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Recent Approaches of Ocular Disease and Its Herbal Product Treatment: An Updates

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ABSTRACT

One of the most common causes of permanent vision loss is glaucoma. Damage to the optic nerve and retinal ganglion cells, the root cause of visual field impairment, is typically the result of elevated intraocular pressure. Some patients' illness worsens even when treated with eye medications that reduce intraocular pressure. The pathophysiology of glaucoma is not only thought to involve mechanical and vascular dysfunctions of the eye, but also oxidative stress, neuroinflammation, and excitotoxicity. Therefore, natural compounds with antioxidant and anti-inflammatory qualities may offer a different strategy for treating glaucoma. This review summarizes the most up-to-date preclinical and clinical research on natural compounds that have been proven to contain neuroprotective characteristics for retinal ganglion cells and, consequently, may be useful in the treatment of glaucoma. Baicalein, forskolin, marijuana, ginsenoside, resveratrol, and hesperidin are all effective at lowering intraocular pressure. On the other hand, antioxidant, anti-inflammatory, and anti-apoptosis mechanisms are among those through which Ginkgo biloba, More research is needed to determine whether natural items can be used as a safe and effective treatment for glaucoma.

Keywords- Opthalmic disease, Glucoma, Herbal remedies, Intraocular disease.

I. INTRODUCTION

There is a sizable market for herbal remedies. The annual market for "traditional" herbal products is estimated by the World Health Organization to be over USD 80 billion [1]. There are some nations (like Brazil) and/or areas (like the EU) where their use as medications is controlled [2]. Herbal medications contain one or more active compounds derived from plants, and they must be chemically described to meet the requirements of the regulator as outlined in the pharmacopoeia or official monographs [3]. Extraction is commonly used to ensure pharmacologically relevant concentrations of active components and consistency between batches of a herb. However, it could also just be raw materials that haven't been touched much. If these items have been given the green light by the appropriate regulatory bodies, they can be used by patients as medications [4]. Taking herbal supplements alongside prescribed medications can increase the risk of side effects, as is the case with any medical treatment. The pharmacological and/or toxicological effect of the medicine or natural product may therefore change [5]. Both pharmacodynamic and pharmacokinetic mechanisms underlie herbal-drug interactions. The pharmacological impact of the medicine or herbal supplement is altered as

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a result of pharmacodynamic interaction. When one medicine or herbal supplement affects the ADME of another, it is said to have a pharmacokinetic interaction [6].

The widespread idea that herbal products are safe has led to underreporting and a lack of information about potential side effects and interactions associated with their usage among patients and healthcare providers.[7][8] To add extra confusion, most herbal treatments are OTC (over-the-counter). As a result, little is known about how often and why people use these herbal products all over the world. Regulators are also hindered in their ability to evaluate and anticipate the magnitude of potential interactions or adverse effects because two herbal products containing the same herbal active may differ in strength and bioavailability, leading to different therapeutical and toxicological outcomes [9,10].

Garlic (Allium sativum) is one herb that might interact negatively with medications. Many purported health benefits of garlic are used to promote it. Garlic has many health benefits, one of which is a decreased risk of cancer, and particularly gastrointestinal cancer. To prevent blood clots, consume garlic. Garlic increases the international normalized ratio when used with warfarin. This means the patient's coagulation may be compromised for a longer period of time, making them more likely to sustain a bleeding episode. Prior to starting warfarin medication, patients who have a high garlic intake through their diet should be assessed [11,12,13]. In a complex healthcare environment, catastrophic results may occur because healthcare professionals are more familiar with drug-drug interactions than herbal ones. To address this challenge, it is necessary to establish a mechanism for reporting issues based on evidence of herbal-drug interactions. [14][15] The system in question must also determine the gravity of the threat and the likelihood of interactions. There is a widespread misconception that herbal remedies can be substituted for conventional medical treatment. Patients who solely rely on herbal remedies run the danger of either not receiving treatment or having their disease worsen because of a lack of data for those remedies. [16][17] Polypharmacy, or the use of many medications, can have negative effects on patients, especially when combined with the use of herbal supplements that interact with each other. Herbal supplements may be purchased by patients after they have obtained the medicine, with little to no thought given to the possibility of an interaction. Patients' susceptibility to these dangers [18,19,20] need protection from healthcare systems. [21][22]

The pharmacokinetic effects of herbal medications have been studied and reviewed by our team for quite some time now [23,24,25]. Predicting HDI requires knowledge of how long it takes for a xenobiotic (herbal medication) to be absorbed, distributed, metabolized, and excreted from the body.

This is difficult because of the chemical complexity of herbal medications. To begin, the pKa and pH of the surrounding medium may affect how well the various active and inactive chemicals therein are absorbed orally. P-glycoprotein (P-gp) and other transporters can reduce the body's ability to take in xenobiotics by using up the drug's energy and returning it to the digestive tract [26,27,28].

Absorption is followed by metabolism. A molecule with distinct chemical and pharmacological properties is produced during this biphasic pharmacokinetic period. The liver is responsible for first-pass metabolism of the orally delivered medication, with the remaining metabolism occurring in various organs. During Phase 1 of metabolism, the cytochrome P450 isozymes (mostly CYP3A4/5 enzymes) are responsible for modifying the compound's structure through oxidation, reduction, or hydroxylation. The products of Phase 1 are then conjugated by UDP-glucuronosyltransferase enzymes (UGT) in Phase 2. A molecule's structure can be changed through metabolism, which can lessen or even abolish its function. It can also convert inactive compounds (like prodrugs) into active ones [29,30].

Some molecules that enter the body are expelled [31,32,33]. These compounds may or may not have undergone structural changes. The time it takes to achieve a therapeutic response, the number of doses needed, and the frequency of dosage are all factors that are affected by the elimination rate. The kidneys use a process called glomerular filtration to get rid of most water-soluble substances and metabolites. However, reabsorption limits the kidney's ability to excrete lipid-soluble medicines. The reabsorption and metabolism of lipid-soluble medicines into water-soluble molecules is a necessary mechanism for this to take place. The kidney membrane contains transporters that allow for the excretion of both acidic and basic substances [34,35].

Glaucoma is one of the leading causes of irreversible blindness, causing 6.6% of all blindness in 2021 [36]. 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 [37]. It has been further estimated that by 2040, approximately 111.8 million people worldwide aged between 40 and 80 years old will be affected by glaucoma [38]. Glaucoma is generally caused by intraocular pressure (IOP, >21 mmHg) build-up, resulting from blockage of intraocular fluid and aqueous humor drainage [39]. The elevated IOP progressively damages the retinal ganglion cells (RGCs) and optic nerve, causing visual field constriction that affects the peripheral field initially and the central vision field gradually [40]. Glaucoma patients require lifelong treatment and follow-up, and the disease has a significant negative impact on patients' quality of life in terms of anxiety, psychological well-being, daily life,

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driving and confidence in healthcare [41]. The main risk factors for glaucoma prevalence include age, family history with glaucoma, African American race, thinner central corneal thickness, pseudoexfoliation, pigment dispersion and myopia [42]. Additionally, an association between diabetes, hypertension, triglyceride levels and glaucoma were also identified [43,44]. Furthermore, genetic factors are also known to be risk factors for glaucoma, in which single-nucleotide polymorphisms in numerous genes (e.g., myocilin, apolipoprotein E, X-ray repair cross-complementing group 1, zona pellucida glycoprotein 4) have been shown to be associated with an increased risk of glaucoma [45,46,47].

Glaucoma can be classified into two major types, i.e., open-angle (OAG) and angle-closure glaucoma (ACG), according to the physical obstruction of the aqueous humor drainage system, and the appearance of the iridocorneal angle and trabecular meshwork (TM) [48]. Alternatively, it can also be categorized as primary (idiopathic, not associated with other diseases or conditions) or secondary (attributed to underlying diseases or conditions, such as trauma, long-term medication, ophthalmic surgery, uveitis, necrotic tumors, diabetes or syndromic conditions) [49,50].

In primary OAG (POAG), aqueous humor drainage is obstructed or inadequate as there is an internal blockage within the TM [51]. In contrast, primary ACG (PACG) is characterized by the presence of a physical obstacle to the aqueous drainage as the iris is adhered to the cornea, obstructing the flow of aqueous humor to the TM and the uveoscleral drainage [52,53]. Symptoms appear more drastically in PACG, which results in a rapid reduction in the vision field, leading to total blindness. Other symptoms include ocular pain, headache, nausea, vomiting, multicolored halos and blurred vision [54,55]. Additionally, PACG is an ophthalmic emergency that requires immediate treatment to prevent the progression of irreversible ocular damage [56].

II. OXIDATIVE STRESS AND NEUROINFLAMMATION IN GLAUCOMA

Microglia and Astroglia

Müller cells and astrocytes, which make up microglia and astroglia, respectively, offer metabolic support of neurons, neurological regulation of ionic concentrations, and neuroprotective actions (8, 10-12), and are involved in inflammatory responses inside the retina (9). Cell surface antigens CD11b/c and chemokine fractalkine receptor (CX3CR1) are expressed by microglial cells, which develop from blood monocytes that migrate to the central nervous system (CNS) (57). Beginning as erythromyeloid progenitors, they complete their development in microglia (58) via one of many colony-stimulating factor 1 receptor (CSF-1R) (59), IL-34 (60), or TGF- (61)-dependent differentiation pathways. When fully developed, astroglia and microglia contribute to the inflammatory response triggered by damage-associated molecular patterns (DAMPs) secreted by brain cells (62-64). When intraocular pressure (IOP) is high, retinal ganglion cells (RGCs) release heat shock proteins (HSPs) (65), and tenascin-C is increased in astrocytes and promotes toll-like receptor (TLR) activation (66). Microglia release cytokines and chemokines (67,68) during the neuroinflammatory response, including complement factors, tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6), which all help to increase the reaction and promote the morphological alterations of microglia into macrophages (69). Activated macrophages can take on either the M1 or M2 phenotype. Anti-inflammatory mediators such as IL-10, TGF-, and the neurotrophic factor insulin-like growth factor (IGF-1) are synthesized by M2, while pro-inflammatory IL-1, IL-12, and TNF- are produced by M1 (70).

Researchers have recently found that infiltrating monocyte-like cells are likely responsible for the early proinflammatory signals (71) in DBA/2J mice with experimental glaucoma, and that the triggering receptor expressed on myeloid cells/TYROsine kinase binding protein (TREM/TYROBP) signaling network is the primary regulator mechanism of microglial responses to elevated IOP.

Signaling proteins allow microglial cells to talk to astroglia. Two kinds of reactive astrocytes, A1 and A2, are separated from astroglia based on this interaction (72,73,74). The effect of A1 is negative (75), while A2 is neuroprotective (76). Microglia and astroglia do work together to control inflammation.

Both the retina and the ONH show upregulation of genes involved in inflammatory pathways (77,78). TLR signaling pathways are the first to be activated; for instance, HSPs boost MHC class II expression and cytokine production (79). Nuclear factor-kappa B (NF-kB) represents the second pathway, which promotes a cascade of inflammatory cytokines (TNF- and IL-6) by increasing expression of the IL-1 cytokine family. Optic nerve TNF- and the proapoptotic protein Fas ligand (FasL) have been linked to glaucoma etiology (80). Oikawa et al. (81) recently shown that in early glaucoma in felines, genes involved in cell proliferation and immunological responses (associated with the TLR and NF-B signaling pathway) are upregulated, and that the types of proliferating cells vary across the ONH. The lamina cribrosa and the prelaminar region included microglia-macrophages, while the retrolaminar region contained a greater number of oligodendrocytes.[82]

III. NATURAL PRODUCT FOR TREATMENT OF GLAUCOMA

Atropa belladonna L.

The topical use of the macerated fruit of *Atropa belladonna* L. by the Egyptians is the first known use of

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a nature-derived agent to treat an ophthalmic disease. The main chemical constituent of this plant is atropine, chemical structure is shown in Figure 1a Chia et al. investigated in a randomized clinical trial that atropine at a low concentration (0.01% eyedrops) was more effective in slowing myopia progression with less visual side effects compared with higher doses. The exact mechanism of non-accommodative anti-myopic activity of atropine is still unknown but there are three possible mechanisms of action (Figure 1b). [83][84] It binds to the muscarinic receptors (MR) of amacrine cells in retina which in turn, increase the release of dopamine which is an inhibitory chemical mediator for eye growth. There is reduction of γ- aminobutyric acid following atropine treatment in myopia induced mice.[85][86] Atropine binds to the scleral fibroblast muscarinic receptors that interfere with scleral remodelling, increase the thickness of scleral fibrous layer, reduce extracellular matrix production by decreasing glycosaminoglycan (GAG) synthesis both in the whole sclera and in isolated scleral chondrocytes and upregulate the mRNA levels of MR1, MR3, and MR4 while downregulating MR2 and MR5 mRNA levels in the sclera from mouse eyes with lens-induced myopia. [87][88]

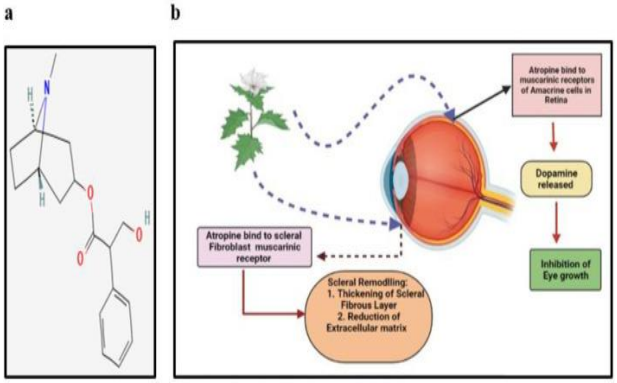


Fig:1 a, The atropine molecule in its chemical form. Myopia: b. The Atropine Action Mechanism

***Coptis teeta* Wall:**

Coptis teeta Wall. is a perennial herb which belongs to the family Ranunculaceae. Rhizome of this plant are used for medicinal purposes that are horizontal to oblique in shape of about 5–15 cm long with fibrous roots and bitter in taste.[89][90] Externally, it is yellowish brown and pith yellow–orange and covered with numerous nodes and rootlets. Traditionally, it has been used in eye diseases, skin diseases, stomach problems, constipation, jaundice, urine disorders and insect bite. The active ingredient of this plant is berberine and the plant contains other alkaloids like coptisine, palmatine, epiberberine and columbamine (Figure 2). It also contains fixed oil, albumin, coloring compound, lignin and sugar showed the anti-trachoma activity of the plant and concluded that berberine was more effective in eradicating Chlamydia trachoma as compared to sulfacetamide and in preventing relapse of symptoms. [91]It also has anti-inflammatory anti-microbial, anti-bacterial and anti-oxidant activity. explored the anti-inflammatory and anti-histaminic activity of Unani formulation consisting of *Coptis teeta, Berberis aristate, Cassia absus, Symplocos racemose* Roxb., and *Azadirachta indica* in rabbits' conjunctiva.

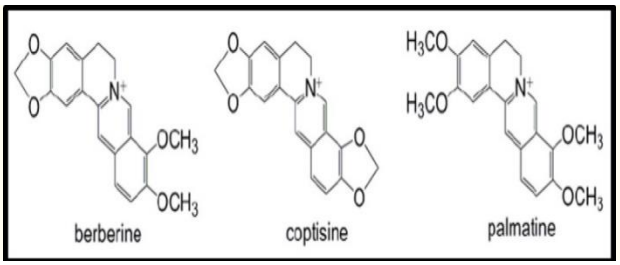
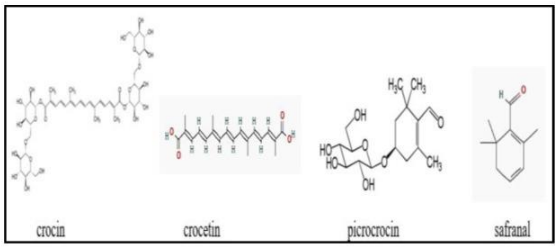


Figure 2: Coptis teeta Wall, its chemical make-up

Crocus sativus L .

Crocus sativus L. is a stemless herb and it belongs to the family Iridaceae. Dried stigmas of flowers are commonly known as Saffron and used in cooking as a coloring and flavoring spice it was known by ancient nations and has remained among the world's costliest substances throughout the history. [92][93] Phytoconstituents are crocin, crocetin, picrocrocin, and safranal as shown in Figure 3a. Traditionally, it is used as a sedative, anti- anxiety, anti-depressant, aphrodisiac, expectorant, and anti-spasmodic agent carried out a double-blind, placebo-controlled, cross over study in age-related macular degeneration and showed that saffron increases the best corrected visual acuity. In an another double-blind, placebo-controlled clinical trial in primary open angle glaucoma (POAG) of 1-month duration, reduction of IOP was shown after three and four weeks compared to placebo, however, it returned to pre-intervention levels after a 4-week wash-out period. In a double-masked, placebo-controlled clinical trial in diabetic macular edema, there was a significant decrease in central macular thickness and increase in best corrected visual acuity along with a significant decrease in HbA1c and fasting blood glucose. [94] Saffron increases oxygen diffusion, improves ocular blood flow, and increases glutathione (GSH) levels that protect against reactive oxygen species (ROS) and apoptosis. The possible mechanisms of action involved in saffron effect are anti-oxidant, anti-apoptotic, and anti-inflammatory activities (Figure 3b).

a



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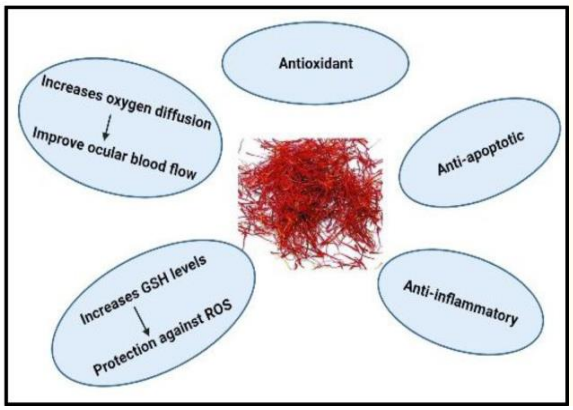
b



Coptis teeta Wall, its chemical make-up is shown in Figure 2.

***Foeniculum vulgare* Mill.**

Fennel is a medicinal plant belonging to the Umbelliferae (Apiaceae) family. It has been used in traditional medicine for various ailments from thousands of years in the East Asian countries, India and China. [95][96] The fruit and root infusions are used as relaxant, estrogenic, analgesic, and anti-inflammatory medicines. Fennel seeds have been shown to have estrogenic, antioxidant, and antihirsutism activities; it increases milk secretion, promotes menstruation, facilitates birth, and alleviates the symptoms of dysmenorrhea, and increases libido and female climacteric and essential oil has antifungal property. Phytochemical studies have shown the presence of numerous valuable compounds, such as volatile compounds (fenchone, estragol, and para-anisaldehyde as shown in Figure 4), flavonoids, and phenols. [97] The Romans believed that fennel seed could help supercharge the vision. It has several pharmacological properties such as anti-inflammatory, oculohypotensive, antioxidant, anti-inflammatory, antispasmodic, antiseptic, carminative, diuretic, anti-ulcer and analgesic effect Evaluated the oculohypotensive effect of aqueous extract of *Foeniculum vulgare* Mill**.** in experimental models of glaucoma. Results revealed that it exhibited 17.49, 21.16 and 22.03% reduction of intraocular pressure (IOP) in normotensive rabbits at 0.3%, 0.6% and 1.2% (w/v) concentrations, respectively. The 0.6% concentration was further evaluated in acute and chronic models of glaucoma.[98] A maximum mean difference of 31.20% was observed between vehicle-treated and extract-treated eyes in water loading model while a maximum mean IOP lowering of 31.29% was observed in steroid-induced model of glaucoma. Mechanism of action involved in lowering IOP, might be due to its anticholinesterase activity. Another study showed the protective and therapeutic effects of aqueous extract of *Foeniculum vulgare* Mill. seed eye drops (0.5%) against selenite-induced cataract in rabbits. The results showed a highly significant reduction in lens opacity score in comparison with cataract-induced group. [99]

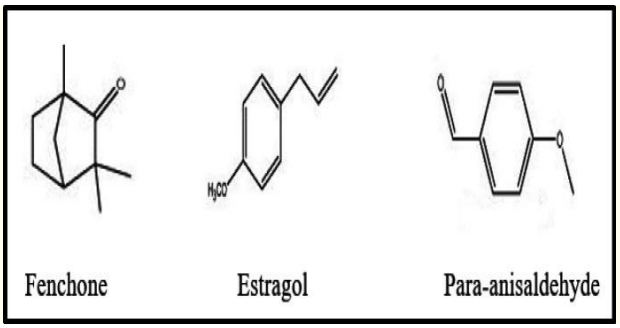


Figure 4: Chemical constituents of Foeniculum vulgare Mill

***Gingko biloba* L.**

Ginkgo biloba L. is one of the most popular herbal supplements used in the world. These trees are one of the oldest trees in the world and they are referred to as "living fossils" dating back over 250 million years. Traditionally, this plant has been used in asthma, circulatory disorders, tinnitus, vertigo and cognitive disorders. It is often prescribed as a nootropic agent in old age and dementia. The main chemical entities are terpenoids (ginkolides, and bilobalides as shown in Figure 5) [100] flavonoids, and proanthocyanides. It increases the ocular blood flow thereby, improves the circulation to the optic nerve head in healthy adult volunteers, and protects the retinal ganglion cells in patients with glaucoma. *In vitro* and clinical studies suggests the use of *G. biloba* L. as an adjuvant in the treatment of normal pressure and high-pressure glaucoma that is resistant to other treatments. [101]

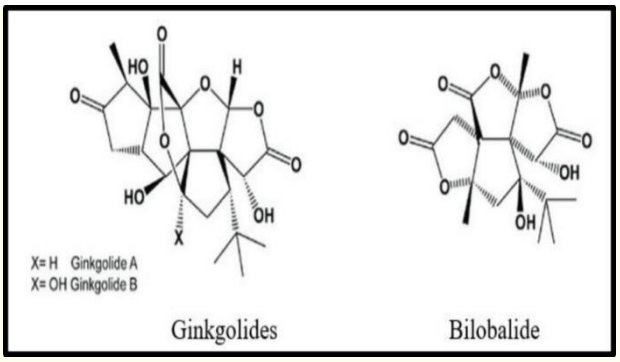


Figure 5: Chemical constituents of Ginkgo biloba L

G. biloba L. is considered a neuroprotective agent as it possesses antioxidant, anti-inflammatory and vasoregulatory actions and has been proposed in the treatment of glaucoma. [102,103,104] It acts by stabilizing the mitochondria as there are abnormal mitochondrial changes that make the retinal ganglion cells more susceptible to oxidative stress. In a study, it was found that *G. biloba* L. decreases the level of reactive oxygen species and protects the mitochondrial membrane in cultured neuronal cells. It also has vasodilatory action which helps in improving the coronary and peripheral circulation and blood viscosity.

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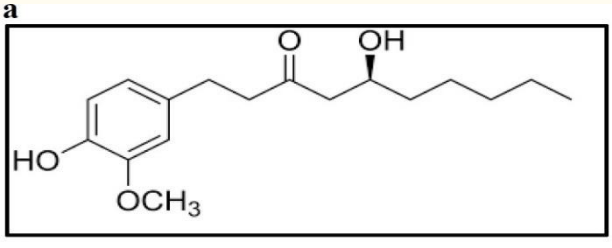
It lowers the low-grade inflammation by reduction in active cells (e.g., glial cells) in low grade inflammation.[105][106] Randomized clinical trials showed improvements in visual field (VF) indices in normal tension glaucoma (NTG) with significant increases in ocular blood flow, blood volume, and velocity. Another study showed a significant improvement in VF indices, superior and inferior retinal nerve fiber layer thickness, malondialdehyde (a plasma derived oxidative stress marker), and glutathione peroxidase (an antioxidant enzyme) in primary open angle glaucoma (POAG), but no significant changes in IOP. [107]

***Zingiber officinale* Roscoe**

Zingiber officinale Roscoe is a perennial herb with fleshy underground rhizomes. It is edible and it has high nutritional and medical values. Various scientific studies reported anticancer, antihypercholesterolaemic, antiarthritis, antibacterial, antiviral, fever reducing, antimetic, and antiulcer effects. The main active component is gingerol as shown in Figure 6a [108] investigated the retinal microvascular changes in diabetic rats treated with *Zingiber officinale* Roscoe extract containing 5% of 6-gingerol, orally. Results showed a significant reduction in hyperglycemia, the diameter of the retinal vessels, and vascular basement membrane thickness.[109] Improvement in the structural changes of the retinal vasculature was associated with significantly reduced expression of nuclear factor-κB (NF-κB) and reduced activity of tumour necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF) in the retinal tissue. In another study, the anti-glaucoma activity of aqueous methanolic extract of ginger against carbomer-induced experimental glaucoma in rabbits have been evaluated. [110] Results showed a significant decrease in IOP and serum pseudocholinesterase (Figure 6b). Another study revealed that consumption of (4 g) of fresh ginger has a significant effect on the rate of tear production. Gingerol has a stimulatory action on parasympathetic autonomic nervous system (ANS) that results in contraction of muscles and increases in glandular secretion (lacrimal gland) showed that ginger extract has protective effects against toxicity induced by ethanol in the eye of male rats, by its antioxidant activity and through improving regulation of homocysteine synthesis and homeostasis of trace elements.[111]



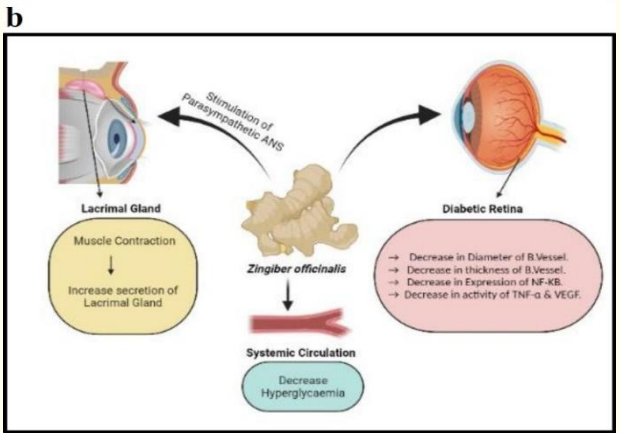


Figure 6: Gingerol's chemical structure is shown in a, & Zingiber officinalis's mechanism of action is shown in b,

Guidelines for assessing the safety and effectiveness of natural products have been established by the World Health Organization [112]. The quality and processing of plant materials, as well as general pharmacological, pharmacodynamic, and toxicological evaluations, are all addressed in this guideline, which can be used in both preclinical and clinical research evaluating herbal medications. Although this review highlights the efficacy of using crude extracts from whole plants or a specific section of any herbal plant to treat glaucoma, the discovery and isolation of an active phytochemical may also be helpful, particularly in the drug development process. A polypharmacy effect in the treatment of glaucoma may be achieved by the crude extracts' large variety of phytochemicals working in concert with one another [113]. Similarly, a number of studies have found that a combination of molecules can effectively lower IOP in patients with POAG. The mechanism or molecule responsible for these results may be difficult to isolate for study. For instance, IOP in POAG patients was reduced after they took two tablets of a dietary supplement comprising 150 milligrams of C. forskohlii extract (15 milligrams of forskolin), 200 milligrams of rutin, 0.7 milligrams of vitamin B1, and 0.8 milligrams of vitamin B2 twice daily for 30 days [114]. Patients at risk of POAG who have been using multi-dose eye drops containing preservatives on a regular basis have had less ocular discomfort after taking the same supplements [115] and have had lower increases in intraocular pressure (IOP) after neodymium:YAG laser iridotomy [116]. Further reduction in IOP and improvement in pattern electroretinogram amplitude at 6, 9, and 12 months, and foveal sensitivity at 12 months were observed in POAG patients compensated by IOP-lowering drugs who took tablets containing C. forskohlii extract, homotaurine, carnosine, folic acid, vitamins of the B group, and magnesium [117]. A comparable supplement was shown to reduce IOP, increase light and contrast sensitivity, and boost quality of life in patients with POAG in another

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trial [118] after being taken daily for 4 months. IOP was also lowered in patients with POAG who took extracts of bilberry fruit and French maritime pine bark, both rich in anthocyanins [119].

Prostaglandin analogues, beta blockers, carbonic anhydrase inhibitors, adrenergic agonists, miotics, and hyperosmotic agents are just some of the many types of eye drops used to treat glaucoma [120]. Poor eye drop administration is a leading cause of patient noncompliance in glaucoma treatment [121]. Problems include the medication's quick drainage due to gravity and washout by tearing or the nasolacrimal duct [122], as well as the drug's poor bioavailability across the blood-retinal barrier (typically 7-10 L, maximum 50 L). Nanoparticles, nanoemulsions, and nano lipid vesicles are only a few examples of nanoformulations that may improve phytochemicals' bioavailability in the eye. Compared to baicalein solution, the bioavailability of baicalein loaded with trimethyl chitosan nanoparticles was higher and the pre-ocular retention period was greater [123]. D--tocopherol poly(ethylene glycol) 1000 succinate nanoparticles (20 nm in diameter) were used in a curcumin-loaded nanocarrier formulation, as described by Davis et al. [124]. Curcumin nanocarriers applied topically twice daily for three weeks significantly reduced RGC loss in an oxidative stress-induced rat model [125]. Retinal cells were shown to be protected by curcumin nanocarriers from CoCl2-induced hypoxia and glutamate-induced toxicity in vitro [126], according to the same study. Similar results were seen when human TM cells were exposed to H2O2-induced oxidative stress and then treated with a chitosan-gelatin-based hydrogel containing curcumin-loaded nanoparticles (reduced expression of TNF and IL-1 and -6, associated with downregulated mitochondrial ROS production; [127]). In addition to curcumin, other anti-hypertensive agents have been shown to be effective in adult normotensive rabbits, including co-encapsulated resveratrol and quercetin in chitosan nanoparticles and sodium alginate-poly (vinyl alcohol) electrospun nanofibers of forskolin [128,129]. This research supports the use of phytochemical nanoformulations as an alternative to currently available glaucoma eye drops in clinical practice.

Last but not least, an appropriate approach should be employed to deal with a study's aims. Here we show that several research have exploited the Bcl-2/Bax ratio to infer that the treatment substance affects activation of the intrinsic apoptotic pathway in RGCs. Yet, the idea that Bcl-2 and Bax expressions are in a stoichiometric 1:1 balance in cells reflects the old 'rheostat' model of the Bcl-2 family's protein function, a hypothetical model that was disproved more than two decades ago when it was shown that a 1:1 interaction of these proteins was a laboratory artifact [130][131]. Furthermore, it was revealed that the long form of Bcl-X (Bcl-XL) is 16 times more numerous than Bcl-2 in retinal cells (including the GCL) expressing anti-apoptotic proteins [132].[133][134] Furthermore, Bcl-2 expression in adult RGCs is controversial [276], and it may be restricted to the Müller cells in the retina. As a result, it is possible that variations in Bcl-XL expression correlate better with RGC apoptosis than the reporting of the Bcl-2/Bax ratio.[135]

IV. CONCLUSION

One of the most common causes of vision loss is glaucoma. Recent data have gained insight into glaucoma pathogenesis, which involves a complex interaction of LC cupping, insufficient ocular blood supply, oxidative stress and neuroinflammation. The use of natural products with antioxidant, anti-inflammatory and anti-apoptotic properties may prove to be beneficial in the treatment of glaucoma. Furthermore, natural products are easily available and are cost effective. Natural products have been shown to protect against RGC loss in in vitro and in vivo preclinical studies, as well as in clinical trials. The present review highlighted various natural products such as GBE, *L. barbarum*, *D. kaki*, *T. wilfordii*, saffron, curcumin, anthocyanin, caffeine, coenzyme Q10 and vitamins B_3, D and E that confer neuroprotective effects on RGCs. Additionally, IOP has been shown to be reduced by treatment with marijuana, baicalein, forskolin, ginsenoside, resveratrol and hesperidin. GB, ginseng, anthocyanins and *L. barbarum* were reported to increase ocular blood flow in glaucoma. Additionally, caffeine administration has been shown to reduce IOP through its adenosine receptor antagonist properties. Although these may serve as alternative targets for glaucoma treatment other than IOP-lowering drugs, more evidence is required to warrant the recommendation of these novel targets. Admittedly, a few of these natural products have had no or limited clinical testing, restricting their potential use in the treatment of glaucoma. Nevertheless, it is important to ensure that the bioavailability and safety of these natural products are checked in well-designed randomized clinical trials to further determine their therapeutic potential in glaucoma.

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