S. Food and Drug Administration or the European Food Safety Authority.⁶⁵ RES is considered a dietary supplement rather than a medication, so it does not have an official recommended daily allowance or dietary reference intake. However, studies have shown that a typical daily dose of RES for potential health benefits ranges from 150 to 500 mg.^{66,67} While the dietary recommendation of RES depends on individual needs, RES is generally considered safe and well tolerated in humans at doses of up to 5 g/day.⁶⁸ However, some studies have reported potential adverse effects of RES, especially at high doses. These effects may include gastrointestinal symptoms as well as possible interactions with certain drugs.⁶⁹⁻⁷² Animal studies have also indicated possible harmful effects of high-dose RES on the liver and kidneys.^{73,74} Overall, RES is considered safe and well tolerated at standard doses, but further research is needed to fully understand the potential benefits and disadvantages of high-dose RES supplementation.

3 | OVERVIEW OF GLAUCOMA

The treatment options for glaucoma may include various therapies such as eye drops, laser treatment, or surgery.⁷⁵ The specific treatment approach depends on factors like the type and severity of glaucoma, the patient's overall health, and any underlying medical conditions.⁷⁶

Although treatment can slow down the progression of glaucoma, any vision loss that has already occurred is irreversible. The following are some common therapies used to manage glaucoma:

- i. Medicines: eye drops or oral medications are typically used to reduce IOP.⁷⁷ The main objective of these drugs is to regulate the volume of fluid in the eye, known as aqueous humor, by either decreasing its production or increasing its outflow, to manage IOP.⁷⁸ Medications may need to be administered long term and require regular monitoring.
- ii. Laser therapy: laser trabeculoplasty and laser peripheral iridotomy are two common laser techniques used to treat glaucoma.⁷⁹ Laser trabeculoplasty is a procedure that enhances the outflow of fluid from the eye. On the contrary, laser peripheral iridotomy involves creating a small hole in the iris, which helps facilitate fluid flow and alleviate pressure.^{80,81}
- iii. Surgical procedures: in situations where medications and laser therapy fail to be effective, surgical interventions may be required. Trabeculectomy, which involves the creation of a new drainage channel, and drainage implant surgery are examples of surgical treatments used to lower IOP.^{82,83} MIGS procedures are revolutionary surgical approaches that attempt to lower IOP with less stress and faster recovery compared with previous surgeries.⁸⁴ These operations involve the use of small devices or implants to enhance the outflow of fluid from the eye.⁸⁵

Several molecular pathways have been hypothesized to produce glaucoma, including oxidative stress, mitochondrial malfunction, and endoplasmic reticulum (ER) stress.^{86–88} Oxidative stress has been identified to play a potential role in the development and progression of a spectrum of visual disorders such as glaucoma.⁸⁹ Disruption of the balance between free radical formation and antioxidant defenses can result in oxidative stress and damage to cells and tissues.¹⁶ Oxidative damage to trabecular meshwork cells would promote RGC death followed by trabecular dysgenesis and IOP elevation due to aqueous flow obstruction.⁹⁰ Mitochondrial function dysregulation relates to the pathophysiology of glaucoma and is considered a primary component in its progression.⁹¹ In glaucoma, malfunctioning mitochondria can decrease adenosine triphosphate (ATP) generation, cause oxidative stress, and decrease cellular metabolism.⁹² Mitochondria play an important role in ROS formation. Dysfunctional mitochondria can lead to an imbalance in ROS production, causing oxidative stress that negatively impacts RGC survival.³¹ ROS-mediated effects and mitochondrial dynamics are interconnected in the context of retinal injury and neurodegeneration, highlighting the importance of mitochondrial health in protecting RGCs.⁹² Moreover, in diabetic mice, retinal mitochondria experience increased oxidative damage, with elevated superoxide levels, decreased antioxidant defense systems, and altered electron transport complexes, particularly complex III, leading to mitochondrial dysfunction and oxidative stress in the retina.⁹³

Mitochondrial failure can induce apoptotic pathways, leading to the death of RGCs, which are the major cells involved in glaucoma.⁹⁴ In addition, investigations have demonstrated that hereditary factors

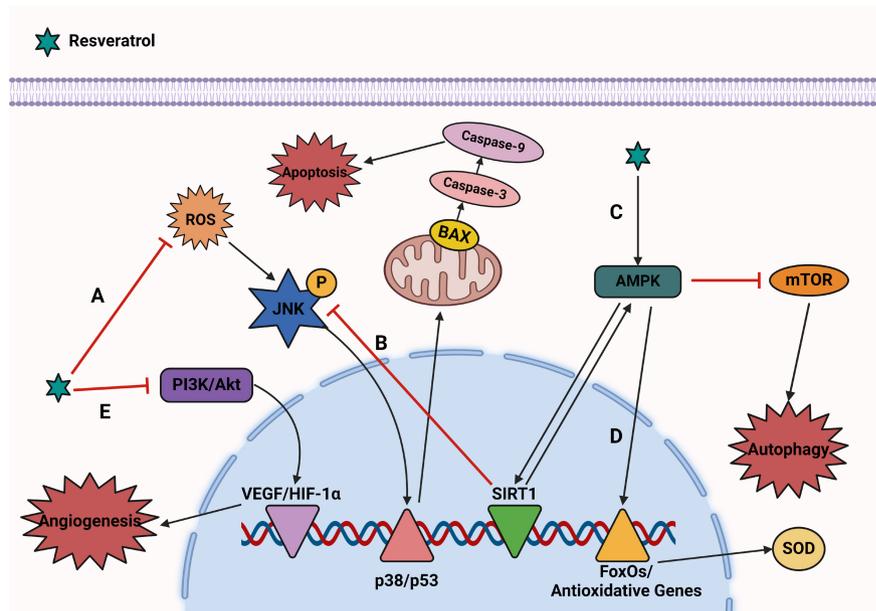
play an essential role in the pathogenesis of glaucoma. Mutations in *MYOC*, *OPTN*, *WDR36*, and *CYP1B1* are among the most widely reported genetic risk factors for the disease. These genes are implicated in maintaining the stability and proper functioning of mitochondria, ensuring they can produce energy efficiently. These genes also play a role in regulating the levels of ROS within cells to prevent oxidative stress. Therefore, understanding the roles of *MYOC*, *OPTN*, *WDR36*, and *CYP1B1* genes in maintaining mitochondrial health and ROS balance is important for comprehending how genetic mutations in these genes can impact the risk of developing glaucoma.^{95,96}

4 | NEUROPROTECTIVE EFFECTS OF RES ON RGCs IN GLAUCOMA

Glaucoma, a common global source of irreversible visual loss, significantly results in progressive loss of RGCs.⁹⁷ Understanding the activities of RGCs in glaucoma is important for establishing effective therapeutic techniques to protect and preserve these cells. Targeting the underlying processes of RGC destruction, such as lowering IOP, enhancing neuroprotection, and regulating inflammation, may help halt the course of glaucoma while preserving visual function. Several pathways are responsible for the pathophysiology of glaucoma, which eventually impair RGCs and result in vision loss. In this context, RES exerts several protective cellular and molecular effects on RGCs (Figure 2).

One proposed mechanism is related to ischemic injury and ErbB2 signaling pathway. The retinal ischemia/reperfusion (I/R) injury model is a method used to induce retinal damage in mice.⁹⁸ In this model, retinal I/R damage was induced by quickly cannulating the anterior chambers of both eyes of adult male C57BL/6 J mice with a stainless needle.⁹⁹ In the study by Luo et al., one eye of the mice was subjected to increased IOP above the systolic blood pressure for 60 min, whereas the other eye acted as the control and maintained a normal IOP. After the 60-min period, the needle was removed from the eye, and the mice were killed at different time points (0, 1, 3, and 7 days) after I/R injury. The aim of this model was to induce retinal I/R damage in mice, which was subsequently utilized to evaluate the effects of RES on the loss of RGCs and impairment of retinal function.¹⁰⁰ ErbB2 belongs to the ErbB family of receptor tyrosine kinases, which is also known as HER2.¹⁰¹ It is a key component in controlling cell growth, survival, and differentiation.¹⁰² ErbB2 is implicated in different cellular functions such as the control of the neurological system, heart, and mammary glands.^{103–105} Seong et al. showed that RES successfully decreased retinal cell death caused by I/R injury in the GCL of the retina. This was demonstrated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay, which showed a considerably larger number of TUNEL-positive cells in the I/R group than in the control group. However, the I/R+RES group exhibited a much-reduced number of TUNEL-positive cells compared to the I/R group. The study demonstrated that RES efficiently lowered the expression of ErbB2 in the retina after I/R injury. These results emphasized the potential of RES as a therapeutic intervention to prevent hypoxia-induced RGC death linked with ErbB2.³⁵ Moreover, ErbB2 is associated with

FIGURE 2 Molecular mechanisms of resveratrol (RES) on RGCs (retinal ganglion cells). (A) RES suppresses the activation of JNK (c-Jun N-terminal kinase), p38, and p53 signaling pathways induced by ROS (reactive oxygen species); (B) RES suppresses the phosphorylation of JNK via Sirt1; (C) RES activates AMP-activated protein kinase and leads to Sirt1 activation as well as inhibits autophagy; (D) RES promotes the transcription function of FoxOs and facilitates the transcription of antioxidative genes as well as activates SOD (superoxide dismutase); (E) RES inhibits HIF-1 α /VEGF (vascular endothelial growth factor) by downregulating PI3K/Akt.



apoptosis regulation, a critical cellular process linked to neuronal cell death.³⁵ As an upstream regulator, ErbB2 plays a significant role in controlling apoptosis, making it a major target in the modulation of cell death mechanisms.³⁵ The expression levels of ErbB2, affected by hypoxia, indicate its involvement in apoptosis regulation in RGCs.³⁵

Apoptosis involves the activation of enzymes caspase-3 and cleaved caspase-9. Caspase-3, belonging to the caspase family of proteases, is a key enzyme in apoptosis.¹⁰⁶ This enzyme becomes active on receiving signals that trigger programmed cell death, such as DNA damage, cellular stress, or signaling from other caspases.¹⁰⁷ On activation, caspase-3 initiates the cleavage and activation of distinct cellular proteins, leading to the typical changes linked with apoptosis.¹⁰⁸ These alterations include DNA fragmentation, cytoskeletal disintegration, nuclear condensation, and membrane blebbing.¹⁰⁹ Caspase-9 plays a vital role in apoptosis and is classified as an initiator caspase due to its significant contribution to initiating the apoptotic cascade.^{110,111} Caspase-9 is primarily activated through the intrinsic or mitochondrial mechanism of apoptosis, which is triggered by cellular stressors like DNA or cellular damage.¹¹² The formation of the apoptosome complex, consisting of cytochrome c, Apaf-1, and ATP, is essential in activating caspase-9 in this pathway.¹¹³ MAPKs are a group of enzymes that play an important role in various physiological functions, including cell proliferation, differentiation, survival, and response to external signals.¹¹⁴ MAPKs participate in signal transduction pathways that transmit signals from the cell membrane to the nucleus, leading to changes in gene expression and cellular function.¹¹⁵ The MAPK family consists of several components, including extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNK), and p38 MAPKs.^{116,117} Activation of each component of the MAPK family is driven by unique upstream kinases that respond to various stimuli.¹¹⁸ ERKs are principally responsible for cell proliferation, differentiation, and survival.¹¹⁹ They are activated by growth factors, hormones, and mitogens, and their activation regulates genome activity and cellular proliferation.^{120,121}

JNKs play a role in stress reactions, inflammation, and apoptosis. They are activated by numerous stress signals, including UV radiation, thermal shock, and pro-inflammatory cytokines.¹²²⁻¹²⁴ p38 MAPKs are also engaged in stress reactions and inflammation. p38 MAPK activation can influence gene expression, cell cycle progression, and inflammatory responses.¹²⁵⁻¹²⁷ Ye and Meng observed that RES has protective effects on H₂O₂-induced apoptosis in RGCs. The study demonstrated that H₂O₂ enhanced the levels of cleaved caspase-3 and caspase-9, which are important for beginning and driving apoptosis, but RES counteracted this impact. This finding demonstrates that RES has high antioxidant capabilities against H₂O₂-induced damage in RGCs. Additionally, the researchers noted that RES was able to decrease ERK, JNK, and p38 signaling pathways in RGC-5 cells caused by H₂O₂. These three MAPKs contributed to intracellular metabolism control and response to external stress. The study suggests that the protective effects of RES may be attributed to the inhibition of these MAPK pathways.¹⁸

IOP following glaucoma is the major origin of ischemic injury. Hypoxia in the retina and optic nerve of glaucomatous eyes activates several factors like HIF-1 α . HIF-1 α is a transcription factor that is necessary for maintaining cellular homeostasis in response to oxygen deprivation produced by tissue ischemia and is primarily present in the nucleus and cytoplasm of cells.^{128,129} The HIF-1 complex is formed by the dimerization of HIF-1 α and HIF-1 β , which in turn promote the activation of genes involved in erythropoiesis, neuroprotection, angiogenesis, apoptosis, and necrosis.^{130,131} Vascular endothelial growth factor (VEGF), a signaling molecule, plays a vital role in the process of angiogenesis.¹³² VEGF supports the formation of endothelial cells, which are the building blocks of blood vessels.¹³³ It contributes to various physiological activities, including embryonic development, wound healing, and production of new blood vessels in response to tissue ischemia.¹³⁴ However, excessive or dysregulated expression of VEGF can lead to pathological situations, such as retinal neovascularization and vascular leakage.¹³⁵ The research

conducted by Ji et al. indicated that RES protected RGCs by decreasing the HIF-1 α /VEGF and p38/p53 signaling axes as well as increasing the PI3K/Akt pathway. The HIF-1 α /VEGF axis is connected with retinal ischemia injury, whereas the p38/p53 pathway is responsible for RGC apoptosis. Additionally, the PI3K/Akt pathway enhanced cell survival and inhibited apoptosis. RES treatment reduced the overexpression of the HIF-1 α /VEGF and p38/p53 pathways during I/R injury although activating the downregulation of the PI3K/Akt pathway. This led to an increase in retinal function after injury-induced functional damage, demonstrating that RES could ameliorate retinal ischemia injury-induced RGC loss and retinal function degradation.⁹⁹

As mentioned, oxidative stress and apoptosis are the most important mechanisms in retinal degeneration in glaucoma. Sirtuins are one of the protective proteins against oxidative stress and RGC death. Sirtuin-1 (Sirt1) is a member of the sirtuin family of proteins that are nicotinamide adenine dinucleotide-dependent deacetylases.¹³⁶ Sirt1 plays a role in several cellular processes, including antiapoptosis, antiaging, and regulation of genomic activity and metabolism.^{137,138} It is considered a therapeutic target for the treatment of neurodegenerative illnesses such as Alzheimer's disease, PD, and polyglutamine disease.^{139,140} According to Wu et al., RES has a favorable impact on RGCs and their axons after retinal I/R injury. This research demonstrated that RES could protect RGC axons from damage by decreasing the phosphorylation of JNK proteins via Sirt1. These results revealed that RES may have therapeutic implications in optic nerve degeneration.³⁴ Moreover, the stimulation of Bax leads to permanent destruction to mitochondria, regulates the release of apoptotic proteins, and finally prompts caspase activation to launch the apoptotic cascade.¹⁴¹ The intrinsic apoptotic axis begins with Bax activation, followed by pore formation in the mitochondrial outer membrane that occurs from Bax activation, dimerization, and oligomerization.¹⁴² This results in the release of signaling molecules such as cytochrome c, which finally stimulates the start of caspases, particularly cleaved caspase-3.¹⁴³ Phosphorylated-Akt, the active version of the protein Akt, is a serine/threonine kinase that plays an important role in cell survival, proliferation, and many cellular activities.¹⁴⁴ Akt can be activated via phosphorylation, leading to its activation and subsequent signaling cascade.¹⁴⁵ Phosphorylation of Akt at certain locations, such as serine 473 and threonine 308, results in its activation and enables it to phosphorylate downstream targets related to cell survival and growth pathways.¹⁴⁶ Sirt1 was discovered by Luo et al. as a required component for the neuroprotective activities of RES on RGCs after retinal I/R damage in mice. The most effective concentration of RES was found to be 100 μ mol/L. The increase in Sirt1 levels caused by RES was found to have a significant impact on RGC apoptosis, leading to increased levels of phospho-Akt and lower expressions of Bax and cleaved caspase-3.¹⁰⁰

Mitochondrial dysfunction is another destructive mechanism in glaucoma that leads to RGC loss. R28 cells are retinal neuronal-like cells that were first obtained from the retina of postnatal day 1 rat and have been defined as a model for RGCs.¹⁴⁷ R28 cells have been

employed in several investigations to examine the processes of RGC mortality and to evaluate prospective treatment medications for RGC injury.¹⁴⁸ Optic atrophy 1 (Opa1) plays a vital role in mitochondrial fusion and modification of crista structures.¹⁴⁹ Opa1 is in the inner mitochondrial membrane and participates in the preservation of mitochondrial shape, function, and dynamics.¹⁵⁰ Opa1 regulates mitochondrial fusion by encouraging the fusion of the inner mitochondrial membrane, which is required for the preservation of mitochondrial function and crista structure.¹⁵¹ SOD is an enzyme that performs an important function in antioxidant defense mechanisms within cells.¹⁶ SOD neutralizes damaging superoxide radicals, which are extremely reactive chemicals that can produce oxidative injury to cells.¹⁵² By converting superoxide radicals into less-damaging molecules, SOD lowers oxidative stress and contributes to the preservation of cellular health.⁵³ Pang et al. revealed that RES exerts protective effects on retinal injuries induced by I/R and serum deprivation. The treatment of RES increased the vitality of retinal cells (R28 cells) and somewhat relieved apoptosis. Additionally, the researchers showed that RES altered Opa1 expression and SOD activity, both of which are expected to enhance the protective effects of RES on RGCs.³¹

Another important targeting factor is Brn-3a to protect RGCs in glaucoma. Brn-3a is a transcription factor that belongs to the brain-specific homeobox/POU domain protein family.¹⁵³ This protein is necessary for the formation and survival of RGCs by regulating gene expression required for RGC development and function. Brn-3a is selectively expressed in RGCs, where it is important for their development and function.¹⁵⁴ SMI-32, a monoclonal antibody, specifically targets a nonphosphorylated epitope of the neurofilament heavy chain.¹⁵⁵ This antibody is often used as a marker for mature neurons, such as RGCs.¹⁵⁶ Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and contributes to the development and maintenance of the nervous system.¹⁵⁷ BDNF is a member of the neurotrophin family of growth factors and contributes to the development and maintenance of the nervous system.¹⁵⁸ Tropomyosin receptor kinase B (TrkB), is activated by interacting with BDNF and other neurotrophins.¹⁵⁹ Activation of TrkB signaling pathways enhances cell survival, synaptic plasticity, and neuroprotection.¹⁶⁰ The results of the experiments by Cao et al. revealed that RES, injected intravitreally, protected RGCs from high IOP-induced cell death through several mechanisms, making it a promising therapeutic intervention for glaucoma. In particular, they showed that intravitreal injection of 30- μ mol/L RES remarkably enhanced the expression of Sirt1 and reduced ROS production in RGCs, improved Brn-3a and SMI-32 expression, and caused a large reduction in TUNEL-positive cells in RGCs. The effects of RES on BDNF in Müller glial cells (MGCs) and TrkB expression in RGCs were studied in this work. RES treatment increased BDNF gene expression in MGCs. In particular, exposure to 140- μ mol/L RES led to a substantial increase in BDNF gene expression, unlike the control group. Additionally, the study confirmed the increase in TrkB expression in RGCs after RES therapy. These findings suggested that RES promotes BDNF-TrkB signaling between MGCs and RGCs, which is important for the preservation and survival of RGCs.¹⁶¹

Besides oxidative stress, inflammation plays a major role in glaucoma.¹⁶² Glaucoma is linked to chronic low-grade inflammation in the retina and optic nerve.¹⁶³ Inflammation can contribute to the progression of glaucoma through various mechanisms:

- i. Stimulation of immune cells: in reaction to injury or stress, immune cells such as microglia and astrocytes in the retina and optic nerve become activated and release pro-inflammatory mediators (IL-1 β , IL-6, and TNF α).^{164,165} This activation can lead to the production of cytokines and chemokines, which can contribute to neuronal injury and cell death.¹⁶⁶ ROS can act as signaling molecules in inflammatory processes. They can modulate the activity of transcription factors like nuclear factor kappa B, which regulates the expression of pro-inflammatory genes, leading to the production of cytokines, chemokines, and adhesion molecules involved in inflammation.¹⁶⁷ Additionally, ROS can induce oxidative damage in cells, causing the release of damage-associated molecular patterns and activating the inflammasome assembly, leading to the production of pro-inflammatory cytokines such as IL-1 β and IL-18.^{168,169}
- ii. Gliosis: gliosis refers to the reaction of glial cells, such as astrocytes and Müller cells, to injury or stress.¹⁷⁰ In glaucoma, gliosis is characterized by the proliferation and hypertrophy of glial cells. Gliosis can lead to the formation of a glial scar, which can impair the regeneration and function of neurons.¹⁷¹
- iii. Excitotoxicity: inflammation can release excitatory neurotransmitters, such as glutamate, which can cause excitotoxicity and neuronal death.¹⁷² Excitotoxicity is believed to be a major contributor to RGC death in glaucoma.¹⁷³

Overall, inflammation in glaucoma is associated with the loss of RGCs and damage to the optic nerve. Targeting inflammation and its pathways could potentially be a therapeutic approach for treating glaucoma. According to Luo et al., treatment with RES may effectively prevent RGC cell death and reduce inflammation associated with gliosis after I/R damage. The study demonstrated a decrease in TUNEL labeling, inhibition of the early increase in the proapoptotic protein Bax, and a subsequent decrease in the levels of cleaved caspase-3, all indicating the antiapoptotic properties of RES. These findings suggest that RES may prevent RGC cell death by blocking the apoptotic pathway dependent on Bax and caspase-3. Thus, RES could be a valuable treatment option for glaucoma caused by I/R injury.¹⁷⁴

ER stress is another pathway responsible for the destructive mechanisms of glaucoma. The unfolded protein response (UPR) is a cellular stress response pathway that is activated when there is an aggregation of unfolded or misfolded proteins in the ER.¹⁷⁵ The main goal of the UPR is to restore ER homeostasis and promote cell survival.¹⁷⁶ UPR proteins consist of molecular chaperones and transcription factors that play an important role in the UPR pathway. Some examples of UPR proteins are provided here.

Binding immunoglobulin protein (BiP, also known as GRP-78) is an ER chaperone that assists in protein folding and prevents protein aggregation.¹⁷⁷ It is upregulated during ER stress and helps to properly fold unfolded proteins.¹⁷⁸

- i. The transcription factor C/EBP homologous protein (CHOP), also known as DNA damage-inducible transcript 3 or growth and DNA damage protein-153, is induced during ER stress.¹⁷⁹ CHOP is involved in regulating the gene expression responsible for ER stress signaling and apoptosis.¹⁸⁰
- ii. X-box binding protein-1 (XBP-1) is a transcription factor that is activated during ER stress and plays an important role in regulating genes associated with protein folding, ER-associated degradation, and lipid metabolism.¹⁸¹

According to Lindsey et al., RES supplementation may stop the loss of RGC dendrites after optic nerve damage. Additionally, optic nerve compression altered the expression of specific UPR proteins, such as BiP, CHOP, and XBP-1. However, this effect was less significant in mice that received RES in their diet. These findings suggest that long-term RES supplementation in the diet can protect against RGC dendrite loss and regulate the UPR in the retina after optic nerve damage.¹⁸²

Optic nerve transection (ONT) is a surgical treatment utilized in animal models to simulate optic nerve injury. In this surgery, the optic nerve is intentionally cut or severed, often in a controlled and standardized manner.¹⁸³ The objective of ONT is to produce a model that simulates optic nerve injury or degeneration, allowing researchers to evaluate the impacts of such damage on RGCs and explore novel neuroprotective therapies.¹⁸⁴ In the ONT procedure, an incision is made in the lateral conjunctiva, and the optic nerve is exposed through blunt dissection. A longitudinal incision is then made in the optic nerve sheath, and a cross section of the optic nerve is formed, avoiding harming the surrounding blood supply. After the surgery, the incision is repaired with sutures, and suitable ophthalmic ointment is given.¹⁸⁴ According to another study by Kim et al., the neuroprotective efficacy of RES was evaluated in an ONT model. The results demonstrated that administration of ≥ 3.1 $\mu\text{mol/L}$ of RES exhibited a substantial neuroprotective impact on the RGCs of the RES-treated group compared with the control group. The number of RGCs in eyes treated with RES was substantially larger than that in eyes treated with a control drug (Phosphate buffered saline) in transected rats. The study demonstrated that RES may exert a therapeutic effect in treating optic nerve illnesses via activating the Sirt1 pathway and exhibiting its neuroprotective effects.¹⁸⁵

Additionally, riluzole reduces glutamate release and blocks voltage-gated sodium channels.^{186,187} These activities of riluzole help minimize excitotoxicity and prevent the degeneration of RGCs.¹⁸⁸ In addition, riluzole possesses antioxidant capabilities and can protect RGCs from oxidative stress-induced damage to the optic nerve.¹⁸⁸ Pirhan et al. revealed that both riluzole and RES, when taken alone or in combination, significantly slowed RGC degradation in an experimental glaucoma paradigm. According to this study, RES therapy was found to have a substantial effect on RGC density in the experimental

Authors	Dosage of RES	Type of study/ model	Mechanisms
Seong et al. ³⁵	20 mg/kg	Mice	RES reduced the expression of ErbB2 protein in the retina after I/R injury
Ye and Meng ¹⁸	5, 10, or 20 μmol/L	RGC-5 cells	RES suppressed the activation of ERK, JNK, and p38 signaling pathways in RGC-5 cells induced by H ₂ O ₂
Ji et al. ⁹⁹	20 mg/kg	Mice	RES suppressed the overexpression of the HIF-1α/VEGF and p38/p53 pathways after I/R injury while activating the downregulation of the PI3K/Akt pathway
Wu et al. ³⁴	250 mg/kg	Rat	RES protected RGC axons from injuries by suppressing the phosphorylation of JNK proteins via Sirt1
Pang et al. ³¹	2 mg/kg	Rat	RES enhanced the viability of retinal cells (R28 cells) and partially alleviated apoptosis
Cao et al. ¹⁶¹	1 μL of 3 μmol/L or 30 μmol/L (intravitreal injection)	Mice	RES elevated Sirt1 expression and reduced the production of ROS in RGCs, improved Brn-3a and SMI-32 expressions, and caused a marked reduction in TUNEL-positive cells in RGCs
Luo et al. ¹⁰⁰	10, 50, and 100 μmol/L (intravitreal injection)	Mice	RES elevated the levels of phospho-Akt and decreased the expressions of Bax and cleaved caspase-3
Luo et al. ¹⁷⁴	250 mg/kg	Rat	RES inhibited RGC death by blocking the Bax-caspase-3-dependent apoptotic pathway, indicating its potential therapeutic effectiveness against glaucoma-induced I/R injury
Pirhan et al. ¹⁸⁸	10 mg/kg	Rat	RES delayed the production of RGCs

TABLE 1 Studies consistent with the purpose of this study.

Abbreviations: ERK, extracellular signal-regulated kinase; HIF-1α, hypoxia-inducible factor-1 alpha; IR, ischemia/reperfusion; JNK, c-Jun N-terminal kinase; RES, resveratrol; RGC, retinal ganglion cell; ROS, reactive oxygen species; Sirt1, sirtuin-1; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF, vascular endothelial growth factor.

glaucoma paradigm. The RGC density in the group undergoing RES therapy was found to be the highest among all groups.¹⁸⁸

Table 1 presents a summary of the study results.

5 | CONCLUSIONS

Numerous antioxidants have been studied for possible therapeutic benefits in the management of glaucoma. These include natural antioxidants such as RES and curcumin, vitamins C and E, and carotenoids such as lutein and zeaxanthin. These antioxidants have been reported to exert neuroprotective effects on RGCs and may

be advantageous in the prevention and treatment of glaucoma by protecting RGCs from damage and encouraging their survival. RES is a natural polyphenol found in numerous plants such as grapes and berries. The findings showed that (1) RES exerts cellular and molecular effects on RGCs by promoting cell growth, reducing apoptosis, and decreasing oxidative stress in H₂O₂-exposed RGCs; (2) RES can protect RGC axons by preventing the phosphorylation of JNK proteins through Sirt1; (3) RES can reduce the loss of RGCs and impairment of retinal function caused by IR injury; this impact occurs by suppressing the HIF-1α/VEGF and p38/p53 pathways, which are implicated in cell death and inflammation, while activating the PI3K/Akt pathway, which promotes cell

survival and growth; and (4) RES prevents oxidative stress damage in RGCs and suppresses the activation of MAPK signaling axis. This study explored the therapeutic potential of RES in protecting RGCs from glaucoma-induced cell death. Our findings revealed that intravitreal treatment of RES efficiently rescued RGCs from high IOP-induced cell death through various routes. These data show that RES may have therapeutic potential for glaucoma therapy. However, further investigations are required to thoroughly evaluate the efficacy of RES as a therapy for retinal cell loss in glaucoma.

AUTHOR CONTRIBUTIONS

Seyed Arash Aghaei Meibodi and Sulieman Ibraheem Shelash Al-Hawary: investigation; Jitendra Gupta, and Ibrohim B. Sapaev: resources; Mazin A. A. Najm, Marim Alwawe, and Mozghan Nazifi: data curation; Maryam Golmohammadi, Seyed Arash Aghaei Meibodi, & Mohammad Yasin Zamanian: writing—original draft preparation; Maryam Golmohammadi and Mohammad Yasin Zamanian: writing—review and editing; Gervason Moriasi: visualization; Mohammad Yasin Zamanian and Mohammadreza Rahmani: supervision; Mohammad Yasin Zamanian and Maryam Golmohammadi: project administration. All authors have read and agreed to the published version of the manuscript.

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