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SHORT REVIEW

Natural Bioactives in the Management of Glaucoma: A Recent Update

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Abstract

Medicinal plant-derived natural bioactives have drawn a lot of interest due to their potential as a treatment for glaucoma. Flavonoids, terpenoids, and alkaloids are among the phytochemicals with neuroprotective, anti-inflammatory, and antioxidant qualities that might reduce damage to retinal ganglion cells. Important plant-based substances, including bilberry (*Vaccinium myrtillus*), *Ginkgo biloba, Cannabis sativa, Panax ginseng, Scutellaria baicalensis* Georgi, and *Coleus forskohlii,* have shown promise in lowering Intraocular Pressure (IOP) and preventing neurodegeneration brought on by oxidative stress. These bioactive work by modifying oxidative stress biomarkers, including SOD, GS, 8-OHdG, MDA, PC, NO, and AGEs, as well as inflammation biomarkers like MMP-9, VEGF, TNF-alpha, IL-5, IL-12, IL-15, IFN-γ, MCP-1, and IL-8. They protect retinal ganglion cells by scavenging free radicals, lowering inflammatory mediators, and improving ocular blood flow. More studies into formulation techniques and bioavailability improvement are essential in creating successful plant-based therapies, as there is growing evidence that natural chemicals can help treat glaucoma. Our study highlights the need for more investigation into clinical trials to improve the bioavailability and therapeutic effectiveness of these plant-derived bioactives in treating glaucoma.

Major Findings: Natural compounds, such as *Ginkgo biloba, baicalein, forskolin*, and *ginsenosides*, exhibit significant potential, having neuroprotective, antioxidant, and IOP-lowering effects in the management of glaucoma.

Keywords: Biomarkers, Glaucoma Natural products, Neuroprotection, Ocular Drug Delivery

1. Introduction

In 2010, glaucoma was responsible for approximately 6.6% of global blindness cases, making it one of the leading causes of irreversible vision loss[1]. According to the World Health Organization (WHO) report on vision, glaucoma affects approximately 6.9 million of the 2.2 billion people who are thought to have vision impairment worldwide. Glaucoma is expected to affect approximately 111.8 million people between the ages of 40 and 80 globally by 2040[2]. Glaucoma is a complex condition with several risk factors that lead to structural alterations in the retina and optic nerve head, as well as Retinal Ganglion Cell (RGC) loss, as depicted in Figure 1[3]. The primary strategy for treating glaucoma is still lowering Intraocular Pressure (IOP), which is a significant cause of optic nerve damage. However, since several other variables contribute to the disease's course, it is clear that IOP by itself cannot adequately explain the disease's complicated pathogenesis[4]. Research on neuroprotection is expanding quickly. This subject is complex since it is a novel therapeutic option for debilitating conditions that can become worse even with the best care, like glaucoma. Given the widespread use of herbal remedies, eye care providers ought to inform their glaucoma patients about the treatment efficiency, safety, and efficacy. These days, treating eye problems with natural therapies, including vitamins, minerals, and plants, is growing in popularity[5]. Alternative drugs have been utilized by up to 52% of the general population and have a $109 billion global industry[6].

Nowadays, the pharmaceutical industry uses standardized methods to extract active chemicals from

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therapeutic plants. Prescription medications in the US are governed by the Food and Drug Administration (FDA), ensuring standards are followed. However, this strict regulatory system does not apply to dietary supplements or herbal medications[7]. Since glaucoma results in Retinal Ganglion Cell (RGC) degeneration, neuroprotection has gained more attention as a possible strategy to prevent or delay the structural and functional damage caused by the condition. Investigating the function of herbal medications in treating glaucoma may yield essential insights since natural remedies are becoming increasingly popular due to their perceived efficacy and decreased risk of adverse effects.

The increasing awareness of using plant-based bioactive substances, including baicalin, ginsenosides, quercetin, and anthocyanins for glaucoma treatment, influenced the selection of this strategy. These phytoconstituents have demonstrated encouraging neuroprotective, anti-inflammatory, and IOP-lowering properties in preclinical research. However, their low ocular bioavailability limits their clinical effectiveness. Therefore, this review highlights the therapeutic significance of these drugs and formulation techniques that can overcome delivery problems, such as cyclodextrin complexes, liposomes, and nanoemulsions.

Further, the review aims to evaluate the data regarding the most popular herbal remedies for managing and treating glaucoma. By examining existing scientific data, one can better comprehend the possible advantages of using these natural bioactives as a glaucoma adjunctive therapy.

This sign emphasizes the possible function of natural chemicals in reversing these alterations.

2. Natural Products Used to Treat Glaucoma

The therapeutic potential of natural products in treating glaucoma has attracted much interest, mainly because of their neuroprotective and antioxidant qualities. Antioxidants are a possible alternative therapy strategy, while oxidative stress and neuroinflammation are significant elements in the progression of glaucoma[8]. Lowering Intraocular Pressure (IOP) with pharmacological agents like IOP-reducing eye drops and surgical or laser-based interventions like trabeculoplasty, trabeculectomy, and deep sclerectomy is the primary strategy for managing glaucoma[9]. However, disease progression can still happen even after IOP levels have returned to normal. The elevated intraocular pressure affects neurotrophic factor transport, optic nerve injury, and retinal ganglion cells, as represented in Figure 2. The challenges associated with conventional treatments have generated attention in complementary and alternative therapies for treating glaucoma. Surveys indicate a notable frequency of CAM use among glaucoma patients, with reported adoption rates of 10% in Canada, 22% in Saudi Arabia, and as high as 67% in Palestine[10-12]. Many individuals utilizing these therapies have perceived them to be therapeutically beneficial, and the Clinical studies evaluating natural remedies for the treatment of glaucoma are mentioned in Table 1. Natural substances provide a strong

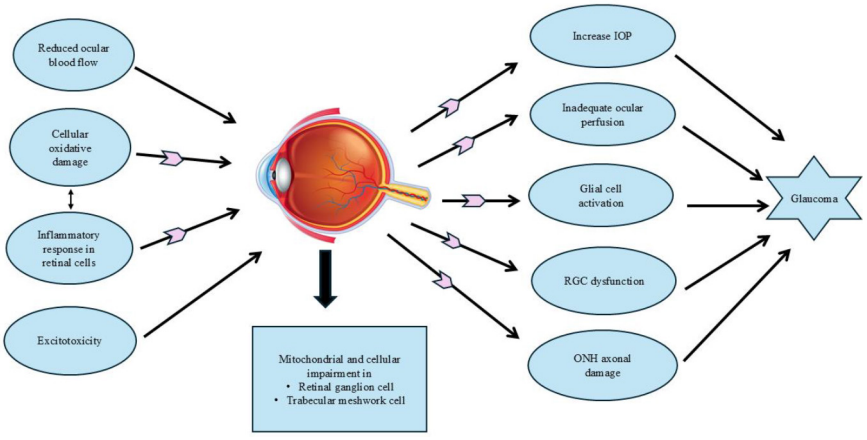


Figure 1. Contribution of oxidative stress, neuroinflammation, reduced blood supply to the eyes, and neurotoxic consequences to the pathological development of glaucoma.

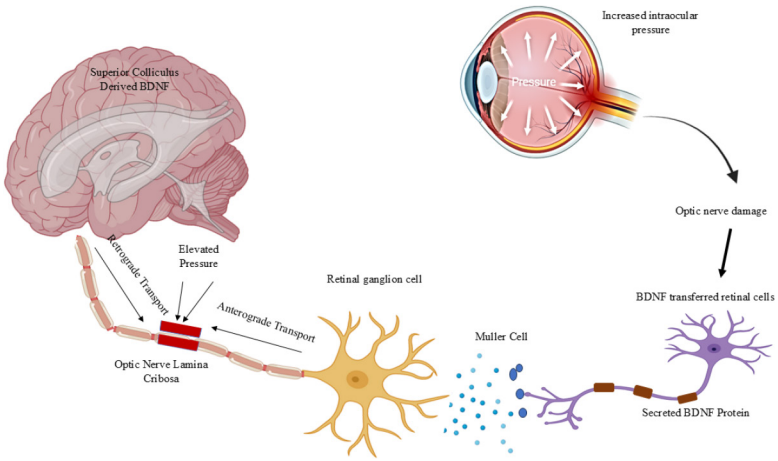


Figure 2. Effects of elevated intraocular pressure on neurotrophic factor transport, optic nerve injury, and retinal ganglion cells. It represents how axonal transport abnormalities, BDNF transfer, and Muller cells contribute to glaucomatous neurodegeneration[13].

substitute for synthetic medications because of their numerous modes of action, fewer adverse effects, and potential to treat underlying disease processes, including inflammation and oxidative damage. Synthetic drugs frequently have drawbacks, including adverse effects, possible resistance, and a limited ability to control symptoms rather than stop the growth of disease. Natural substances are being studied more and more to treat glaucoma more comprehensively for their dual functions in oxidative stress reduction and neuroprotection. Some natural bioactive compounds in the treatment of glaucoma have been presented in the preceding section. A summary of some plants gives limited glaucoma effectiveness, as in Table 2.

2.1 *G. biloba*

Ginkgo biloba Extract (GBE) originates from a native Chinese tree and is high in terpenoids and flavonoids. Over 60 bioactive substances are present, including 30 unique compounds that aren't present in any other natural source[14]. Furthermore, among elderly persons, it is one of the most often-used herbal supplements[15]. Among the many bioactive substances found in *G. biloba*, flavonoids are particularly important for their neuroprotective and antioxidant properties, making them highly essential to treating glaucoma. According to research, GBE maintained the integrity of the mitochondrial membrane in cultured neuronal cells and lowered ROS levels[16]. These effects are mediated through inhibition of caspase-3 activity, upregulation of the anti-apoptotic protein Bcl-2, and enhancement of mitochondrial antioxidant defense, which collectively prevent retinal ganglion cell apoptosis. It has been demonstrated that GBE has rheological effects that may increase blood viscosity and vasodilatory qualities, improving peripheral and coronary blood flow[17,18].

Furthermore, research has demonstrated that GBE reduces the activity of glial cells and other cells involved in low-grade inflammation[19]. Its anti-inflammatory, vasoregulatory, and antioxidant qualities help qualify it as a neuroprotective agent, making it a viable treatment choice for managing glaucoma. There have been four RCTs (Randomized Controlled Trials) that have looked into how GBE affects glaucoma. Patients with Normal Tension Glaucoma (NTG) were involved in the first research, a double-blind crossover experiment. Those individuals were enrolled into two groups and given either GBE for 4 weeks, followed by an 8-week placebo, or the reverse order[20]. Compared to the baseline, Visual Field (VF) indices showed a considerable improvement following supplementation with GBE. However, this benefit did not last beyond the washout period, and there were no apparent changes in Intraocular Pressure (IOP). A comparable crossover investigation was conducted, which did not confirm these results and found no noteworthy variations in IOP[21]. The treatment regimens and durations in the 2 investigations were the same; however, the second research included individuals with recently diagnosed NTG who were already taking topical hypotensive drugs. The 1st study

included a European population, whereas the 2nd study had an Asian group, suggesting that variations in patient ethnicity may have also contributed.

Flavonoids, which are abundant in *G. biloba*, are substances that may provide therapeutic advantages for glaucoma therapy. Supercritical carbon dioxide extraction is used to extract flavonoids and terpenoids. In this method, carbon dioxide is used as a solvent at high temperatures and pressure, which produces highly pure extracts with minimal solvent residue. These techniques maintain the bioactivity of phytochemicals without causing heat degradation; they are recommended for sensitive phytochemicals[22,23].

2.2 Bilberry *(V. myrtillus)*

The bilberry, also known as the European blueberry, whortleberry, or huckleberry, is a tiny shrub member of the *Vaccinium* genus. In both the European Pharmacopoeia and historical texts, it is identified as *Myrtilli Fructus*[24]. The shrub has a 35-60 cm maximum height. The black or blue fruit is spherical, around 5 to 9 mm across[25]. Bilberries have been utilized for a long time to treat eye disorders[26]. Bilberries low adaptation to environmental conditions makes cultivation challenging. In addition, shrub development and fruit production are greatly influenced by weather patterns, soil composition, light exposure, and gardening methods[27]. Bilberries are abundant in phenolic compounds, such as tannins and ellagitannins, and flavonols like quercetin and catechins that treat glaucoma. Recent research on mice investigated the effects of oral bilberry extract anthocyanins at doses of 100 mg/kg/day and 500 mg/kg/day. Bilberry extract was found to increase the production of molecular chaperones, particularly glucose-regulated protein 78 (Grp78) and Grp94, and to aid in reducing Retinal Ganglion Cell (RGC) death. These neuroprotective benefits are obtained through suppressing NF-κB signalling, which lowers pro-inflammatory cytokines that cause glaucomatous damage, and activating the Nrf2 signalling pathway, which improves antioxidant defense in retinal ganglion cells. Bilberry extract's neuroprotective properties following injury to the visual nerve may be attributed to this rise in protein levels[28]. A retrospective analysis of 332 NTG patients evaluated the effects of *G. biloba* Extract (GBE) (n = 103), anthocyanins (n = 132), and no therapy (n = 97). The findings indicated that anthocyanin and GBE treatment may help NTG patients visual function by improving the mean deviation of the Humphrey Visual Field (HVF)[29]. Anthocyanins are essential for both retinal function and health. According to research on bilberries and blackcurrants, these substances support improved visual performance by enhancing retinal microcirculation, lowering oxidative stress, and maintaining retinal structure[30]. In a study by Milbury *et al.*, bilberry-derived anthocyanins and phenolic compounds can activate enzymes like GST-pi, Retinal Pigment Epithelium (RPE) cells, and heme-oxygenase. This suggests that the chemicals may have a role in boosting antioxidant defense by activating controlled genes[31].

Several sophisticated extraction methods have been developed to separate anthocyanins from bilberries *(V. myrtillus),* which have potential advantages in treating glaucoma. One such method is Ultrasound-Assisted Extraction (UAE), in which ultrasonic vibrations break down plant cell walls to increase the release of anthocyanins into the solvent solution. This method increases extraction efficiency without affecting antioxidant activity. Supercritical carbon dioxide extraction with ethanol as a cosolvent is another sophisticated technique that enables the selective recovery of phenolic and anthocyanin chemicals under regulated temperature and pressure conditions[32,33].

2.3 *Marijuana (C. sativa)*

Cannabis, sometimes known as *marijuana*, thousands of years has been spent using in medicine, but it has not always been accepted in Western healthcare[34]. In 1937, marijuana became illegal in the United States. However, California was the 1st state to authorize its usage for medicinal purposes in 1996. Since then, medical marijuana has been licensed in 32 more states and the District of Columbia. More people with glaucoma are considering using marijuana as a treatment option as legalization and social acceptability increase[35]. Among the more than 400 chemical compounds found in marijuana, the main components that give it its physiological effects are Cannabidiol (CBD) and Δ-9-Tetrahydrocannabinol (THC)[36].

Hepler and Frank observed that using marijuana reduced intraocular pressure by around 30% in a small sample of healthy individuals[37]. However, only 60-65%

of the subjects showed this impact[38]. According to research conducted in Colorado, only 7.6% of glaucoma experts had ever suggested marijuana for glaucoma, 51% of dispensaries advocated it, and 2.6% of patients had used it. The findings highlight the gap between dispensary advice and medical guidance, and there is a need for better patient education[39]. The particular mechanism by which marijuana affects the eyes is yet unknown[36].

CB1 and CB2 are the 2 primary G-protein-coupled receptors that comprise the endocannabinoid system. CB1 is found on presynaptic neurons and participates in Schlemm's canal, trabecular meshwork, ciliary muscles, and ciliary body. It also suppresses the release of neurotransmitters. Both trabecular and uveoscleral outflow are facilitated by their presence, which suggests a function in controlling the formation of aqueous humor. Activation of CB1 receptors by THC reduces intraocular pressure by inhibiting adenylate cyclase, decreasing cAMP levels, and modulating aqueous humor secretion *via* effects on the ciliary epithelium. Furthermore, activation of the CB2 receptor lowers neuroinflammation by suppressing pro-inflammatory cytokines, including TNF-α and IL-6, perhaps providing neuroprotection to retinal ganglion cells. Meanwhile, CB2 regulates the release of cytokines in the immune system[40]. Another study found that THC has a comparatively short-lived effect on blood pressure, lasting about 3 to 4 hours. Numerous techniques, including topical, intravenous, sublingual, oral, and inhalation, can be used to administer THC. The limited ocular penetration of cannabis extracts, which are highly lipophilic and have low aqueous solubility, makes topical administration, surprisingly, the least effective treatment for glaucoma[41]. When applied topically, CBD was shown to raise Intraocular Pressure (IOP) in mice eyes, in contrast to THC, with prominent effects occurring 1 and 4 hours after treatment[42].

Several techniques that are involved in the extraction and purification of cannabinoids from *C. sativa* have been developed; one of the methods is the supercritical carbon dioxide extraction technique used to separate cannabinoids from *C. sativa*. This method produces a high-purity extract with little solvent residue by dissolving lipophilic substances like THC and CBD in carbon dioxide at high pressure and temperature. Ethanol can also be used as a cosolvent to increase yield and selectivity. This approach is highly recommended due to its environmental sustainability, safety, and capacity to maintain the cannabinoids' bioactivity[43].

2.4 *S. baicalensis* Georgi

Scutellaria baicalensis Georgi, often called the Baikal skullcap or Chinese skullcap, is mainly used in traditional Chinese medicine[44]. The properties of this plant include antiviral, antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, antibacterial, liver-protective, and anticancer effects[45-47]. *S. baicalensis* uses several kinds of mechanisms in its mode of action. One important flavonoid, baicalein, minimizes apoptosis caused by Ocular Hypertension (OHT) by upregulating the anti-apoptotic protein Bcl-2, which lowers Intraocular Pressure (IOP) and shields retinal ganglion cells[48].

Both baicalin and baicalein have demonstrated neuroprotective properties against oxidative stress in RGCs. Baicalein effectively protected Retinal Ganglion Cells (RGCs) in 3 different oxidative stress models, according to an *in vitro* study conducted using the RGC-5 cell line[49]. Baicalin also demonstrated dose-dependent neuroprotection in RGC-5 cells against oxidative stressors such as hydrogen peroxide and serum deficiency[50]. According to these findings, baicalin and baicalein may play a part in treating glaucoma as they have strong neuroprotective qualities that may help stop the oxidative stress-induced loss of Retinal Ganglion Cells (RGCs). The Nrf2/HO-1 signalling pathway is activated by baicalin and baicalein, which strengthen antioxidant defense in retinal ganglion cells and have neuroprotective benefits.

Additionally, they hinder the activation of NF-κB, which lowers the production of inflammatory cytokines, including TNF-α and IL-1β. Furthermore, baicalein inhibits apoptotic pathways by maintaining mitochondrial function and suppressing caspase-3 activity. Furthermore, baicalin therapy dramatically increased cell viability, decreased ROS generation, and suppressed the formation of endothelial leukocyte adhesion in cultured human TM cells exposed to H_2O_2, both the pro-inflammatory factor IL-1 and molecule-1 (ELAM-) and the pro-inflammatory factor IL-1[51]. When taken orally, Baikal skullcap is regarded as possibly safe for the majority of people. There have been reports of fever and lung irritation among users of the Baikal

skullcap, which may make them drowsy. However, there is insufficient data to determine if Baikal skullcap was the direct source of these negative consequences.

The chemicals baicalin and baicalein, known for potentially providing neuroprotective benefits in glaucoma treatment, can be extracted and isolated from *S. baicalensis* (Chinese skullcap) using High-Speed Counter-Current Chromatography (HSCCC). This method utilizes two immiscible liquid phases, enabling high-purity separation without solid supports. Another effective technique involves ionic liquid-based biphasic systems that use eco-friendly solvents to achieve high yields of flavonoids with minimal degradation risk. These methods preserve the bioactivity of essential components while improving the extract's quality[52].

2.5 *P. ginseng*

Ginseng is part of the *Araliaceae* family's *Panax* genus, which has nine different species, including *P. ginseng*, also called Korean ginseng, *P. ginseng*, often called Chinese ginseng, *Panax japonicum*, also called Japanese ginseng, and *Panax quinquefolius*, also called American ginseng[53]. For a long time, Ginseng has been considered the supreme herb because of its well-established capacity to enhance people's physical and mental well-being[54]. Many phytochemicals, including phenols, acidic polysaccharides, and ginsenosides (triterpenoid saponins), are found in ginseng[55]. Instead of focusing on whole ginseng or its other components, most studies have concentrated on certain ginsenosides to treat various illnesses. The primary active components in ginseng are called ginsenosides. Under excessive glutamate, the ginsenoside saponins Rb1 and Rg3 could stop mechanisms that trigger apoptotic cascades, such as lipid peroxidation[56]. Ginsenoside Rb1 prevents retinal ganglion cells from dying because hydrogen peroxide causes oxidative damage. This protective effect is mediated by activating the PI3K/Akt signalling pathway, which promotes cell survival and upregulates Bcl-2 expression while inhibiting pro-apoptotic markers like Bax and caspase-3. Ginsenosides also mitigate oxidative stress by increasing the activity of antioxidant enzymes including Glutathione Peroxidase (GPx) and Superoxide Dismutase (SOD), which helps to preserve retinal ganglion cells in glaucoma.

Additionally, glaucoma patients taking 3 grams of Korean red ginseng daily for 4 weeks reported less discomfort in their eyes and better daytime vision[57]. According to clinical experiments on individuals with glaucoma, Korean Red Ginseng (KRG) had taken orally notably enhanced retinal circulation in the temporal peripapillary regions. Vascular enlargement and reduced blood flow are significant warning signs for glaucoma-related optic nerve damage; therefore, enhancing retinal blood flow may help avoid it[58]. Furthermore, following 8 weeks of Korean Red Ginseng treatment, glaucoma patients revealed a substantial increase in tear film stability, indicating that KRG may help alleviate dry eye syndrome in glaucoma patients[59]. Thus, ginseng's anti-apoptotic and antioxidative qualities are advantageous in ophthalmic diseases and to separate ginsenosides from *P. ginseng*, Pressurized Liquid Extraction (PLE) and Ultrasound-Assisted Extraction (UAE) are 2 of the most used techniques for ginsenoside extraction from *P. ginseng*. PLE produces large quantities of ginsenosides with slight degradation by effectively isolating bioactive molecules using high pressure and temperature. UAE uses ultrasonic waves to break down cell walls and improve solvent penetration, which makes it a quicker and more effective method of extracting phytochemicals[60,61].

2.6 *C. forskohlii*

For many years, *Ayurvedic* and Hindu traditional medicine have utilized *C. forskohlii*. Its root, which has long been prized for its therapeutic properties, includes the main bioactive ingredient, forskolin[62]. A diterpenoid known as forskolin is abundant in C. *forskohlii's* (*C. forskohlii*) leaves, roots, and tubers mode of action is activating the adenylyl cyclase. This enzyme raises the concentration of the cyclic Adenosine Monophosphate (cAMP) in cells. Then, the improved cAMP functions as a signalling molecule that controls several biological functions, including secretion, energy balance, and ion transport. In ocular physiology, the rise in cAMP affect's ciliary epithelial function, lowering aqueous humor production and ultimately lowering Intraocular Pressure (IOP). Therefore, forskolin might be used as a treatment for glaucoma[56]. Forskolin reduces intraocular pressure by activating ciliary epithelial cells adenylyl cyclase, which raises cAMP levels and inhibits aqueous humor formation. Furthermore, in retinal ganglion cells, forskolin has neuroprotective benefits by upregulating Bcl-2 and decreasing inflammatory

cytokines like TNF-α and IL-6 while downregulating pro-apoptotic markers like caspase-3 and Bax. The primary bioactive ingredient, forskolin, has been demonstrated to inhibit mast cell and basophil degranulation, which lowers histamine release. In an isolated bovine eye model, an earlier study showed that arterial perfusion of forskolin at doses of 30, 100, and 1000 nM dramatically decreased the rate of aqueous humor generation[63]. A double-blind randomized controlled experiment showed that forskolin can lower Intraocular Pressure (IOP), which may cause its hypotensive effect[64]. IOP dramatically dropped among individuals treated with 1% w/v forskolin aqueous eye drops for primary open-angle glaucoma, which were given as 2 drops every 3 days for 4 weeks[65]. Studies on animals have proven that in models of hypertension, glaucoma, and optic nerve injury in rodents, to prevent the loss of RGCs, a diet rich in forskolin, homotaurine, spearmint, and vitamins B1, B6, and B12[65].

Research indicated that lowering the release of cytokines like iNOS, IL-6, and TNF-α, the forskolin supplement combination might lessen inflammatory processes. Ultimately, this decrease prevented RGC death and maintained visual function by lowering apoptotic indicators such as the Bax/Bcl-2 ratio and active caspase-3 levels[66]. In mouse models of glaucoma, the forskolin supplement combination did not show any effect on increasing IOP, in contrast to the results of clinical investigations. Therefore, an investigation of the impact of forskolin in glaucoma clinical research is necessary. To get forskolin in its active state, the hydrotropic extraction method is commonly used to extract forskolin, increasing its water solubility and producing up to 85% pure forskolin. This technique is very effective and environmentally friendly, particularly for isolating lipophilic chemicals like diterpenoids. Furthermore, the Three-Phase Partitioning (TPP) method recovers forskolin with minimum degradation and high purity by combining t-butanol, water, and ammonium sulfate[67,68]. The various bioactive compounds that have a role in glaucoma therapy are mentioned in Table 3.

3. Biomarkers of Oxidative Stress and Inflammation in Glaucoma

Recent research on diagnosing ocular diseases increasingly focuses on identifying specific biomarkers in ocular or systemic fluids because of their promising clinical applications. According to how they are collected, biomarkers are categorized as invasive from aqueous fluid, vitreous, or retinal samples. In contrast, non-intrusive biomarkers might come from biological fluids like urine, plasma, or tears. Nevertheless, it might be challenging to compare results from different research inquiries due to variances in the analytical methods employed for biomarker identification and the varying illness stages of the recruited individuals.

This section provides an overview of the biomarkers associated with inflammatory reactions and oxidative stress connected to the glaucoma pathophysiology. Figure 3 illustrates the interaction between inflammation, oxidative stress, and neuroprotection in glaucoma, highlighting the roles of Muller glia, bipolar cells, and retinal epithelium in maintaining retinal homeostasis and regulating neurotrophic factors.

Figure 3 highlights the role of Reactive Oxygen Species (ROS) in Retinal Ganglion Cell (RGC) apoptosis and neurodegeneration. Mitochondrial dysfunction leads to excessive ROS production, triggering oxidative stress and inflammation. Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) contribute to RGC damage. Muller glia, bipolar cells, and retinal epithelium regulate oxidative stress responses and neurotrophic factor release (BDNF, NGF) for retinal survival. The balance between oxidative damage and antioxidant pathways influences glaucoma progression and potential therapeutic strategies.

AGEs, or advanced glycation end products, may be biomarkers for glaucoma prognosis and early identification found that AGE levels were much greater in glaucoma patient's blood and aqueous fluid samples compared to the control group[94]. Another way to monitor AGE accumulation is with a sensor that detects skin autofluorescence levels directly related to AGE concentration[95].

Compounds originating from oxidative stress are suggested as possible indicators. Patients suffering from POAG[96] have higher levels of free radical Nitric Oxide (NO) in their aqueous fluid and serum[97]. Among the most regularly used biomarkers are Protein Carbonyls (PC), which are universally acknowledged as essential markers of protein oxidation. Patients with Pseudoexfoliative Glaucoma (PXG) have demonstrated increased levels in their serum and aqueous humor[94,96]. Lipid peroxidation produces Malondialdehyde (MDA),

Table 1. Clinical studies evaluating natural remedies for the treatment of glaucoma

S. No	Natural Compound	Study Type	Mode of Action	Result	References
1	Citicoline	Cross-over, randomized, placebo-controlled study.	Citicoline supports mitochondrial activity, neurotransmitter production, and phospholipid metabolism, which improves neuronal function and may improve visual processing and Retinal Ganglion Cell (RGC) survival.	Compared to a placebo, citicoline oral solution dramatically enhanced glaucoma patients quality of life and visual function metrics, indicating a neuroprotective effect in disease treatment.	[69]
2	Homotaurine	Clinical study (human trial).	The supplement's ingredients may help retinal ganglion cells mitochondria function, neuroprotection, and antioxidant effects. While homotaurine has neuroprotective properties, forskolin decreases the formation of aqueous humor.	According to the study, POAG patients who took the supplement regularly could preserve their visual function, suggesting possible neuroprotective advantages separate from lowering Intraocular Pressure (IOP).	[70]
3	*G. biloba* extract	Clinical study.	GBE may help with visual field degradation by improving ocular blood flow and reducing peripheral vasospasm.	The study discovered that certain NTG patients, especially those with peripheral vasospasm, improved visual field damage after receiving GBE.	[71]
4	Forskolin	Open, case-controlled study.	Forskolin reduces intraocular pressure by raising cAMP, while rutin enhances ocular blood flow and offers antioxidant defense.	IOP decreased by 10% while taking supplements of forskolin and rutin; in patients whose baseline IOP was ≥21 mmHg, this reduction was 15%, while controls exhibited no change.	[72]
5	Ginseng	A prospective, double-masked, randomly selected trial.	Enhancing ocular perfusion with red ginseng may increase contrast sensitivity.	In individuals with early or moderate glaucoma, contrast sensitivity, and ocular discomfort improved during the day, whereas contrast sensitivity improved at night.	[57]
6	Vitamin B3	Randomized, crossover, double-masked clinical study.	By raising NAD+ levels, nicotinamide (Vitamin B3) supplementation supports the activity of retinal ganglion cells.	Vmax ratio improved by 12.6%; 27% had ≥1 dB visual field improvement; PhNR Vmax improved by 14.8% on nicotinamide compared to 5.2% on placebo.	[73]
7	Hesperidin, crocetin, and tamarindus	Single-arm, prospective study.	Antioxidant supplementation (hesperidin, crocetin, and *T. indica*) reduces oxidative stress.	A significant drop in 8-OHdG levels at weeks 4, 8, 12, and 16, with a notable rise in BAP at weeks 8 and 12 in severe oxidative stress cases.	[74]
8	Coenzyme Q10	A controlled, prospective clinical study.	Coenzyme Q10, in combination with vitamin E, improves visual cortical responses (VEP) and inner retinal function (PERG).	After 6 and 12 months, the therapy group showed a significant increase in PERG P50-N95 and VEP N75-P100 amplitudes ($P<0.01$) and reduced PERG P50 and VEP P100 implicit times, with no changes in the control group.	[75]

Table 2. A summary of some plants gives limited effectiveness in glaucoma

S. No	Natural Compound	Mechanism of Action	Reason for Limited Effectiveness	References
1	Resveratrol	Enhances MMP-2 activity and lowers oxidative stress in glaucoma by exhibiting anti-inflammatory, anti-apoptotic, and antioxidant properties in trabecular meshwork cells.	Low bioavailability, few clinical investigations, and the requirement for formulations suitable for long-term IOP reduction.	76
2	Quercetin	Quercetin protects retinal ganglion cells by reducing reactive oxygen species and demonstrating antioxidant qualities.	Despite its antioxidant properties, quercetin's efficacy in treating glaucoma is limited by its low bioavailability and lack of clinical research.	77
3	Hesperidin	lowers IOP, improves BMP4 signaling, and has neuroprotective and antioxidant properties that shield RGCs.	Inadequate clinical research and the requirement for efficient delivery systems.	78,79
4	Curcumin	Curcumin lowers retinal ganglion cell oxidative stress and apoptosis by exhibiting anti-inflammatory and antioxidant qualities.	Curcumin's potential for glaucoma treatment is limited by low bioavailability and insufficient clinical studies.	80
5	Caffeine	Caffeine uses anti-inflammatory and antioxidant pathways to provide neuroprotective effects on retinal ganglion cells.	An excessive amount of coffee may raise intraocular pressure, preventing any neuroprotective effects.	80
6	Saffron	Saffron has neuroprotective and antioxidant properties.	A lack of clinical evidence and data on intraocular pressure-lowering limits efficacy in treating glaucoma.	81
7	Rutin	RGCs are protected by blocking pro-apoptotic pathways, lowering IOP, and increasing neurotrophic factors.	Inadequate absorption and limited human experiments.	82
8	Chrysin	Improves cognitive functions and has anti-inflammatory and neuroprotective properties.	Limited medicinal uses and a quick metabolism.	83

Table 3. Bioactive compounds isolated from medicinal plants and their role in glaucoma treatment

S. No.	Plant Name	Class of Bioactive Compounds	Examples of Bioactive Compounds	Function in the Treatment of Glaucoma	References
1	*G. Biloba*	Flavonol glycosides	Kaempferol, isorhamnetin, and quercetin	Antioxidant, neuroprotective, lowers RGC damage and oxidative stress.	84,85
		Biflavones	Ginkgetin and bilobetin	Enhances blood flow, reduces inflammation, and stops neurodegeneration.	86
		Terpenoids	Ginkgolides, bilobalide	Neuroprotection, vasodilation, and oxidative stress reduction	87
2	Bilberry (*V. myrtillus*)	Anthocyanins	Flavonoid anthocyanosides	Antioxidant that lowers inflammation, strengthens collagen, and promotes vascular health.	29,88
3	Marijuana (*C. sativa*)	Phytocannabinoids	Cannabidiol and Δ-9-tetrahydrocannabinol	Reduces Intraocular Pressure (IOP) and has neuroprotective benefits.	89
4	*S.baicalensis* Georgi	Flavonoids	Baicalein, wogonin and baicalin	Anti-inflammatory, lowers IL-8, and shields RGCs	90,91
5	*P. ginseng*	Triterpenoid saponins	Ginsenosides	Prevents apoptosis pathways and preserves RGCs	55,92
6	*C. forskohlii*	Diterpenoid	Forskolin	Reduces IOP, promotes vasodilation, and has anti-inflammatory properties	93

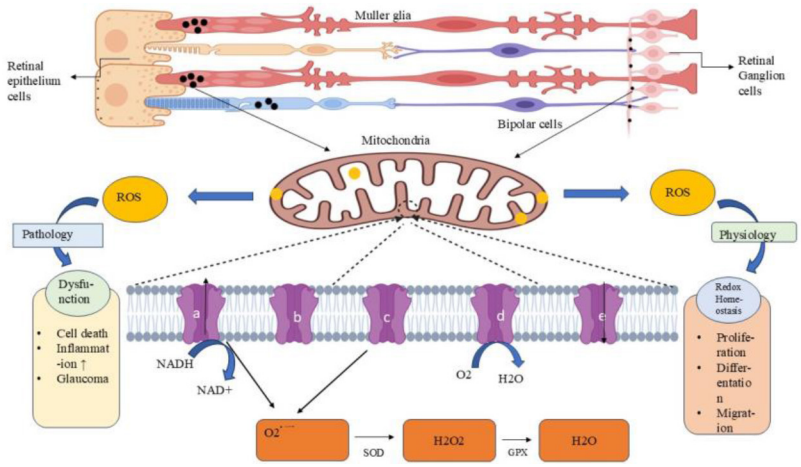


Figure 3. Oxidative stress and neuroprotective pathways in glaucoma.

which is seen in higher concentrations in the plasma and the aqueous humor of glaucoma patients[96,98-101]. Malonyl dialdehyde levels are a crucial indicator of the advancement of glaucoma as they seem to be connected to the degree of visual field loss in PACG and POAG[102,103]. Glaucoma patients' blood and aqueous fluid had greater levels of the biomarker of oxidative DNA damage, 8-hydroxy-2-deoxyguanosine (8-OHdG), than controls[104-108]. According to Kondkar *et al.*, the levels of 8-OHdG in plasma and aqueous humor are positively correlated 8-OHdG had a significant rate of false positives when evaluated with an ELISA kit, which suggests that it may not be a viable clinical biomarker for POAG[109]. This biomarker can also be found in urine, albeit the association is less effective. Thus, a reduction in antioxidant capacity is associated with increased oxidant agents. In this regard, the significantly reduced concentration of antioxidants such as Glutathione Synthase (GS) and SOD in POAG patients relative to controls raises the possibility that they may be used as biomarkers.

Many cytokines and chemokines are released as a result of the inflammatory response. Studies have shown that tear samples from glaucoma patients had higher amounts of IL-4, IL-12, IL-15 (110), IL-6 (111), and IL-8[99]. According to Agarkov *et al.* the tear films IL-2, IL-17, and IL-8 may be helpful to indicators for glaucoma diagnosis and prognosis[112]. Tear samples have drawn clinical attention as a non-invasive substitute for the invasive process of collecting aqueous humor samples. However, research evaluating the relationship between tear and aqueous humor composition has found no association[110,113]. Patients suffering from different types of glaucoma were discovered to possess higher levels of IL-5, IL-12, IL-15, IFN-γ, Monocyte Chemoattractant Protein-1 (MCP-1), interferon gamma-induced protein-10 (IP-10), IL-8, Macrophage Inflammatory Protein-1 alpha (MIP-1α), and Macrophage Inflammatory Protein-1 beta (MIP-1β)[114-118,110].

According to Chono *et al.* IL-8 showed the most incredible odds ratio between PXG and Neovascular Glaucoma (NVG), and its levels were associated with visual field abnormalities and preoperative Intraocular Pressure (IOP) in PXG patients[119]. And their findings, IL-8 in the aqueous humor could predict surgical results in cases with refractory glaucoma. There has been discussion over the expression of Tumor Necrosis Factor-alpha (TNF-α) since high levels of this protein have been linked to RGC mortality in glaucoma patients. POAG and PXG have been linked to increase TNF-α levels in plasma and aqueous humor[120-124], indicating that it may be a biomarker for the diagnosis and development of glaucoma[122]. TNF-α may also predict surgical results in the treatment of glaucoma[125]. The cytokine Vascular Endothelial Growth Factor (VEGF) is essential for inflammation and neovascularization. POAG is linked to increased VEGF levels in the aqueous fluid, which are primarily associated with Neovascular Glaucoma (NVG)[116,126-129]. VEGF expression is believed to be connected to the intensity of glaucoma, aiding the beginning and development of Neovascular Glaucoma (NVG), and its levels have

been observed to correlate with other cytokines. Compared to controls, patients with POAG have often shown higher MMP-9 activity in their aqueous humor and tear samples and in the early stages of PACG, POAG, and PXG[116,130]. To predict the beginning and progression of POAG, a linear multivariate regression model has been developed using the levels of MMP-9 in the tear film[131]. The central inflammation and oxidative stress indicators are also mentioned in Table 4.

Table 4. The main inflammation and oxidative stress indicators in clinical trials analyzing their association with glaucoma

S. No.	Disease	Molecular Disorder	Biomarkers	References
1	Glaucoma	Inflam mation	MMP-9	116
			VEGF	126
			TNF-alpha	121
			IL-5, IL-12, IL-15 IFN-, (MIP-1) IL-8, MCP-1(α) (IP)-10	108,114
			IL-2, IL-17, IL-8	112
			IL-4, IL-12, IL-15 IL-6, IL-8	111
2	Glaucoma	Oxidative stress	SOD and GS	107
			8-OHdG.	104
			MDA	132,133
			PC	94,132
			NO	96
			AGES	94

4. Formulation Techniques and Challenges with Bioavailability

Natural bioactives can potentially treat glaucoma, but their clinical use is frequently limited by their quick pre-corneal elimination, low permeability across ocular barriers, and poor aqueous solubility. Novel medication delivery methods, such as nanoformulation that enhance the solubility, bioavailability, and retention of phytoconstituents at the ocular site include liposomes, nanoemulsions, polymeric nanoparticles, and cyclodextrin inclusion complexes. These delivery systems have effectively integrated natural glaucoma treatments, improving their therapeutic results and reducing systemic adverse effects. Some formulations prepared using bioactives for the treatment of glaucoma are depicted in Table 5.

5. Conclusion and Future Perspective

This review emphasizes the potential of some natural products; particularly forskolin, *P. ginseng*, Bilberry, Baicalein, Marijuana, and *G. biloba* Extract (GBE), as promising adjunctive therapies in managing glaucoma. These products are especially useful in addressing the drawbacks of traditional treatments like prostaglandin analogs and β-blockers. These restrictions include problems with patient compliance, possible systemic adverse effects, and inadequate absorption. These natural substances are appealing because of their diverse modes of action, which target key components of the pathophysiology of glaucoma. GBE has anti-inflammatory, vasoregulatory, and antioxidant

Table 5. Plant-based bioactives in glaucoma: Existing formulations and their benefits

S. No	Bioactive Compound	Formulation Type	Benefits of glaucoma treatment	References
1	Baicalein	Liposomal formulation.	Increases corneal penetration and gives RGCs antioxidant treatment; the release is stable for 90 days.	134
2	Forskolin	1% aqueous eye drops.	Clinically demonstrated to considerably reduce intraocular pressure in open-angle glaucoma in comparison to timolol.	135
3	Ginsenoside Rg3	Liposome formulation (RGC targeted).	Prevents retinal damage by acting as an antioxidant and anti-inflammatory.	136
4	Anthocyanins	Liposomal or nano-emulsion system.	Increase corneal retention and stability while improving the administration of antioxidants.	137
5	*G. biloba* extract (EGb 761)	Topical eye drops.	Significantly decreased steroid-induced rise of intraocular pressure and maintained trabecular meshwork function in a glaucoma rabbit model.	138

properties. Bilberry has neuroprotective effects and enhances neuronal conduction. Marijuana may help to stop the retinal ganglion cells demise, while forskolin decreases IOP by influencing the formation of aqueous fluid. While these drugs target important indicators such as inflammatory cytokines (TNF-α, IL-6, IL-8), oxidative stress markers (reactive oxygen species, malondialdehyde), and neurotrophic factors, their practical use is currently limited by issues including poor ocular penetration and quick removal. Future studies should integrate these natural compounds into advanced ocular delivery systems, including liposomes, nanoemulsions, cyclodextrin inclusion complexes, and in situ gels, to improve bioavailability and targeted administration. Such approaches have been shown to enhance corneal permeability, increase solubility, and provide sustained drug release, key factors in improving the therapeutic potential of poorly soluble phytoconstituents. Their safety and effectiveness will also need to be confirmed by thorough, long-term clinical trials, and research on individualized treatment plans informed by biomarker analysis will be necessary. In the end, natural products have the potential to support more comprehensive and successful approaches to glaucoma management by addressing these issues and expanding our knowledge of their mechanisms. This would enhance current treatments and improve outcomes for patients at risk of losing their vision.

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7. Author Contribution

All authors contributed to the study's conception and design. DB performed a review of literature resources and writing of the first draft. RM and AR performed conceptualization, curation of literature, and editing. RKM validated scientific content. All authors have read and agreed to the published version of the manuscript.

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