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Review Article

Emerging neuroprotective paradigms in glaucoma: Pharmacotherapy and technological insights

Prarthana Sonawane[1], Yash Davane[1], Siddhesh Pingale[1], Tanvi Rede[1], Ajay Bhagwat[1]*, Rohit Doke[2]

[1]Dept. of Pharmacy, Samarth College of Pharmacy, Belhe, Maharashtra, India
[2]Dept. of Pharmacology, Jaihind College of Pharmacy, Vadgaon Sahani, Maharashtra, India

Abstract

Glaucoma remains one of the leading causes of irreversible blindness worldwide, driven by the progressive loss of retinal ganglion cells (RGCs) and their axons. Conventional management strategies predominantly focus on reducing intraocular pressure (IOP); however, many patients continue to experience RGC degeneration despite effective IOP control. This underscores the need for neuroprotective approaches that directly preserve RGCs and optic nerve function. This review explores current pharmacological strategies, including brimonidine, neurotrophic factors, memantine, Ginkgo biloba extract, citicoline, nicotinamide, insulin, and resveratrol, all of which demonstrate neuroprotective potential in preclinical and early clinical studies. Furthermore, we discuss emerging technologies such as stem cell therapy, gene therapy, mitochondrial-targeted treatments, and nanotechnology-based systems that aim to prevent or reverse glaucomatous neurodegeneration. Together, these approaches highlight a shift toward comprehensive glaucoma management that goes beyond IOP control. Continued research and well-designed clinical trials are essential to translate these promising strategies into routine clinical practice and to improve long-term visual outcomes for patients with glaucoma.

Keywords: Glaucoma, Neuroprotection, Gene therapy, Pharmacological strategies, Emerging technologies.

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1. Introduction

Intraocular pressure (IOP) remains the only well-established and modifiable risk factor for glaucoma; however, disease progression persists in certain patients despite optimal control with medical or surgical interventions.[1] This indicates the involvement of additional non-IOP–related mechanisms in visual loss. Such factors include neuroinflammation, oxidative stress, calcium-mediated pathways, impaired autophagy, reactive gliosis, translaminar cribrosa pressure imbalance, and the possible propagation of misfolded proteins. Interestingly, several neurodegenerative processes observed in primary open-angle glaucoma share similarities with those in alzheimer's disease (AD) and other tauopathies, including chronic traumatic encephalopathy.[2] Synaptic dysfunction and aberrant synaptic remodeling, considered central in AD pathogenesis, have also been implicated in glaucomatous neurodegeneration. Moreover, genetic associations, such as Apolipoprotein E variants, appear to increase susceptibility to POAG.[3] Repeated episodes of IOP elevation may exert compressive stress on the optic nerve head, thereby promoting tau accumulation, abnormal phosphorylation, and mislocalization, ultimately contributing to retinal ganglion cell damage and glaucomatous progression.[4]

Although current therapeutic approaches predominantly focus on lowering intraocular pressure (IOP), retinal ganglion cell (RGC) loss can still occur at normal IOP levels, and many patients experience progressive visual decline despite effective pressure control. Growing evidence implicates additional mechanisms—including oxidative stress, excitotoxicity, vascular dysregulation, and neuroinflammation—in the pathogenesis of glaucoma. These insights have driven increasing interest in neuroprotective strategies that target the preservation of RGCs and the optic

Corresponding author: Ajay Bhagwat
Email: bhagwatajay44@gmail.com

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nerve directly, independent of IOP reduction. Such interventions aim to slow or prevent the neurodegenerative cascade, thereby stabilizing or improving visual outcomes. By prioritizing neuroprotection, researchers seek to shift glaucoma management toward approaches that not only delay progression but may eventually halt or even reverse optic nerve damage. This review aims to provide a comprehensive, up-to-date synthesis of the pathophysiological mechanisms underlying neurodegeneration in glaucoma, with a special emphasis on both IOP-dependent and IOP-independent pathways. It also highlights current and emerging neuroprotective strategies—ranging from pharmacological interventions to novel technologies—designed to preserve RGC function and prevent vision loss. By integrating mechanistic insights with therapeutic perspectives, this article seeks to inform clinicians, researchers, and drug developers about promising avenues for future research and personalized glaucoma management.

2. Pathophysiology of Neurodegeneration in Glaucoma

2.1. Role of intraocular pressure (IOP)

Elevated intraocular pressure (IOP) is the primary modifiable risk factor for glaucoma. Increased IOP deforms the lamina cribrosa and optic nerve head (ONH), impairs axonal transport, and initiates retinal ganglion cell (RGC) death.[5] However, disease progression can occur even with normal IOP (normal-tension glaucoma), indicating additional mechanisms. IOP-induced biomechanical stress also promotes extracellular matrix remodeling, mitochondrial dysfunction, and local ischemic and inflammatory signaling. Susceptibility depends on ONH biomechanics, vascular health, and mitochondrial resilience.[6] While IOP reduction remains the first-line treatment, neuroprotection targeting axonal metabolism, glial activity, and blood flow is increasingly emphasized to slow disease beyond pressure control.[7]

2.2. Oxidative stress and mitochondrial dysfunction

RGCs have high energy requirements, making them sensitive to mitochondrial dysfunction and oxidative stress. Elevated IOP and ischemia increase reactive oxygen species (ROS), leading to lipid, protein, and DNA damage, ATP depletion, and apoptosis.[8] Mitochondrial DNA mutations and aging further impair energy production and mitophagy. Dysfunctional mitochondria exacerbate ROS generation and activate pro-apoptotic signaling, contributing to progressive axonal loss.[9] Experimental evidence supports protective effects of antioxidants, coenzyme Q10, nicotinamide, and agents that enhance mitochondrial biogenesis.[10] Combining redox modulation with IOP control may help prevent pressure-independent neurodegeneration and preserve visual function in glaucoma patients.

2.3. Excitotoxicity and calcium dysregulation

Glutamate excitotoxicity is a key driver of RGC death in glaucoma. Elevated extracellular glutamate overactivated NMDA and Ca2+-permeable AMPA receptors, causing calcium influx, mitochondrial collapse, ROS production, and apoptosis. Glial dysfunction and impaired glutamate transport exacerbate toxicity.[12,13] Excess calcium activates calpains and nitric oxide synthase, further damaging axons. NMDA receptor antagonists and calcium channel modulators protect RGCs in preclinical models, highlighting therapeutic potential.[14,15] Excitotoxicity interacts with mitochondrial failure, forming a vicious cycle that amplifies neurodegeneration.[16]

2.4. Neuroinflammation and glial activation

Microglia and astrocytes respond to IOP stress and axonal injury by adopting pro-inflammatory phenotypes. Activated glia release cytokines, complement proteins, and ROS, worsening axonal damage and RGC loss. Astrocytes remodel the lamina cribrosa and alter blood-retinal barrier function.[17-19] Complement activation and inflammasome signaling are consistently upregulated in experimental and human glaucoma. Targeting glial activation—through complement inhibition, inflammasome blockers, or microglial modulators—represents a promising adjunctive approach to IOP-lowering therapy.[20,21]

2.5. Vascular dysregulation and ischemia

Glaucoma is associated with reduced optic nerve head perfusion, impaired autoregulation, and vasospasm. Intermittent hypoperfusion followed by reperfusion promotes oxidative stress, excitotoxicity, and RGC apoptosis. Optical coherence tomography angiography (OCTA) shows decreased peripapillary vessel density in progressing glaucoma. Endothelin-1 overexpression, nitric oxide imbalance, and glial-vascular unit changes contribute to vascular dysregulation. Addressing systemic vascular risk factors and exploring vasoregulatory or endothelin antagonists may improve outcomes, especially in normal-tension glaucoma.[22-24]

3. Pharmacological Strategies for Neuroprotection

3.1. Brimonidine

Brimonidine, an α2-adrenergic receptor agonist, is primarily prescribed to lower intraocular pressure (IOP) in glaucoma but has also shown promising neuroprotective effects beyond IOP regulation.[25] Its quinoxaline structure containing an imidazoline ring facilitates receptor binding in the eye, enabling multiple protective mechanisms for retinal ganglion cells (RGCs). Preclinical studies indicate that brimonidine supports RGC survival and prevents damage from diverse insults such as NMDA-induced excitotoxicity, ischemia, optic neuritis, and ocular hypertension.[26] Neuroprotection is partly mediated by modulation of apoptotic pathways through upregulation of anti-apoptotic proteins (Bcl-2/Bcl-

XL) and suppression of pro-apoptotic proteins (Bax). Additionally, brimonidine enhances the expression of neurotrophic factors including brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF), which play crucial roles in neuronal repair.[27] It also reduces excitotoxic damage by altering NMDA receptor activity and limiting glutamate accumulation after injury. Another important mechanism involves the attenuation of amyloid-β accumulation, a factor implicated in RGC degeneration. Furthermore, brimonidine has been linked to improved vascular autoregulation, reduced ischemic retinal injury, and enhanced neuronal regeneration.[28] Synergistic benefits have been observed when brimonidine is combined with ripasudil, a Rho kinase inhibitor. This combination enhances RGC survival through complementary pathways, including suppression of inflammatory mediators and increased trophic support. Clinical evidence, though mixed, supports a potential neuroprotective role for brimonidine. In the Low-pressure Glaucoma Treatment Study, patients treated with brimonidine experienced less visual field loss compared to those receiving timolol, despite similar IOP reduction. Brimonidine also improved contrast sensitivity and may preserve retinal nerve fiber layer thickness independently of IOP effects. However, high dropout rates due to side effects limit the strength of these conclusions.[29]

3.2. Neurotrophic factors

Neurotrophic factors (NTFs) are vital proteins that regulate neuronal development, survival, and repair.[30] By binding to their corresponding receptors, they activate tyrosine kinase signaling cascades that support neuroprotective processes such as axonal regeneration and functional enhancement of neurons.[31] Among them, nerve growth factor (NGF), BDNF, ciliary neurotrophic factor (CNTF), fibroblast growth factor-2 (FGF-2), glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), and neuritin have been identified as highly relevant in the context of glaucoma.

BDNF is particularly important for retinal ganglion cell (RGC) survival. It prevents apoptosis by activating extracellular signal-regulated kinases (Erk1/2) and c-jun while inhibiting caspase-2 through its TrkB receptor.[32] Clinical studies have reported reduced BDNF concentrations in both serum and aqueous humor of patients with normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG). Experimental models further confirm its therapeutic role, showing that BDNF supplementation improves RGC viability and protects against amyloid-β–induced apoptosis. CNTF, locally produced by RGCs, functions through a heterotrimeric receptor complex comprising CNTF receptor α, gp130, and leukemia inhibitory factor receptor β. Single intravitreal injections of CNTF demonstrated significant neuroprotection in preclinical studies. To achieve sustained delivery, the NT-501 implant—a polymer capsule containing genetically modified human cells that secrete CNTF—has been developed. Current clinical trials are assessing the efficacy of this encapsulated cell therapy for glaucoma management. NGF, acting via TrkA and p75 neurotrophin receptors (p75NTR), supports neuronal survival, axonal regeneration, and repair.[33] Topical NGF administration has preserved RGCs and axons in experimental ocular hypertension models, while recombinant human NGF (rhNGF) has shown potential to enhance neuroprotection and neuroregeneration. Despite these encouraging findings, clinical translation remains limited by challenges in ensuring efficient, targeted, and long-term delivery of NTFs to the retina.

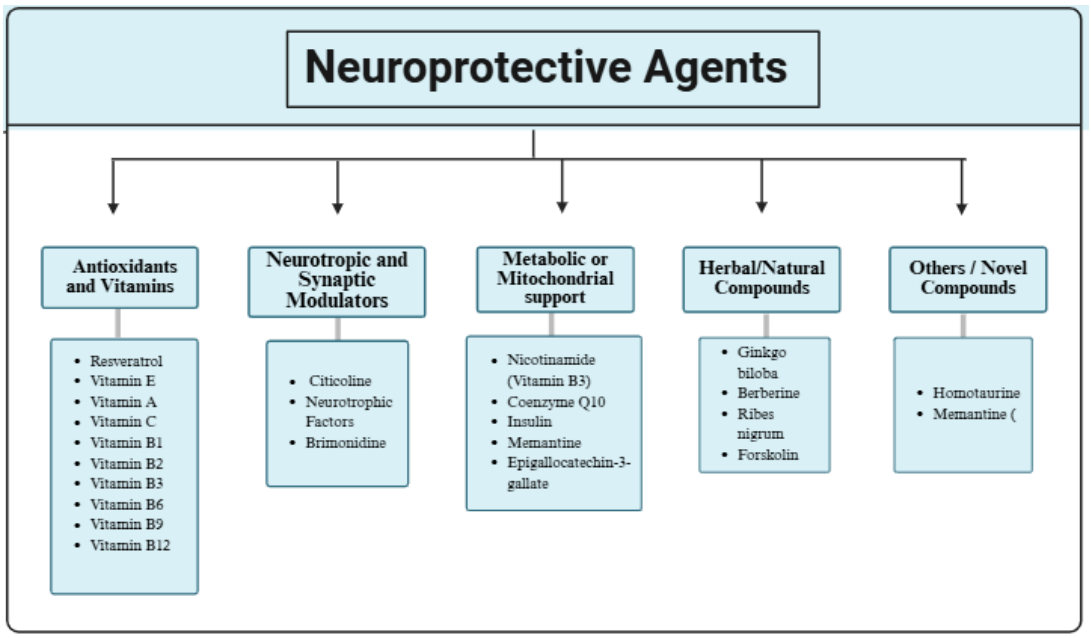

Figure 1: Pharmacological Interventions for Neuroprotection in glaucoma

3.3. Homotaurine

Homotaurine, also referred to as tramiprosate or 3-APS (3-amino-1-propanesulfonic acid), is a naturally occurring amino sulfonate first isolated from marine red algae.[34] It is notable for its ability to influence nervous system function by enhancing nerve signal transmission and exhibiting neuromodulatory effects. Research has shown that homotaurine interacts with several biological pathways in both cell-based and animal models, displaying properties that are cytoprotective, neuroprotective, and neurotropic.[35] Structurally similar to GABA (γ-aminobutyric acid), homotaurine acts as a strong agonist of GABA receptors, particularly GABA-A, which supports its role in reducing pain and exerting analgesic effects, potentially through opioid and cholinergic mechanisms. As a sulfur-containing amino acid, it may also guard cells against oxidative DNA damage from free radicals.

A key therapeutic interest in homotaurine lies in its capacity to inhibit the formation of β-amyloid plaques.[36] These plaques are associated with neuronal cell death and neurodegenerative conditions, including Alzheimer's disease. This action also holds significance for ocular health, as β-amyloid has been implicated in retinal ganglion cell (RGC) apoptosis observed in glaucoma models.

Recent findings highlight the enhanced neuroprotective effects of combining homotaurine with citicoline.[37] This combination has been shown to reduce cell death in retinal cells exposed to harmful stimuli like glutamate and high glucose levels. Moreover, a multicenter randomized clinical trial reported that four months of daily oral supplementation with this combination improved the function of inner retinal cells. This improvement occurred without changes in intraocular pressure and was accompanied by better visual field performance and an improved quality of life, indicating its potential in managing glaucoma and other neurodegenerative eye disorders.[38]

3.4. Coenzyme Q10

Coenzyme Q10 (CoQ10), also called ubiquinone or ubidecarenone, is a naturally occurring lipid-soluble molecule found in all animal and plant cells. The "Q" refers to its quinone structure.[38] Although it is primarily synthesized within the body, small amounts are obtained through diet, especially from organ meats, fish, nuts, and oils, while lower levels are found in dairy, fruits, vegetables, and cereals. CoQ10 is vital for cellular energy production, functioning as a key component of the mitochondrial electron transport chain.[39] It transfers electrons and protons between complexes I/II and complex III within the inner mitochondrial membrane. In its reduced form, ubiquinol, CoQ10 also acts as a powerful antioxidant. It neutralizes free radicals and helps regenerate other antioxidants like vitamins C and E, thereby protecting cellular membranes, proteins, and mitochondrial DNA from oxidative damage.[40]

Given the role of mitochondrial dysfunction and oxidative stress in many diseases, CoQ10 has therapeutic potential across a range of conditions—including cardiovascular, neurological, oncological, and immune-related disorders. Levels of CoQ10 naturally decline with age, particularly in brain tissue, making it a candidate for addressing age-related neurodegenerative diseases such as Alzheimer's, Parkinson's, multiple sclerosis, and glaucoma.[41] However, CoQ10's effectiveness in ocular treatments is limited by its large molecular size and poor solubility, which hinder its absorption through the eye.[42] It is also expelled from cells by P-glycoprotein transporters. Co-administration with vitamin E can improve its ocular bioavailability by blocking this efflux mechanism.

Numerous studies in vitro and in animal models have demonstrated CoQ10's neuroprotective effects, particularly for retinal ganglion cells (RGCs). It reduces oxidative stress, limits apoptosis, and inhibits activation of damaging glial cells.[43] Clinical evidence also supports its role in improving retinal function and visual responses in glaucoma patients when administered with vitamin E, especially in topical formulations or dietary supplements.

3.5. Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a prominent polyphenol belonging to the catechin group and is the most abundant catechin in green tea, accounting for 50–70% of its total catechin content.[44] Due to its significant presence, EGCG is the primary focus of much green tea-related research. Despite its promising biological properties, the clinical application of EGCG is hindered by its low oral bioavailability. In both humans and rodents, only 0.1% to 0.3% of orally ingested EGCG reaches the bloodstream, and it is quickly metabolized and cleared from the plasma within eight hours due to processes like glucuronidation, methylation, sulfation, and microbial breakdown. This makes targeted delivery a major challenge. Despite these limitations, EGCG is widely recognized for its potent antioxidant capacity and diverse biological actions. It exhibits anti-inflammatory and vasodilatory properties, all of which contribute to its neuroprotective effects. Additionally, EGCG has demonstrated anti-aging capabilities through free radical scavenging and has shown promise in cancer prevention and treatment.[45] In terms of ocular health, particularly in relation to glaucoma, EGCG has shown beneficial effects in experimental models. In a mouse model involving optic nerve crush, systemic administration of EGCG helped preserve retinal ganglion cells (RGCs), suggesting its potential as a therapeutic agent for optic nerve injuries and neurodegenerative eye conditions such as glaucoma.[46]

3.6. Vitamins

Vitamins are essential organic compounds required in small amounts for various physiological processes. They function

as coenzymes, antioxidants, cofactors in redox reactions, or hormones, and are crucial for regulating biochemical pathways.[47] Their neuroprotective potential is largely attributed to their antioxidant properties, which help combat oxidative stress—a known contributor to neurodegenerative conditions like glaucoma.

Numerous studies have investigated whether dietary or supplemental intake of antioxidant vitamins influences glaucoma risk, but the results have been mixed and often inconclusive. For instance, a U.S. cross-sectional study (2005–2006) found no significant link between the intake or blood levels of vitamins A and E and glaucoma prevalence.[48] However, vitamin C supplementation—both at low and high doses—was associated with a reduced likelihood of glaucoma, even though serum levels of vitamin C did not reflect the same correlation.

A large prospective study involving over 116,000 adults aged 40 and above, tracked over an average of 9.1 years, similarly found no strong association between the risk of primary open-angle glaucoma (POAG) and dietary intake of vitamins A, C, E, or carotenoids. Nonetheless, increased consumption of fruits and vegetables rich in vitamins A, B2, C, and carotenoids appeared to lower glaucoma risk among older women. In The Rotterdam Study, which followed 3,502 individuals aged 55 and older, most antioxidant vitamins (C and E) and carotenoids showed no significant association with glaucoma incidence.[49] However, participants with high intakes of vitamin B1 and retinol equivalents had nearly half the risk of developing open-angle glaucoma.

3.7. Vitamin B1 (thiamine)

Vitamin B1 (thiamine) is a vital nutrient that acts as a cofactor in several essential biochemical reactions necessary for normal growth and bodily functions. It is naturally present in a variety of foods, including meats, whole grains, eggs, legumes, fish, and nuts. Although rare, a deficiency in thiamine can lead to optic neuropathy, typically characterized by severe, bilateral vision impairment accompanied by optic disc swelling.[50] Research into the relationship between vitamin B1 and glaucoma has produced conflicting results. The Rotterdam Study found that a higher intake of thiamine may offer protective benefits against open-angle glaucoma.[51] However, another study by Giaconi and colleagues did not observe any significant association between vitamin B1 intake and glaucoma risk.

3.8. Vitamin B2 (riboflavin)

Vitamin B2 (riboflavin) is another important B vitamin that plays a key role in cellular energy production.[52] It is an integral part of coenzymes such as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), both of which are involved in the mitochondrial electron transport chain. Riboflavin is found in a wide range of foods, including poultry, fish, eggs, dairy products, and various plant-based sources. In terms of ocular health, a study conducted by Coleman et al. reported that women who consumed at least 2 mg of vitamin B2 per day from dietary sources experienced a reduced risk of developing glaucoma.[53] These findings suggest that riboflavin may play a neuroprotective role in preserving visual function, although more research is needed to confirm its clinical relevance in glaucoma prevention or management.

3.9. Vitamin B3

Vitamin B3, commonly known as niacin, includes two main forms: nicotinic acid and nicotinamide. Nicotinamide, a water-soluble amide, serves as a precursor to nicotinamide adenine dinucleotide (NAD+), a vital coenzyme involved in energy metabolism and redox reactions.[54] It plays a critical role in ATP production through glycolysis and contributes to the synthesis of cellular components such as fatty acids, steroids, and cholesterol. NAD+ mainly supports energy-producing (catabolic) pathways, while its phosphate form, NADP, functions in biosynthetic (anabolic) processes. Dietary sources of nicotinamide include meat, eggs, dairy products, fish, tea, coffee, and fortified cereals, while vegetables offer smaller amounts. The body can also synthesize it from the amino acid tryptophan. Nicotinamide is efficiently absorbed when taken orally, widely distributed in tissues, metabolized in the liver, and excreted by the kidneys. The recommended daily intake is about 15 mg, and even high doses are generally well-tolerated. Beyond energy metabolism, nicotinamide exhibits anti-inflammatory, antioxidant, and photoprotective properties. It contributes to DNA repair, membrane stability, and neuronal survival. Altered NAD+ levels, especially with aging, have been linked to neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's, highlighting the neuroprotective role of nicotinamide.[55]

In ophthalmology, particularly in glaucoma research, nicotinamide has shown potential benefits. Animal studies demonstrated that nicotinamide supplementation protects retinal ganglion cells (RGCs) by reducing mitochondrial vulnerability and preventing degeneration. A clinical trial involving glaucoma patients on IOP-lowering treatment found that oral nicotinamide led to early improvements in inner retinal function.[56] Moreover, individuals with primary open-angle glaucoma were observed to have significantly lower nicotinamide levels than healthy controls.

3.10. Vitamins B6, B9, and B12

Vitamins B6, B9, and B12 play critical roles in maintaining cellular health, especially within the nervous system and ocular functions. Vitamin B6 is a water-soluble vitamin consisting of six related compounds, with pyridoxal phosphate serving as its biologically active form. It is commonly found in foods like fish, poultry, and plant-based items. This vitamin functions as a coenzyme in around 160 metabolic processes, including gluconeogenesis, amino acid metabolism, and lipid synthesis. Additionally, it helps

regulate homocysteine, an amino acid that can contribute to oxidative stress and apoptosis in retinal ganglion cells (RGCs).

Vitamin B9, known as folate or folic acid, is essential for DNA and RNA synthesis and also aids in breaking down homocysteine. It is primarily sourced from leafy vegetables and legumes. Folate deficiency in adults has been associated with cognitive impairments and visual system disorders, such as nutritional amblyopia and optic nerve damage.[57] Low folate levels are linked to nutritional optic neuropathy, which can manifest as gradual vision loss, central scotomas, and altered color perception.

Vitamin B12, or cobalamin, is found only in animal-derived foods like meat, fish, and eggs. It is crucial for energy metabolism, DNA synthesis, red blood cell formation, and neurological function.[58] A deficiency, often due to inadequate dietary intake, can result in pernicious anemia, elevated homocysteine, and neurological complications—including optic neuropathy, sometimes even before anemia presents. Studies have noted lower vitamin B12 levels in open-angle glaucoma patients, although not all research confirms significant differences for B6 or B9. Nonetheless, reduced levels of B6, B9, and B12 are strongly associated with increased homocysteine, a factor linked to oxidative damage in glaucoma and pseudoexfoliation glaucoma cases.[59]

3.11. Vitamin C

Vitamin C, or ascorbic acid, is a powerful antioxidant that supports redox balance, reduces age-related inflammation, and maintains vascular health. Unlike many animals, humans cannot produce vitamin C and must obtain it through diet, primarily from fruits and vegetables. Its neuroprotective potential has been explored in relation to glaucoma, but findings are mixed. Some studies found lower vitamin C levels in patients with normal tension glaucoma, while others saw no differences in open-angle glaucoma cases.[60] A large cross-sectional study of adults over 40 suggested a possible link between vitamin C supplementation and reduced glaucoma risk, though the evidence was weak.

3.12. Vitamin A

Vitamin A, or retinol, is an antioxidant obtained from foods like dairy, fish, meat, and plants. Its activity is largely due to carotenoids, particularly β-carotene, which is especially important in brain health and may help reduce neuron loss in conditions involving oxidative stress.[61] Research on the link between vitamin A and glaucoma has produced mixed findings. One study found higher vitamin A levels in primary open-angle glaucoma patients than in those with normal tension glaucoma, while others found no significant differences. However, the Rotterdam Study suggested that high dietary intake of retinol may reduce the risk of developing open-angle glaucoma by half.[62]

3.13. Vitamin E

Vitamin E is a fat-soluble vitamin consisting of eight forms, including four tocopherols and four tocotrienols, with α-tocopherol (αT) being the most researched due to its strong antioxidant properties against free radical damage.[63] It is commonly found in seeds like peanuts, almonds, and sunflower seeds, as well as oils such as corn, soybean, and peanut oil. Vitamin E is absorbed alongside dietary fats in the intestines, and αT is preferentially transported by the liver to tissues via lipoproteins. Adults need about 15 mg daily. Studies in rats show vitamin E deficiency leads to more retinal ganglion cell death under high intraocular pressure, while in humans, vitamin E supplementation may slow glaucoma progression and protect against nerve damage.[64]

3.14. Forskolin

Forskolin is a natural diterpene extracted from the leaves, roots, and tubers of the Coleus forskohlii plant. It works by increasing cyclic adenosine monophosphate (cAMP) levels within cells, offering neuroprotective benefits. Research has shown that forskolin can reduce intraocular pressure (IOP) in both animals and humans, helping to protect retinal ganglion cells (RGCs) from damage associated with glaucoma.[65] In a double-blind, randomized trial, patients with primary open-angle glaucoma treated with 1% forskolin eye drops experienced a significant IOP reduction, likely due to decreased aqueous humor production. Additionally, dietary supplements containing forskolin not only lowered IOP but also improved retinal function, as indicated by enhanced pattern electroretinogram amplitude. Animal studies further demonstrate that a combination of forskolin with homotaurine, spearmint, and B vitamins reduces inflammation and apoptosis markers, preserving RGCs and visual function in glaucoma models—even without affecting IOP.[66] These findings highlight forskolin's potential as a therapeutic agent for glaucoma management.

3.15 Ribes nigrum

Ribes nigrum, commonly known as blackcurrant and native to Europe and Asian Russia, includes about 160 species and has been traditionally used to treat conditions like glaucoma, cardiovascular diseases, hepatitis, hyperlipidemia, and hypertension. Blackcurrant is rich in polyphenols, particularly four types of anthocyanins, which are being studied for their effects on glaucoma progression. In a randomized, placebo-controlled trial, Ohguro and colleagues showed that blackcurrant anthocyanins (BCACs) significantly improved ocular blood flow and visual fields in patients using antiglaucoma medications, although no significant changes were found in intraocular pressure (IOP) or systemic conditions.[67] Another study by the same group reported a notable reduction in mean IOP in both healthy individuals and glaucoma patients after two years of BCAC supplementation. These findings suggest that BCACs could be a safe and effective adjunct supplement for glaucoma

patients already on treatment, as well as for healthy individuals.[68]

3.16. Berberine

Berberine, a natural compound found in Berberis plants, exhibits a wide range of pharmacological effects, including antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties. Although its clinical use is limited by poor solubility and bioavailability, preclinical research highlights its potential in treating various conditions. Berberine can cross the blood-brain barrier and has shown protective effects against neurotoxicity, ischemia-reperfusion injury, and chronic neurodegenerative diseases such as Alzheimer's, Parkinson's, depression, and epilepsy.[69] Its neuroprotective actions involve complex mechanisms like reducing oxidative stress, inflammation, and cell death. While human studies are mostly focused on Alzheimer's and Parkinson's diseases, berberine holds promise as a therapeutic option for other neurodegenerative disorders, including glaucoma.[70-72] However, further research is essential to better understand its clinical efficacy, optimal dosage, and bioavailability for these uses.

3.17. Ginkgo biloba

Ginkgo biloba, a tree native to East Asia and part of the Gymnosperm species, has a long history of use in traditional Chinese and Japanese medicine. Its leaves contain bioactive compounds such as flavonoids, bioflavonoids, organic acids, and terpene lactones, which contribute to its diverse therapeutic effects. The standardized extract of Ginkgo biloba leaves, known as EGb761, is commonly used in randomized controlled trials and has shown promise in addressing age-related conditions, including neurodegenerative diseases, cognitive decline, and glaucoma.

The potential benefits of Ginkgo biloba extract (GBE) stem from its neuroprotective and antioxidant properties, along with its ability to enhance blood circulation through vasodilation and reduce blood viscosity.[73] In glaucoma research, GBE's protective effects on retinal ganglion cells (RGCs) have primarily been explored in animal models. For example, daily administration of GBE for four weeks following optic nerve crush injury significantly increased RGC survival. Additionally, studies in rats with chronic glaucoma showed that both pre- and early post-treatment with EGb761 offered neuroprotection.

Clinical trials have focused on two main outcomes: improving ocular blood flow and visual field function. Some studies reported increased peripapillary blood flow in patients with normal tension glaucoma after four weeks of oral GBE.[74] Similarly, an antioxidant supplement containing 120 mg/day of GBE improved ocular blood flow in open-angle glaucoma patients over the same period. However, results across studies remain inconsistent, highlighting the need for further investigation to clarify GBE's effectiveness in glaucoma treatment and management.

3.18. Memantine

Memantine is a voltage-dependent, non-competitive antagonist of the NMDA receptor that specifically targets activated glutamatergic receptors. By doing so, it reduces excessive glutamate activity, calcium influx, and the activation of pathways that lead to cell death, all without disrupting normal neurotransmission. Its unique tricyclic amine structure allows it to effectively block the NMDA receptor channel by binding to essential asparagine residues. This action prevents harmful calcium overload while maintaining normal receptor function. In animal studies, memantine has demonstrated neuroprotective properties, enhancing the function of the retina and visual pathways without causing harm to healthy eyes. Despite this, the involvement of increased glutamate levels in glaucoma is still controversial and not clearly established.[75] Large clinical trials have yet to demonstrate a definitive benefit of memantine in treating glaucoma. Specifically, two large, double-blind, placebo-controlled Phase III trials involving 2,296 patients with primary open-angle glaucoma (POAG) over four years found no significant slowing of visual field loss compared to placebo. Future research should focus on patients with early glaucoma and more uniform risk profiles for disease progression. Additionally, studies with longer durations, higher dosages, and different delivery methods of memantine may be necessary to fully assess its potential benefits in glaucoma management.[76]

3.19. Citicoline

Citicoline, or cytidine 5′-diphosphocholine, is a naturally occurring compound recognized for its potential neuroprotective benefits in glaucoma. Structurally, it is composed of cytidine linked through a diphosphate bridge to choline, enabling it to act as a precursor for synthesizing vital phospholipids such as phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, and cardiolipin. These phospholipids are essential components of neuronal cell membranes and play a key role in forming synaptic membranes, which facilitate the release and recycling of neurotransmitters including acetylcholine, dopamine, serotonin, and norepinephrine. Citicoline also helps reduce glutamate-induced excitotoxicity, enhances axonal transport, and lowers oxidative stress by increasing glutathione production.[77]

In animal studies, citicoline has shown significant neuroprotective effects by preserving retinal ganglion cell (RGC) density, improving visual acuity, and maintaining the integrity of the optic nerve's pre-chiasmatic white matter, all without affecting intraocular pressure (IOP). Early clinical research found that intramuscular citicoline improved visual field performance in patients with primary open-angle glaucoma (POAG), with sustained benefits over time.[78] Long-term oral administration has been associated with slower progression of glaucomatous damage, reflected in improved retinal nerve fiber layer (RNFL) and ganglion cell

complex thickness. Additionally, topical citicoline eye drops demonstrated positive effects on retinocortical function but caused more side effects than oral forms.

Citicoline's neuroprotective promise in glaucoma has prompted numerous ongoing clinical trials.[79] While initial preclinical and early clinical results are encouraging, larger, more rigorous studies are needed to confirm its efficacy and establish its role in glaucoma treatment. These investigations will help determine whether citicoline can become a standard therapeutic option for patients with glaucoma.

3.20. Nicotinamide

Nicotinamide, also known as vitamin B3 or NAM, is a precursor to nicotinamide adenine dinucleotide (NAD), an essential coenzyme involved in cellular metabolism. NAD levels naturally decline with age, contributing to mitochondrial dysfunction, inflammation, oxidative stress, and ultimately neurodegeneration.[80] Nicotinamide helps restore NAD concentrations, supporting mitochondrial function and cellular energy metabolism, while also playing roles in calcium balance, vascular regulation, and maintaining neuronal health.[81]

Studies in mice have demonstrated that high-dose oral nicotinamide can counteract age-related retinal NAD depletion. It protects retinal ganglion cells (RGCs) by preventing cell loss and nuclear shrinkage, enhancing mitochondrial health, and reducing oxidative damage associated with glaucoma. When combined with NADPH and N-acetylcysteine (NAC), nicotinamide has shown synergistic effects, decreasing apoptosis, axonal injury, and lipid peroxidation in RGCs, while also suppressing inflammation and glial activation in Müller cells.[82] This highlights its potential as a neuroprotective and anti-inflammatory therapy for glaucoma.

Human research supports nicotinamide's promise as well. Patients with primary open-angle glaucoma (POAG) exhibit significantly lower plasma NAD levels than healthy individuals, indicating systemic NAD deficiency in glaucoma. Supplementation with oral nicotinamide has been shown to improve RGC function independently of intraocular pressure. A Phase II clinical trial reported short-term visual improvements in moderate open-angle glaucoma patients treated with nicotinamide combined with pyruvate.

Several clinical trials are ongoing to assess the long-term effects of nicotinamide in glaucoma. The Glaucoma Nicotinamide Trial (TGNT) is evaluating neuroprotective benefits in 660 patients with open-angle glaucoma, and a Phase III randomized controlled trial is studying the impact of oral nicotinamide on visual field progression over 27 months.[83] These investigations aim to clarify nicotinamide's potential role in glaucoma therapy.

3.21. Insulin

Insulin plays a crucial role in the mTOR signaling pathway, which is vital for the energy metabolism of retinal ganglion cells (RGCs). It activates both mTORC1 and mTORC2 complexes, influencing neuronal survival, neurotransmission, and glucose uptake.[84] Disrupted insulin signaling has been associated with neurodegenerative conditions, including glaucoma. Insulin supports glucose transport, encourages dendritic regeneration, and aids in maintaining neuronal health. Activation of mTORC1 and mTORC2 by insulin is essential for dendrite repair and synapse restoration in RGCs. Intranasal insulin delivery has been found to effectively cross the blood-brain barrier without adverse effects and has demonstrated safety in treating Alzheimer's disease and mild cognitive impairment.[85] Although no clinical trials have yet tested insulin therapy in glaucoma patients, preclinical studies indicate that externally administered insulin may help protect RGCs. Overall, both intranasal and topical insulin hold promise as therapeutic options for neurodegenerative diseases, but additional research is necessary to confirm their effectiveness.

3.22. Resveratrol (RES)

Resveratrol (RES), a polyphenolic antioxidant, has demonstrated potential in slowing the progression of glaucoma by supporting the health of retinal ganglion cells (RGCs).[86] It promotes cell growth, reduces programmed cell death (apoptosis), and lessens oxidative stress, particularly in RGCs exposed to harmful agents like hydrogen peroxide. RES protects the axons of RGCs by blocking JNK protein phosphorylation and inhibiting the MAPK signaling pathway.[87] It helps maintain retinal function by regulating pathways involving HIF-1α, VEGF, and p38/p53, while also activating the PI3K/Akt pathway to enhance cell survival. Additionally, intravitreal delivery of RES has been effective in shielding RGCs from damage caused by elevated intraocular pressure.

4. Emerging Technologies in Glaucoma Neuroprotection

4.1. Stem cell therapy

Stem cell therapy has emerged as a promising approach for treating neurodegenerative diseases such as glaucoma by offering both regenerative and neuroprotective benefits. This therapy supports the regeneration of retinal ganglion cells (RGCs), encourages their differentiation into new functional cells, and fosters a neurotrophic environment that aids in the survival of damaged RGCs. Among the various types, mesenchymal stem cells (MSCs) are particularly notable for their ability to transform into neurons and glial cells. MSCs exert multiple therapeutic effects, including promoting neuronal growth, modulating immune and inflammatory responses, enhancing blood vessel formation, and reducing cell death and demyelination. They also secrete vital

neurotrophic and growth factors like PDGF, BDNF, CNTF, and GDNF, which support cell survival and tissue regeneration.

Animal studies have shown that MSCs, when injected into the eye, can preserve RGCs, reduce inflammation, and protect ocular structures. However, translating these findings into clinical success has been challenging. For instance, one clinical trial reported no visual improvement and noted serious complications such as retinal detachment, raising concerns about safety. Ongoing trials are now exploring various delivery methods and safety profiles of stem cell therapies in advanced glaucoma patients.

Human embryonic stem cells (hESCs) also show potential due to their ability to become any cell type, including RGCs. Preclinical studies have shown successful integration and light response mediation, though ethical and scientific concerns persist. Other stem cell types, including neuronal progenitor cells, oligodendrocyte precursor cells, and adipose-derived cells, are also under investigation. Despite the therapeutic promise, stem cell treatments face risks such as tumor formation, inflammation, and structural damage to the eye. Continued research, careful risk assessment, and large-scale clinical trials are essential to improve the safety and efficacy of stem cell therapy in glaucoma treatment.

4.2. Gene therapy

Gene therapy represents a promising approach for protecting and treating the optic nerve in glaucoma, offering the potential to manage and even reverse damage caused by the disease. This strategy involves altering specific genes linked to glaucoma development and delivering protective factors to support the survival of retinal ganglion cells (RGCs). Research has demonstrated that CRISPR-based editing of the myocilin gene can significantly reduce intraocular pressure and prevent damage in mouse models of glaucoma. Other genetic targets currently under study include tunica interna endothelial cell kinase (TEK), BDNF, and its receptor TrkB, all of which play key roles in maintaining RGC health. Additionally, various other genes are being explored for their unique functions in glaucoma therapy. These include CaMKII (involved in cell signaling), complement C3 inhibitor (linked to immune modulation), VEGF variants (regulating blood vessel growth), the AAV-γ-synuclein promoter, and anti-apoptotic genes like Bcl-XL and XIAP. Genes related to mitochondrial function (NMNAT1, SOD2), cellular repair (Protrudin), and neuronal survival (NFATc4, Tau, MAX) are also being investigated.

Despite its potential, gene therapy in glaucoma faces several challenges. These include the disease's complex genetic basis, difficulties in achieving efficient and targeted gene delivery, and concerns about the risk of unintended genetic changes (mutagenesis). However, advances in gene-editing technologies and improvements in whole-genome sequencing are paving the way for the discovery of new therapeutic targets and the refinement of current methods, potentially enhancing the effectiveness and safety of gene therapy for glaucoma.

4.3. Mitochondrial-targeted therapies and transplantation

Mitochondria are essential organelles responsible for cellular energy production and play a key role in regulating calcium balance, cell signaling, apoptosis, and synaptic function. Retinal ganglion cells (RGCs), which have high energy requirements, depend heavily on mitochondrial activity to maintain normal function. As a result, these cells are particularly vulnerable to mitochondrial dysfunction. Metabolic stress is a major contributing factor in the damage and degeneration of RGCs observed in glaucoma.

To combat this, several neuroprotective strategies have been explored. These include dietary interventions, antioxidant supplementation to reduce oxidative stress, as well as advanced treatments like stem cell therapy, gene therapy, and mitochondrial transplantation. Among pharmacological approaches, citicoline has been shown to enhance mitochondrial performance and support neuronal health, while nicotinamide, a form of vitamin B3, helps protect the optic nerve and maintain mitochondrial function.

One promising and emerging therapeutic option is mitochondrial transplantation, which involves transferring healthy mitochondria into damaged cells to restore normal energy production and cellular activity. This technique shows potential for treating conditions related to mitochondrial dysfunction, including glaucoma. Overall, targeting mitochondrial health is becoming a critical focus in the development of effective glaucoma treatments.

4.4. Nanotechnologies

Exosomes and nanoparticles are increasingly being explored as innovative therapeutic options for glaucoma. Exosomes are small extracellular vesicles that transport bioactive molecules, including proteins, lipids, and RNAs, and play a role in numerous physiological and pathological processes. In glaucoma models, exosomes have shown notable neuroprotective effects. For example, exosomes derived from bone marrow mesenchymal stem cells (BMSCs) have been found to enhance retinal ganglion cell (RGC) survival and promote axonal regeneration through mechanisms involving microRNAs. Similarly, exosomes from human umbilical cord-derived MSCs have been shown to support RGC survival and activate glial cells in animal studies.

Moreover, small extracellular vesicles engineered to overexpress microRNA-22-3p (miR-22) have demonstrated the ability to protect RGCs from apoptosis and maintain retinal function in NMDA-induced injury models. Despite these promising outcomes, treatments using BMSC- and MSC-derived exosomes have been linked to adverse effects such as excessive gliosis and inflammation. This highlights

the need for further investigation to improve the safety and therapeutic effectiveness of exosome-based treatments.

Nanoparticles also offer valuable potential in glaucoma therapy, particularly as drug delivery systems. They can encapsulate medications within a hydrophobic core, improving drug solubility, stability, and transport across biological barriers like the blood-retinal barrier. This enables more targeted and efficient delivery of therapeutic agents to ocular tissues. While both exosomes and nanoparticles present exciting possibilities for glaucoma treatment, their clinical application is still in early stages. Additional human studies are essential to better understand their therapeutic value, optimize delivery methods, and minimize potential risks, paving the way for their integration into future glaucoma management strategies

5. Conclusion

Glaucoma remains a significant global health burden, underscoring the need for innovative neuroprotective strategies to complement conventional IOP-lowering therapies. Several pharmacological agents—including brimonidine, neurotrophic factors, memantine, Ginkgo biloba extract, citicoline, nicotinamide, insulin, and resveratrol—have shown encouraging neuroprotective effects in preclinical models, with some reporting favorable outcomes in early-phase clinical trials. Beyond pharmacotherapy, emerging approaches such as stem cell therapy, gene therapy, mitochondrial-targeted interventions, and nanotechnology-based delivery systems present exciting opportunities for both neuroprotection and retinal ganglion cell (RGC) regeneration. However, significant translational challenges remain, including establishing long-term safety, optimizing delivery methods, and validating clinical efficacy. Large, well-designed clinical trials are essential to bring these strategies into routine practice. Looking ahead, the future of glaucoma management will likely integrate targeted pharmacological therapies with advanced technologies, forming a multimodal and comprehensive neuroprotective strategy. Personalized medicine approaches—guided by genetic and molecular profiling—may further refine treatment selection, offering tailored and more effective solutions to prevent irreversible vision loss.

6. Author Contribution

Prarthana Sonawane: Data curation; Yash Davane: Data curation; Siddhesh Pingale: Data curation; Tanvi Rede: Data curation; Ajay Bhagwat: Formal analysis; Rohit Doke: Conceptualization, Formal analysis, Writing – review editing.

7. Conflicts of Interests

The authors have no financial interests or conflicts of interests.

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