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Herbal Remedies for Glaucoma

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Abstract: *Glaucoma is one of the leading causes of unrecoverable blindness. It's generally caused by increased intraocular pressure, which results in damage of the optical whim-whams and retinal ganglion cells, eventually leading to visual field dysfunction. Still, indeed with the use of intraocular pressure-lowering eye drops, the complaint still progresses in some cases. In addition to mechanical and vascular dysfunctions of the eye, oxidative stress, neuro inflammation and excitotoxicity have also been intertwined in the pathogenesis of glaucoma. Hence, the use of natural products with antioxidant and anti-inflammatory parcels may represent an indispensable approach for glaucoma treatment. The present review highlights recent preclinical and clinical studies on colorful natural products shown to retain neuroprotective parcels for retinal ganglion cells, which thereby may be effective in the treatment of glaucoma. Intraocular pressure can be reduced by baicalein, forskolin, marijuana, ginsenoside, resveratrol and hesperidin. Alternately, Ginkgo biloba, Lycium barbarum, Diospyros kaki, Tripterygium wilfordii, saffron, curcumin, caffeine, anthocyanin, coenzyme Q10 and vitamins B3 and D have shown neuroprotective goods on retinal ganglion cells via colorful mechanisms, especially antioxidant, anti-inflammatory - apoptosis mechanisms. expansive studies are still needed in the future to ensure natural products' efficacity and safety to serve as anvolition remedy for glaucoma.*

Keywords: glaucoma; herbs; traditional medicine; retinal ganglion cells; intraocular pressure

I. INTRODUCTION

Glaucoma is one of the leading causes of unrecoverable blindness, causing 6.6 of all blindness in 2010. According to the World Health Organization's (WHO) World Report on Vision, of the estimated 2.2 billion people having a vision impairment around the world, glaucoma affects an estimated 6.9 million people. It has been further estimated that by 2040, roughly 111.8 million people worldwide progressed between 40 and 80 times old will be affected by glaucoma. Glaucoma is generally caused by intraocular pressure [IOP,> 21 mmHg] make- up, performing from blockage of intraocular fluid and arid humor drainage. The elevated IOP rashly damages the retinal ganglion cells [RGCs] and optic vagrancy- whams, causing visual field condensation that affects the supplemental field firstly and the central vision field gradually. Patients with glaucoma must have therapy and follow-up for the rest of their lives. The disease significantly lowers a patient's quality of life in terms of anxiety, psychological health, day-to-day functioning, driving, and trust in medical professionals.

Following Risk Factors for Occurrence of Glaucoma [1].

1. Age
2. Family history of glaucoma
3. African American ethnicity
4. A thinner central corneal thickness
5. Pseudoexfoliation
6. pigmant dispersion
7. myopia
8. Genetic factors

Furthermore, a correlation was found between glaucoma, diabetes, hypertension, and lipid levels. Additionally, single-nucleotide polymorphisms in a number of genes (such as myocilin, apolipoprotein E, X-ray repair cross-complementing group1, zona pellucida glycoprotein 4) have been demonstrated to be associated with an increased risk of glaucoma. These genetic factors are also known to be risk factors for glaucoma [1].

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A. Glaucoma:

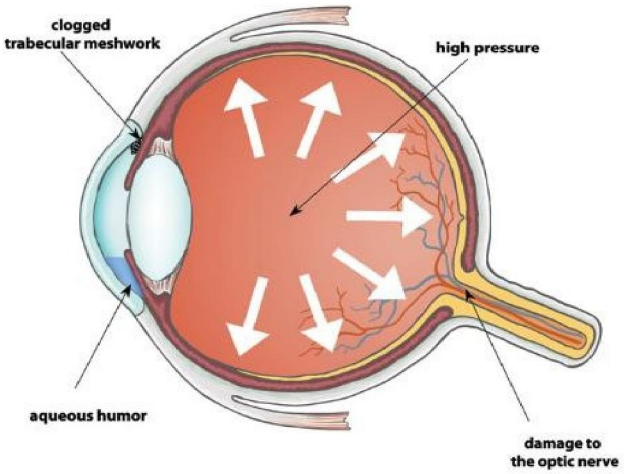

Fig. Glaucoma

B. Types of Glaucoma:

While the source of "primary" glaucoma is unknown, it manifests as optic neuropathy with or without raised intraocular pressure (IOP). On the other hand, "secondary" glaucoma is identified by pathological mechanisms that induce elevated IOP above normal. The anterior eye malfunction, symptoms (RGC loss and optic neuropathy), and treatment (reducing IOP) are shared by both disease types. Diagnosis is still a challenge since glaucoma is frequently discovered after many RGCs (the green cells in Figure 1) have been irreversibly destroyed. The most prevalent varieties of glaucoma do not exhibit Mendelian inheritance, but ethnic groups exhibit notable variations in the prevalence of different forms of glaucoma, indicating the importance of genetic and racial background. For example, Where primary angle closure glaucoma (PACG) is more prevalent in Asia (1.1%), primary open-angle glaucoma (POAG) is more common in Africa (4.2%). However, when it comes to population proportions, Asians continue to represent the majority (~53%) of POAG cases worldwide [2]. Large biological consequences (such as visual neuropathy) are generally rare due to gene mutations, but lesser biological effects are more common due to gene variations [3]. There are no treatments for neuronal degeneration; instead, the only ways to treat all types of glaucoma are to lower IOP pharmacologically, which is the only modifiable risk factor, and, in rare instances, undergo anterior eye surgery and laser photo/thermocoagulation [4,5,6].

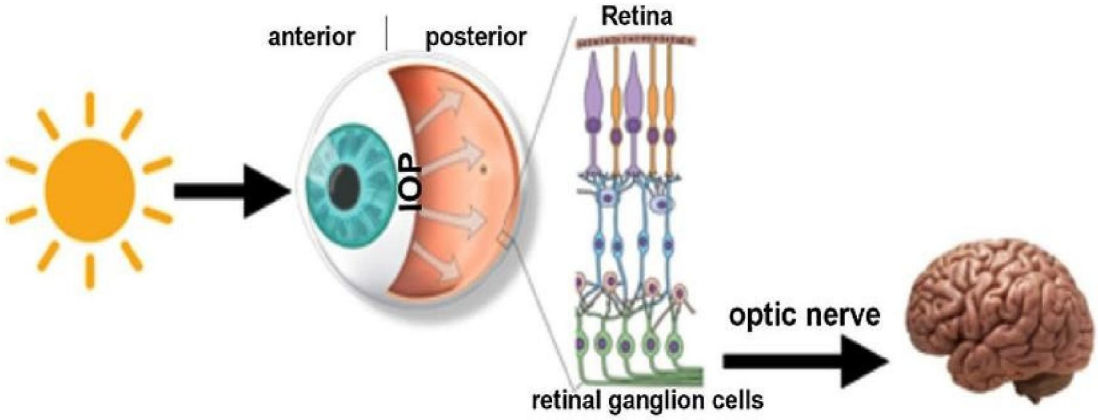

Figure 1. IOP generated in front of the eye (anterior) compromises the function of retinal ganglion cells (green, RGC) located in the back of the eye (posterior). RGC axons traveling through the optic nerve represent the sole output through with the eye communicates the visual signal to the visual areas of the brain. Axonal loss in glaucoma therefore impairs vision and may lead to blindness.

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1. Primary open-angle glaucoma (POAG):

More than 80% of cases of glaucoma in the Western Hemisphere are of POAG, the most prevalent type of the disease. The iridocorneal cleft, which is "open" in normal eyes and POAG (Figures 2A & 2B), is referred to as the "angle" because it allows aqueous humor to flow into the trabecular meshwork and Schlemm's canal. Clinical indicators of POAG include open angle, IOP > 21 mm Hg, and visual field loss linked to ganglion cell axon degeneration (also known as "optic neuropathy"). POAG affects around 8% of Americans over the age of 80, despite being very uncommon in people under 50. African Americans are almost five times more likely to have POAG than Caucasians, with an earlier onset and a faster development curve [7]. However, when evaluating the chances ratio of POAG each decade, individuals with European ancestry are more vulnerable than those with African or Asian heritage [8]. Men appear to be more affected than women. In most POAG cases, the condition can develop to complete blindness without causing pain or discomfort to the patient; however, this can happen if the tension rate is very high and the intraocular pressure (IOP) is greater than or equal to 50 mm Hg.

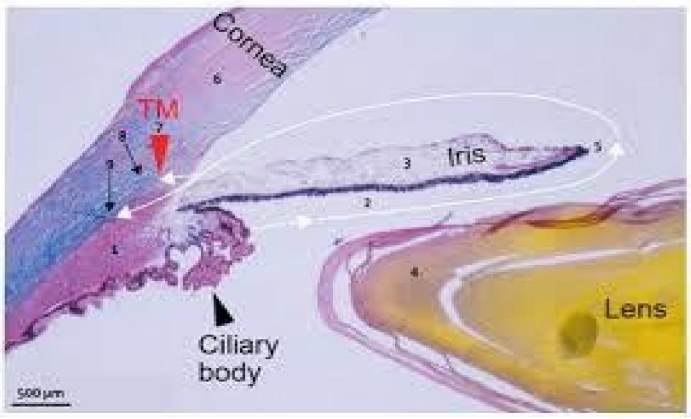

Figure 2A. The site of aqueous humor generation, ciliary body 1, is located in the anterior chamber. Through the pupil 5 and the lens 4 and iris 3, the aqueous humor percolates and draqins (white lines 2) from the posterior chamber into the anterior chamber. The anterior chamber angle encompasses Schlemm's canal 8 and the trabecular meshwork (TM 7 red arrow), and it is situated between the peripheral iris and the peripheral cornea 6. The trabecular meshwork, Schlemm's canal, and the uveo-scleral outflow channel in the ciliary muscle 9 are the exit points for the humor aqueous from the eye. Adapted from Jonas and colleagues, 2017.

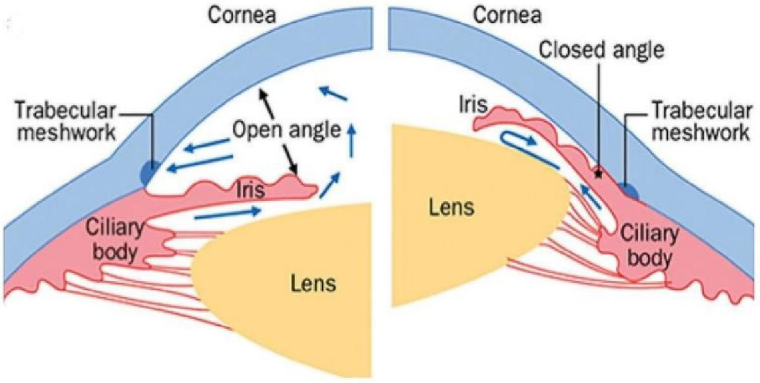

Figure 2B. The anterior eye is schematically diagrammed in Figure 2B for both open angle (left) and closed angel (right) glaucoma. In the case of closed angle glaucoma, the fluid outflow across the Trabecular meshwork (TM) is obstructed by the displacement of the lens and iris. According to Wiggs and Pasquale (2017), 12.

IOP, a significant, heritable risk factor for OAG, ranges from ~7 to >20 mm Hg. Over a period of five to nine years, the chance of getting the condition increases by 10–14% for every 1 mm Hg increase in baseline [9]. The progression of early to late stage POAG takes around 14.4 years in untreated eyes with an IOP between 21 and 25 mm Hg; however,

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with IOPs greater than 30 mm Hg, the lag period is reduced to approximately 2.9 years. People who have myopia may be more susceptible to POAG and increased IOP because their connective tissues may not be as strong [8].

2. Normal-tension glaucoma (NTG):

In around 30% of POAG patients, degenerating RGCs exhibit normal hourglass-shaped axonal loss and visual field abnormalities at "normal" IOP [10]. that is, levels that are continuously less than 21 mm Hg. Risk factors include being a woman, having low blood pressure, being of Japanese descent (more common than in Caucasians), and having vascular dysregulation [11]. Two NTG genes, OPTN and TBK1, which have a 1-2% frequency, are similar to POAG and encode proteins linked to autophagy, an intracellular process that breaks down proteins [12]. The pressure gradient created by excessively low cerebrospinal fluid pressure at the optic nerve head may exacerbate axonal damage in NTG. Some patients' prognoses are improved by IOP-lowering regimens; after 6 years, around 55% of patients who received treatment with IOP-lowering drugs had stable vision, compared to approximately 40% of patients who did not receive treatment [13]. It is possible that patients with NTG have gain-of-function mutations that make them more susceptible to IOP because the pathological reactions in these patients seem to require benign mechanical stimuli. One well-known characteristic of neuropathic pain mechanisms, called similar hypersensitivity (hyperalgesia) to mechanical stimuli, is the altered function of mechanosensitive ion channels in the peripheral nervous system [14].

3. Primary angle-closure glaucoma (PACG):

A disproportionate number of individuals with significant visual loss have angle-closure glaucoma, which is uncommon in Caucasians but common in East Asian groups. Disorders of the iris, lens, and retrolenticular structures are the origin of the pathology. These disorders reduce the angle between the iris and the cornea, preventing the drainage of aqueous fluid (Figure 2B). People with extreme hyperopia (farsightedness) and women are more likely to experience it. Approximately one-third of patients with PACG experience acute symptoms, such as severe pain and nausea, conjunctival hyperemia, corneal edema, and vomiting, which necessitate prompt medical attention, when their IOP suddenly increases (usually beyond 30 mm Hg).Gene association studies have shown that the condition is highly heritable, with genes encoding polymorphisms in extracellular matrix (ECM) components (e.g., MMP, HSP70, NOS3) or ocular development (the Frizzled related MFRP protein, hepatocyte growth factor HGF) being implicated. Collagen XI (COL11A1), pleckstrin homology domain proteins (PLEKHA7, PLEKHC1; necessary for adherens junction stabilization), biosynthesis of acetylcholine (CHAT), protein glycosylation (DPM2), ST18 (suppression of tumorigenicity 18), and transcriptional regulation (GLIS3) are other candidates found by GWAS studies [15]. A period of normal tension may follow an acute PACG, during which the eye takes several days or weeks to recuperate from the shock and begin producing aqueous fluid at a normal rate. This causes the IOP to rise to values that correspond with the degree of angle closure.

4. Secondary glaucoma:

Pathological processes that cause diminished aqueous flow drainage and/or pathological production raise intraocular pressure (IOP) above normal in secondary glaucomas. Pseudoclusive glaucoma, pigmentary glaucoma, neovascular glaucoma, and steroid-induced glaucoma are some of the variations. Protein clumps that build up in the anterior chamber and obstruct the outflow through the trabecular meshwork cause pseudoexfoliative glaucoma. It is more common in Scandinavian communities, shares risk factors with Parkinson's and Alzheimer's illnesses, and has been linked to mutations in the locus encoding CACNA1A, TMEM136, SEMA6A, and other genes as well as the lysyl-oxidase-like 1 (LOXL1) gene. Neovascular glaucoma: the iridocorneal angle ("iris tufts") becomes closed by fibrous material leaking out as a result of blood vessel proliferation. is connected to ischemia of the retina. Diabetes is among the risk factors. Patients who use steroids to control inflammations associated to injuries, corneal transplant rejection, immunological hyperreactivity, and macular edema may develop steroid-induced glaucoma. The trabecular meshwork's resistance to aqueous humor outflow is increased, and IOP is raised, as a result of the structural alterations that follow, including the induction of MYOC. Of those who are "steroid responders," 40% develop POAG if this is left untreated [16]. The "pigment dispersion syndrome," which is brought on by the iris's pigmented epithelial cells' atrophy, is usually the cause of pigmentary glaucoma. Melanin dispersion into the trabecular meshwork increases IOP and obstructs

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aqueous outflow. The Gpnmb gene, which codes for a glycosylated protein associated to lysosomes, and the Tyrp1 gene, which codes for a melanosomal protein with potential structural and enzymatic roles, are mutated in the DBA/2J mouse strain, which exhibits a similar phenotype of chronic glaucoma [17,18]. Some forms of glaucoma are linked to the development of cataracts, specific eye cancers, myopia, uveitis (ocular inflammation), and early onset (juvenile glaucoma).

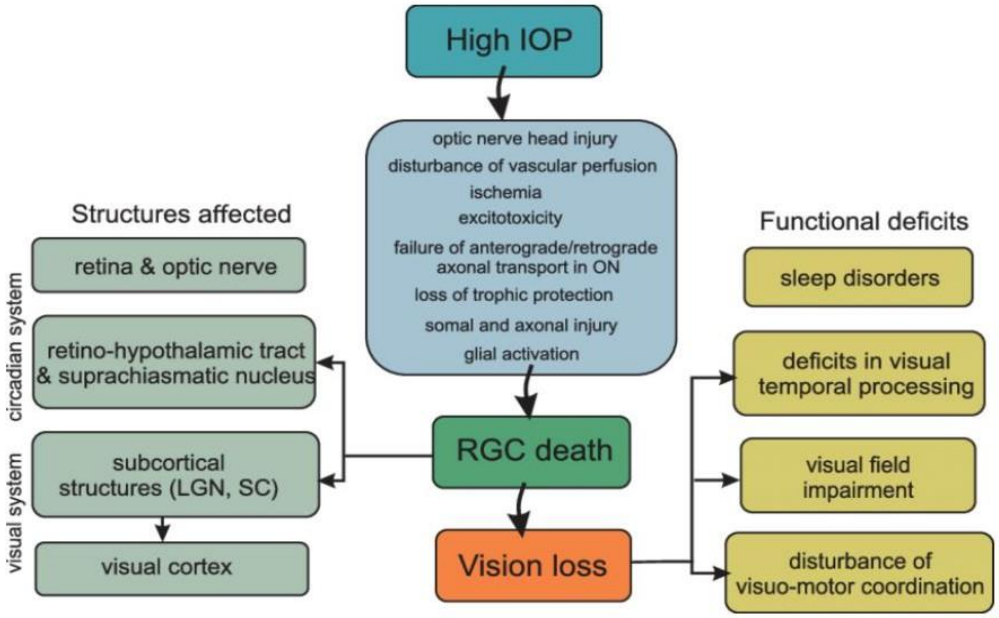
5. Aging and glaucoma:

The aging process and cellular senescence are major risk factors for glaucoma advancement. We lose 10,000 ganglion cells (0.3–0.6%) and 0.58% of TM cells annually; a healthy person with a normal IOP loses roughly 30% of their RGCs by the time they are 80 years old [19]. Reduced axonal transport in the optic nerve (which halves during a rodent's lifetime), decreased quality control mechanisms in ganglion and trabecular cells, and a lower rate of recovery following injury are just a few of the similarities between the loss of ganglion cells in elderly individuals and the general decline in cognitive, motor, and other functions in elderly people. The median age at which glaucoma is diagnosed in 97.6% of people over 40 is 64 years, and the frequency rises sharply from 0.2% to 2.7% in those between the ages of 50 and 59 to 1.6% to 12.8% in those over 80 [20]. Although age is a significant predictor of POAG, we are unsure of the key stress that older eyes' RGCs receive to lessen their resistance to high IOP. The increased rigidity of the ocular structures, or "ocular rigidity," could be one of the contributing factors. This stiffness could enhance trabecular contractility, which raises IOP, and make glia and ganglion cells more vulnerable to pressure-mediated stress. Deficient ocular metabolism in older adults may also be associated with age-dependent oxidative stress and mitochondrial malfunction and depletion of neural defense systems [21].

C. Pathophysiology of Glaucoma:

Numerous cell types in the eye, including RGCs, astrocytes, microglia, and endothelial cells, interact intricately in the pathophysiology of glaucoma. Although various theories have been put out, it is unclear exactly what processes lead to optic nerve injury and RGC death in glaucoma. According to a well recognized theory, elevated IOP causes mechanical stress on the optic nerve head (ONH), which causes RGC death by apoptosis (programmed cell death). Research demonstrates that elevated IOP can cause anatomical alterations in the ONH as well as optic nerve atrophy, which lends credence to this notion. However, additional variables like as oxidative stress, inflammation, neurotrophic factor insufficiency, and mitochondrial dysfunction may possibly play a role in RGC death in glaucoma in addition to IOP [22].

Flow diagram showing key factors involved in the pathogenesis of glaucoma:



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D. NATURAL REMEDIES FOR MANAGEMENT OF GLAUCOMA

The natural remedies which are used for the management of glaucoma are Vitamin C, melatonin, selenium, zinc, tocopherol, beta-carotene, fruits, and vegetables.

1. ITAMIN C /ASCORBIC ACID

Strong, healthy blood vessels, the production of collagen, and the health of joints all depend on vitamin C. The risk of primary open-angle glaucoma has significantly decreased with increased vitamin C intake. By depolymerizing the hyaluronic acid component of the trabecular meshwork, vitamin C lowers intraocular pressure and neutralizes oxygen radicals. Citrus fruits and juices, strawberries, tomatoes, red peppers, broccoli, and potatoes are among the foods high in vitamin C [23].

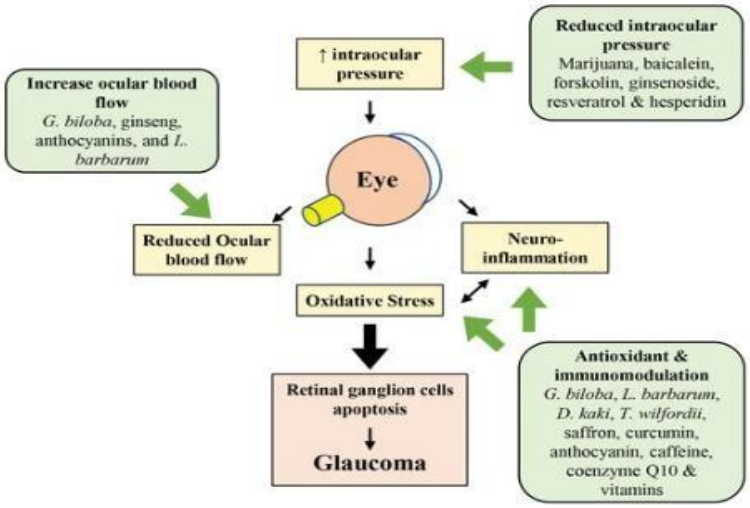
2. FRUITS AND VEGETABLES

Antioxidants are abundant in fruits and vegetables. Regular fruit and leafy green vegetable eating is believed to lower the risk of glaucoma. Vitamins C, E, and A, provitamin A carotenoids (which the body converts to Vitamin A), and other carotenoids lacking Vitamin A activity are among the antioxidants present in fruits and vegetables. These antioxidants directly affect the vascular system that supplies blood to the optic nerve, the individual retinal ganglion cells, and the trabecular meshwork [23]. It has been demonstrated that these antioxidants are more helpful in the treatment of glaucoma.

3. OTHER ANTIOXIDANTS

Aside from beta-carotene, other antioxidants used in the treatment of glaucoma include melatonin, zinc, selenium, alpha-lipoic acid, lutein, glutathione, grape seed extract, and fish oil.

Natural Products Used for Glaucoma Treatment and Their Mechanism of Action:



Antioxidants may offer an alternate method of treating glaucoma due to the roles that oxidative stress and neuroinflammation play in the disease. Currently, IOP reduction with IOP-lowering eye drops is the cornerstone of glaucoma treatment [24]. The European Glaucoma Society guidelines state that surgical trabeculectomy, trabeculotomy, deep sclerectomy, and viscocanalostomy are among the other glaucoma treatments available. Laser trabeculoplasty and cyclodestruction are other options. But in other people, the illness worsens and impairs vision even after the IOP returns to normal [25]. Complementary and alternative medicine, or CAM, has garnered a lot of attention from researchers and is frequently used to treat glaucoma. 10% of patients in a Canadian survey with 1516 glaucoma patients expressly employed complementary and alternative medicine (CAM) for their condition, and 50% of them thought the treatments

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were helpful [26]. According to other recent research, the prevalence of CAM use among eye patients was found to be 67% in Palestine and 22% in Saudi Arabia. The current review encompasses new research on CAMs utilized in the management of glaucoma [27].

1. Ginkgo (Ginkgo biloba)

Fig A: Ginkgo biloba

The Ginkgo biloba tree, from which G. biloba is derived, is most frequently used to treat glaucoma [28]. Patients who have glaucoma benefit more from it. Blood flow is generally decreased in glaucoma sufferers. Compared to high-tension glaucoma, normal-tension glaucoma (NTG) exhibits a more noticeable blood reduction. Without changing intraocular pressure, heart rate, or total blood pressure, G. biloba improves blood flow in the eye. Numerous flavonoids, particularly polyphenolic flavonoids, which are proven to have an antioxidant function by giving electrons to free radicals, are contained in ginkgo [29,30]. These characteristics lend credence to G. biloba's therapeutic benefits in the treatment of NTG. The pathophysiology of glaucoma involves oxidative stressors, disrupted microcirculation, and elevated intraocular pressure. It is well established that
G. biloba possesses antioxidative properties and enhances microcirculation [31]. Furthermore, ginkgo has a stabilizing effect on mitochondria, which are the primary site of damage in glaucoma.

2. Bilberry (Vaccinium myrtillus):

Fig B: Bilberry (vaccinium myrtillus)

Another name for bilberry is Vaccinium myrtillus. Its application in ophthalmology is growing. Flavonoid anthocyanosides, often known as anthocyanins, the active ingredient, have a special affinity for vascular and ocular tissues [32]. Antioxidant qualities, collagen fiber and collagen biosynthesis stabilization, reduced capillary permeability and fragility, and prevention of platelet aggregation are just a few of the ways that anthocyanins work [33]. According to a number of studies, bilberry helps people with NTG see better. This is based on the vascular theory of mechanisms of glaucomatous optic nerve injury. Compared to healthy persons, NTG patients are more likely to experience cerebral small vessel ischemia. By increasing cerebral blood flow, anthocyanin administration enhances best-corrected visual acuity and the mean deviation in VF indicators. This enhances ocular blood flow and improves retinal sensitivity, concentration, and alertness [34].

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3. Curcuma Longa (Turmeric):

Fig C: Curcuma Longa

The active ingredient in the rhizome of Curcuma longa L., also known as turmeric, is curcumin, a yellow color. Antioxidant, anti-inflammatory, anti-cancer, anti-arthritis, anti-asthmatic, antibacterial, antiviral, and antifungal properties are known to be present. Considering curcumin's significant antioxidant properties, it could be another option for treating glaucoma by reducing oxidative stress. Curcumin therapy improved oxidative stress-induced RGC apoptosis and reduced intracellular ROS levels in a rat model with high intraocular pressure. The same study also found that curcumin increased the anti-apoptotic factor Bcl-2 and decreased pro-apoptotic proteins like caspase-3 and Bax. Strong RGC apoptosis and thinning of retinal layers, particularly the GCL, were seen 24 hours after the injury in an ex vivo optic nerve injury model. These findings were linked to a time-dependent rise in the levels of pro-apoptotic markers and caspase-3 and-9, as well as a potent activation of the JNK, c-Jun, and ERK signaling (MAPK) pathways. Curcumin maintained RGC survival and retinal thickness by blocking changes in the MAPK pathways and apoptotic cascade. Another experimental study found that supplementing the diet with curcumin for two days before to I/R could prevent ischemia damage to the retina in a rat retinal I/R injury model. Furthermore, pretreatment with curcumin prevented I/R-induced retinal capillary degeneration. This may be because curcumin inhibits the activation of NF-B and signal transducer and activator of transcription 3 (STAT3), as well as the overexpression of MCP-1, a chemokine that contributes to the inflammatory response by drawing monocytes to injury sites [1].

4. Coleus forskohlii:

Fig D: Coleus forskohlii

Forskohlii Coleus (willd.) Briq. is a native Southeast Asian and Indian medicinal plant. C. forskohlii's leaves, roots, and tubers are abundant in forskolin, a diterpenoid that directly stimulates adenylate cyclase to function as a second messenger cyclic adenosine 3,5-monophosphate (cAMP) booster [1]. Aqueous humor dynamics in the ciliary body and TM are regulated by cAMP, according to studies [35]. Indeed, a prior investigation demonstrated that in an isolated bovine eye preparation, forskolin administered arterially at 30, 100, and 1000 nM significantly decreased the rate of aqueous humor production [1]. As demonstrated in a double-blind, randomized controlled research, POAG patients treated with forskolin 1% w/v aqueous solution eye drops, two drops daily, for four weeks, demonstrated a significant decrease in IOP, which may account for the hypotensive impact of forskolin administration [36].

In a mouse model of optic nerve damage and hypertension glaucoma, researchers found that a diet rich in forskolin, homotaurine, spearmint, and vitamins B1, B6, and B12 could prevent RGC loss. According to both studies, the combination of forskolin supplements may inhibit inflammatory processes by lowering the secretion of cytokines

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(iNOS, IL-6, and TNF-), which in turn may reduce apoptotic markers (Bax/Bcl-2 ratio and active caspase-3), ultimately preventing RGC death and maintaining visual function [37,38]. However, the forskolin supplement mixture had no effect on the rise of IOP in glaucomatous animals, which is in contrast to the clinical investigations [38].

5. Panax ginseng- Ginsenoside:

Fig E: Panax ginseng- Ginsenoside

In the Araliaceae family, Panax ginseng is regarded as one of the most widely used functional foods and medicinal plants. It was demonstrated that giving glaucoma patients 3 g of Korean red ginseng (KRG) daily for 4 weeks improved their daytime contrast sensitivity and ocular pain in a randomized, placebo-controlled, crossover study.Glaucoma patients' tear film stability and overall Ocular Surface Disease Index score significantly improved after 8 weeks of KRG supplementation, indicating that KRG helped glaucoma patients with dry eye syndrome. Furthermore, when OAG patients took 1.5 g of KRG orally three times a day for 12 weeks, their retinal peripapillary blood flow in the temporal peripapillary region significantly improved. Ginsenoside (triterpenoid saponin), phenols, and acidic polysaccharides are only a few of the many phytochemicals found in ginseng. It has been demonstrated that these phytochemicals shield RGCs. In a rat model of optic nerve crush, treatment with whole Panax notoginseng saponin enhanced RGC survival and blocked the cell death pathway. Similarly, in a rabbit model of ultrasound-targeted microbubble optic nerve damage, ginsenoside Rg1 therapy was able to lessen RGC damage. Additionally, ginsenoside Rb1 shields RGCs from apoptosis brought on by oxidative stress from H2O2 and hypoxia from CoCl2 [1].

Table: Characteristics of medicinal plants commonly used by glaucoma patients.

Sr. no	Herbal Medicine	Route of Administration	Mechanism of Action
1.	Ginkgo Biloba	Oral	Antioxidant Mitochondria stabilization Vasorelaxation Blood viscosity reduction Anti-inflammation
2.	Bilberry (Vaccinium myrtillus)	Oral	Antioxidant Capillary and collagen stabilization Anti-inflammation
3.	Marijuana (Cannabis sativa)	Oral, Inhalation, Sublingual, Intravenous, Topical	IOP reduction Anti-inflammation Antioxidant
4.	Coleus forskohlii	Oral	Reduces IOP Improves aqueous humor outflow
5.	Turmeric (Curcuma longa)	Oral	Anti-inflammatory Anti-oxidant effects
6.	Panax ginseng	Oral	Neuroprotective Anti-inflammatory effect

Challenges for Natural Product Application in Glaucoma Treatment:

The WHO has established standards for assessing the effectiveness and safety of natural products, which is crucial for promoting CAM use in the medical system .This guideline offers broad guidelines for preclinical and clinical research on the evaluation of herbal medicines, including general pharmacological, pharmacodynamic, and toxicological

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evaluations as well as the quality and processing of plant materials. As discussed in this review, the use of crude extracts from whole plants or specific parts of any herbal plant is effective in treating glaucoma; however, the identification and isolation of an active phytochemical may also be crucial, particularly during the drug development process. Numerous phytochemicals found in crude extracts have the potential to cure glaucoma through polypharmacy, either separately or in combination [1]. Similarly, a number of studies have shown that using a combination of molecules can effectively lower intraocular pressure in POAG patients. It could be challenging for researchers to pinpoint the precise process or substance causing these results. For example, a dietary supplement comprising 150 mg of C. forskohlii extract (including 15 mg forskolin), 200 mg of rutin, 0.7 mg of vitamin B1, and 0.8 mg of vitamin B2 was administered orally twice daily for 30 days, which helped lower IOP in POAG patients [39]. The same supplements have also been demonstrated to avoid IOP spikes following neodymium: YAG laser iridotomy in patients at risk of POAG and to lessen ocular discomfort in POAG patients brought on by long-term usage of multi-dose eye drops containing preservatives [1]. Additionally, POAG patients compensated by IOP-lowering medications who took supplements with tablets containing C. forskohlii extract, homotaurine, carnosine, folic acid, vitamins of the B group, and magnesium over a 12-month period showed a significant further decrease in IOP as well as an improvement in the pattern electroretinogram amplitude at 6, 9, and 12 months, as well as foveal sensitivity at 12 months [40]. In a different trial, POAG patients who took a comparable supplement daily for four months saw enhanced light and contrast sensitivity, a drop in intraocular pressure, and an improvement in their quality of life . Furthermore, POAG patients who received a 4-week dose of anthocyanin-rich French maritime pine bark and bilberry fruit extracts experienced a decrease in IOP [1].

For the treatment of glaucoma, many eye drops of different classes—including beta blockers, adrenergic agonists, carbonic anhydrase inhibitors, prostaglandin analogs, miotics, and

hyperosmotic agents—are frequently chosen over operations [41]. Due to incorrect eye drop administration practices, patient noncompliance is one of the main problems with glaucoma treatment [42]. Poor drug bioavailability across the blood-retinal barrier, the cul-de-sac's limited retention capacity (typically 7–10 L, maximum 50 L), and the medication's quick drainage due to gravity and washout through tearing or the nasolacrimal duct are additional significant problems [43]. It may be possible to improve the bioavailability of medications to the eye by using different nanoformulations, such as nanoparticles, nanoemulsions, and nanolipid vesicles, to deliver phytochemicals. A longer pre-ocular retention duration and better baicalein bioavailability were demonstrated, for example, by baicalein loaded in trimethyl chitosan nanoparticles as opposed to baicalein solution. According to Davis et al., D-tocopherol polyethene glycol 1000 succinate nanoparticles, each with a diameter of less than 20 nm, were used in a formulation of a curcumin- loaded nanocarrier. Topical administration of curcumin nanocarriers twice a day for three weeks was demonstrated to drastically reduce RGC loss in an OHT rat model; however, this effect was not observed in the group receiving free curcumin therapy. Furthermore, by considerably boosting cell viability, the same study demonstrated that curcumin nanocarriers shielded retinal cells from glutamate-induced toxicity and CoCl2-induced hypoxia in vitro. Similarly, human TM cells exposed to H2O2-induced oxidative stress showed lower levels of apoptosis (reduced TUNEL-positive cells and cleaved caspase-3 protein level) and inflammation (reduced expression of TNF and IL-1 and-6, linked to downregulated mitochondrial ROS production) when a chitosan–gelatin- based hydrogel containing curcumin-loaded nanoparticles was used.In addition to curcumin, co- encapsulated quercetin and resveratrol in chitosan nanoparticles and sodium alginate poly (vinyl alcohol) electrospun forskolin nanofibers demonstrated an effective reduction in intraocular pressure in adult normotensive rabbits.These investigations revealed that phytochemical nanoformulations have encouraging outcomes, supporting their application as a substitute for currently available glaucoma eye drops in clinical settings.

Finally, it is critical to employ an appropriate technique in order to address the study's objectives. As demonstrated by the many research reviewed here, the Bcl-2/Bax ratio was used in several of them to suggest that the therapeutic agent affects the activation of the intrinsic apoptotic pathway in RGCs. However, the idea that the expressions of Bcl-2 and Bax are in a stoichiometric 1:1 balance in cells is a reflection of the old "rheostat" model of the protein function of the Bcl-2 family. This hypothetical model was disproved more than 20 years ago when it was demonstrated that a 1:1 interaction between these proteins was a laboratory artifact. Additionally, the extended version of Bcl-X (Bcl-XL), which was discovered to be 16 times more common than Bcl-2, is the primary anti-apoptotic protein expressed in the retinal cells, including the GCL.Furthermore, the expression of Bcl-2 in adult RGCs is further controversial; it may

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really only be found in Müller cells in the retina. As a result, the Bcl-2/Bax ratio may not be a reliable indicator of RGC apoptosis; rather, variations in Bcl-XL expression may be more closely associated with RGC apoptosis [1].

II. CONCLUSION

Glaucoma is one of the most leading causes of eyesight loss. The etiology of glaucoma includes oxidative stress, inflammation, neurotrophic factor insufficiency, mitochondrial dysfunction, and mechanical stress on the optic nerve head (ONH), which causes RGC death by apoptosis. Treatment for glaucoma may benefit from the use of natural items having anti-inflammatory, anti- apoptotic, and antioxidant qualities. Natural products are also reasonably priced and widely accessible. In vitro and in vivo preclinical research, as well as clinical trials, have demonstrated that natural compounds provide protection against RGC loss. Treatment with ginsenoside, forskolin, and marijuana has been demonstrated to lower IOP. Ginseng and ginkgo biloba have been shown to improve ocular blood flow in glaucoma patients. The potential application of several of these natural compounds in the treatment of glaucoma is limited because they have undergone little to no clinical testing. To further ascertain these natural compounds' therapeutic potential in glaucoma, it is crucial to make sure that their safety and bioavailability are examined in carefully planned randomized clinical trials.

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