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Phytochemical Approaches with their Novel Drug Delivery System towards Treatment of Glaucoma

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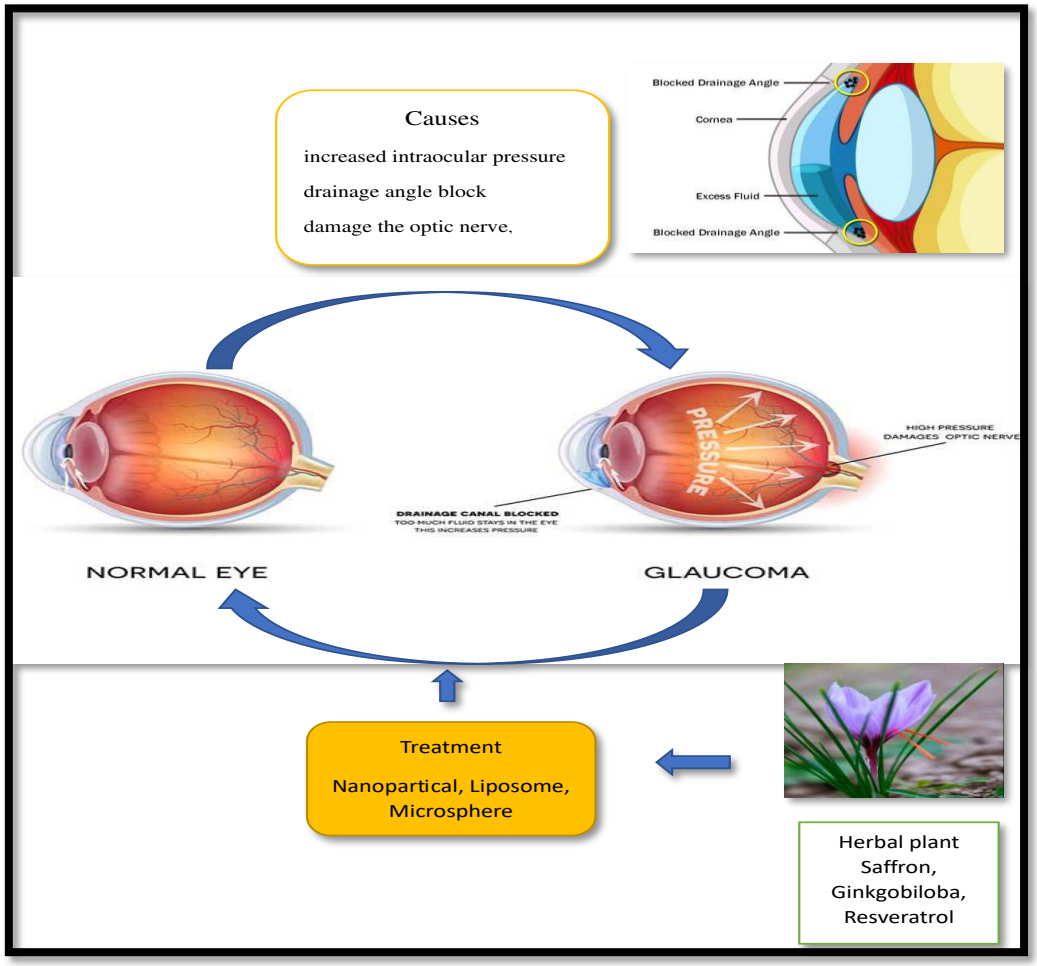
Abstract

Glaucoma is a heterogeneous group of optic neuropathies that share characteristic pathognomonic changes to the optic disc and visual field. Glaucoma is a chronic neurodegenerative disease characterized by retinal ganglion cell loss. There are a number of risk factors associated with glaucoma, including age, ethnicity, and family history. The current standard of therapy for glaucoma involves lowering the intraocular pressure through medical, laser, and/or surgical therapy. Nevertheless, there are an increasing number of glaucoma patients that use alternative medicines to treat their glaucoma or supplement their traditional glaucoma management. *Ginkgo biloba*, Saffron, and medical marijuana are amongst the most commonly used medicinal plants by glaucoma patients. A neurodegenerative disease has a varied pathogenesis scenario, including elevated intraocular pressure, and hypoxic conditions in the retina. The current standard of care for treating glaucoma patients is therapeutic IOP lowering by topical ocular medicines, laser trabeculoplasty, and glaucoma filtration surgery. Several well-controlled clinical trials have demonstrated the importance of IOP-lowering therapy in all phases of the disease. This study explored emerging glaucoma pharmacotherapy approaches based on nanomedicines, such as liposomes, microsphere and nanoparticles. The goal of this article is to provide a thorough overview of the frontier developments, problems, and hotspots that have emerged in the field of nanomedicines, perhaps paving the way for future practical advancements.

Keywords: Glaucoma, neurodegenerative disease, intraocular pressure, neuroretinal tissue medicinal plants.

Graphical Abstract



Representation of development and treatment of glaucoma infection

Introduction

Glaucoma is the main cause of permanent blindness and the second most prevalent cause of bilateral blindness(Quigley, 2006).It represents a wide spectrum of clinical diseases that have as a common endpoint, a characteristic optic neuropathy and distinctive visual field defects, with elevated intraocular pressure (IOP) being a major risk factor (Van Buskirk, 1992). Glaucoma is a group of progressive eye disorders that is characterized by damage to the optic nerve head because of the breakdown of retinal ganglion cells and their axons which merge to form the optic nerve (Allison, 2020). Glaucoma is strongly associated with increased intraocular fluid pressure, as the aqueous humor exerts increased force per area than usual on the internal surface of the eye. This may occur in glaucoma because of blockages in the trabecular meshwork (TM) of the eye, which normally functions to drain aqueous humor from the anterior chamber. Poor drainage results in the accumulation of aqueous humor and causes IOP elevation. Glaucomatous eyes with elevated intraocular pressure have been shown to exhibit abnormalities in both the extracellular matrices of the retina and lamina

cribrosa, which result in decreased function of the optic nerve and therefore lower visual acuity(Wallace , 2016). In 2020, approximately 76 million people suffered from glaucoma and this number is expected to reach 112 million by 2040(Tham, 2014).Risk factors include age and frailty, gender, myopia, genetics, family history, smoking, race, systemic hypotension and hypertension, vasospasm, use of systemic or topical steroids, migraine, obstructive sleep apnea syndrome, and most significantly, increased IOP (McMonnies 2017). There are two major types of glaucoma: primary and secondary glaucoma, both of these have two major subtypes (open-angle and angle-closure) according to the underlying anatomy and pathophysiology. Open-angle glaucoma can be classified into primary open-angle glaucoma (POAG), normal tension glaucoma (NTG), and secondary open-angle glaucoma. POAG is characterized by an increased IOP with progression of the optic nerve; NTG is characterized by normal IOP with progression and optic neuropathy, and secondary open-angle glaucoma is characterized by elevated IOP and/or optic neuropathy(Allison. 2020). Angle-closure glaucoma can be classified into primary angle-closure glaucoma (PACG) and secondary closed angle glaucoma. PACG is further classified into acute (closure of anterior chamber angle with a sudden increase in IOP) and chronic (closure of the anterior chamber angle with a gradual increase in IOP or development of peripheral anterior synechiae)(Allison. 2020). The main goal of virtually all glaucoma therapies today is to reduce IOP by either sup pressing aqueous synthesis or by enhancing trabecular meshwork (TM) and uveoscleral outflow of aqueous humor (López-Guajardo, 2012). Current treatment algorithms are based on decreasing IOP. First-line glaucoma therapy typically starts with eye drops that lower IOP by two mechanisms: suppression of aqueous humor production (beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors) or increase of aqueous humor outflow though the trabecular or uveoscleral pathways (pilocarpine, epinephrine, or prostaglandin analogues) (Weinreb, 2004). Elevated IOP causes changes locally in the eye, so it would logically follow that retrobulbar areas would be less affected and would therefore show fewer changes. Examinations of retrobulbar areas in elevated IOP models support this assumption and have not shown similar extracellular accumulations that are seen in the eye (Morrison, 2005). Drug discovery in the modern era began in the 19th century with the isolation of active compounds from plants, such as morphine from opium(Balunas, 2005). One of the first medicinal plants used for glau coma was pilocarpine – a parasympathomimetic alkaloid extracted from a South American shrub, Pilocarpusmicrophyllus(Rhee, 2001). Pilocarpine causes the contraction of the ciliary muscles, which facilitates the aqueous humor out flow through the trabecular meshwork at the iridocorneal angle in the eye . Although pilocarpine is still available for glaucoma management, its usage has declined due to the availability of modern anti-glaucoma drugs with safer side effect profiles(Allingham, 2020). Today, although the pharmaceutical industry continues to isolate active compounds from medicinal plants, it is achieved using standardized techniques. In the US, these standardized practices are enforced by the Food and Drug

Administration (FDA). The FDA regulates prescription drugs and over the counter drugs, but not alternative medicines, such as herbal medicines and nutritional supplements(Wilkinson, 2011). Despite the paucity of controlled research studies on herbal remedies, a subset of the population uses herbal remedies for their glaucoma and among the most com monly used are ginkgo biloba, bilberry, and marijuana. The majority of these patients learned about alter native medicines through media and relatives, which are not always reliable sources and could put patients at risk(Belyea, 2016; Wan, 2012). Medical marijuana has been shown to have favorable effects on glaucoma management through its IOP lowering ability (Hepler, 1971).T he most severe adverse effects of GBE are related to its antithrombotic properties. Some case reports identify ocular com plications such as retinal hemorrhage and hyphema, while systemic effects as subarachnoid hemorrhage and subdural hematoma(Belyea, 2016). In 1937, marijuana was criminalized in the United States. California was the first state to legalize the medical use of marijuana in 1996. Since then, 32 other states and the District of Columbia have also authorized the use of medical marijuana (Nazarenus, 1971). Marijuana is composed of over 400 compounds, but the main components responsible for its physiological effects are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The mechanism of action by which marijuana exerts its ocular effect is not well understood (Zhan, 2005). The main ocular risk factor for angle closure involves having a crowded anterior segment in a small eye, with as hallow central anterior chamber depth, a thicker and more anteriorly positioned lens ,and short axial length of the eye (Lavanya, 2008).Topical beta blockers (BBs) have been a mainstay of glau coma treatment since their introduction in 1978. Their mechanism of action is reduced aqueous production via blockade of β-adrenoreceptors in the ciliary epithelium(Coakes, 1978).Nonselective β1andβ2 antagonists along with selective β1 antagonists are commercially available. Nonselective agents in cludetimolol, levobunolol, metipranolol, and carteolol.Betaxolol is a selective β1 antagonist. Of these choices, timolol was the first introduced and remains the most commonly used agent. Timolol has been shown to reduce IOP by 20% to 35% on average and remains the US Food and Drug Administration's "criterion standard" drug for glaucoma therapy against which new medications are commonly judged before approval (Marquis, 2005). Levobunolol, available in 0.25% and 0.5% solutions typically administered twice daily, and metipranolol 0.3% administered twice daily have similar efficacy to timolol(Müller, 1986). Local adverse effects of BBs include conjunctivalhyperemia, stinging, superficial punctate keratitis, and dry eye syndrome(Müller, 1986) . Currently, clinical treatments for all glaucoma types aim for lowering IOP through topical hypotensive drugs or surgery. However, these approaches are not sufficiently successful for many patients who continue to lose their vision (Susanna, 2015). Numerous research models have been used to gain a considerable understanding of the pathogenesis of glaucoma, and to assess therapeutic approaches for glaucoma treatments (Almasieh, 2017). Oral administration of vitamin B3 (nicotinamide, precursor of NAD+)wasprotective as both

prophylaxis and an intervention of glaucoma, as shown by the reduced incidence of optic nerve degeneration, prevention of RGC soma and axonal loss and retinal nerve fiber layer thinning and preserved visual function(Williams, 2017). 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. various natural products such as L. barbarum, D. kaki, T. wilfordii, saffron, curcumin, anthocyanin, caffeine, coenzyme Q10 and vitamins B3(Sim, 2022).This article's goal is to assess the available data about the most popular herbal remedies for treating glaucoma and go over their side effects. A literature search was carried out using the Cochrane Library, PubMed, and Google Scholar databases.

Epidemiology

In 2010, 2.1 million persons around the world went blind because of glaucoma(Schuster, 2020). In western Europe, glaucoma is the second most common cause of irreversible blind ness, after age-related macular degeneration (Bourne, 2018). The prevalence of glaucoma in Europe among persons aged 40 to 80 years is 2.93%. Most suffer from open-angle glaucoma, which has a prevalence of 2.51% from age 40 to age 80(Tham, 2014). In Germany, too, most persons with glaucoma have open-angle glaucoma (Höhn, 2018). The prevalence of open-angle glaucoma rises with age 19, from 0.4% at the age of 40–44 years to 2.7% at age 70–74 and 10.0% over age 90 in persons of European ancestry. Men are more commonly affected than women (odds ratio [OR] 1.30 (Kapetanakis, 2016). It was estimated that the global prevalence of diabetes is about 10% of the total population and diabetes accounts for more than 30% of NVG cases(Jeganathan, 2008). The prevalence and composition of NVG are different among countries and races(Yang, 2018). As a secondary systemic disease complication, the disease progression is often slow but irreversible if no early prevention and intervention are made. Studies have confirmed the association between long-term poorly controlled diabetes and the occurrence of NVG (Löffler, 2006).Thus NVG is often an advanced manifestation of DR. The reported prevalence of NVG was 2.1% in overall diabetic patients and rose to 21.3% in patients with PDR (Lee, 1998). We studied 597 eyes with NVG. The incidence was 6.6/10,000. It declined from 13/10,000 in 2008–0.1/10,000 in 2012 ($P < 0.001$). The decline in 2008 coincided with the introduction of intravitreal injection bevacizumab in Saudi Arabia. Males had a significantly higher NVG risk (odds ratio [OR] = 2.2). Diabetes and hypertension were associated with NVG in 88% and 42.7% of cases, respectively. In 377 (72%) diabetic patients, the glycemic control was poor (HbA1C >7%). Visual acuity was 20/20–20/40 in 14 (2%), 20/50–20/200 in 79 (13%), 20/200–20/400 in 456 (76%), and <20/400 in 45

(7%) eyes. Intraocular pressure was higher than 30 mmHg in 438 (73%) eyes. The cup-to-disc (CD) ratio was >0.8 in 86 (14%) eyes. During the early period (2002–2007) and later period (2008–2012), CD ratio (χ^2 = 4, P = 0.09) and anterior chamber angle (P = 0.8) were not different. The presence of NVG in contralateral eye (OR = 0.8, P = 0.3) in both periods was similar (Al-Bahlal, 2017).

Risk factor

Risk factors are angle closure include female sex, olderage ,and Asian ethnicity (eg, Chinese) discussed in **Fig. (1)**. Eyes with angle closure tend to share certain biometric characteristics. The main ocular risk factor for angle closure involves having acrowded anterior segment in a small eye, with as hallow central anterior chamber depth, a thicker and more anteriorly positioned lens, and short axial length of the eye(Sakai, 2005). With anterior segment optical coherencetomography,otheranatomical risk factors for angle closure have been recently identified such as smaller anterior chamber width ,area and volume, thicker irides with greater iris curvature, and a greater lens vault (Nongpiur, 2011).Glaucoma risk increases with age.As a consequence, glaucoma can be expected to be associated with other age related diseases such as macular degeneration(Le, 2003). In the Ocular Hypertension Treatment (OHT) study, male gender was found by univariate analysis to be a useful predictor for the onset of primary open angle glaucoma(Gordon, 2002). A Bayesian meta-analysis found that men were more likely to have OAG with the reservation that gender influence depends on the definition of glaucoma.For example, a review of the literature concluded that women are at higher risk for angle-closure glaucomabut that there is no clear gender predilection for OAG (Vajaranant, 2010). These findings may only be relevant to the groups studied. That women usually live longer than men increases their risk for glaucoma and glaucoma blindness (Rudnicka, 2006). A review of the findings from 11 population-based studies found a wide range in the prevalence of POAG among populations of the "same race"(Kosoko-Lasaki, 2006).A higher glaucoma prevalence has been found in Asian populations including a higher incidence of primary angle-closure glaucoma compared to white patients(Cho, 2014).

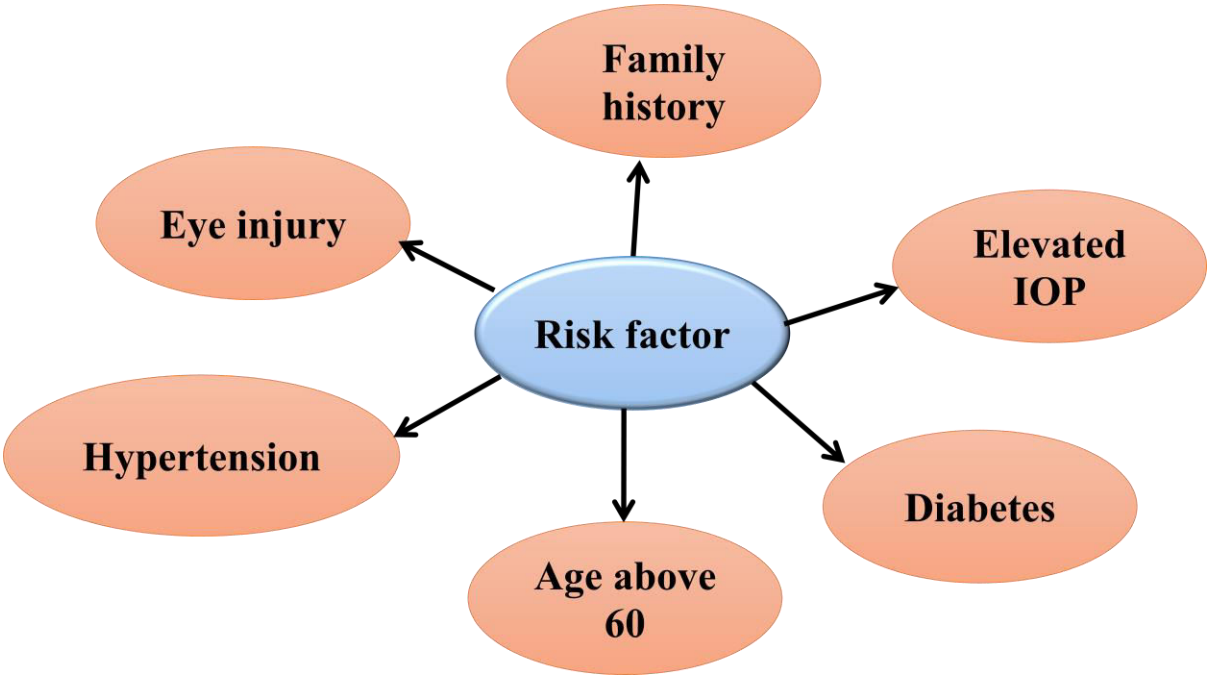


Fig. (1). Risk factor of associated with glaucoma.

Phathophysiology

Although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is related to retinal ganglion cell death. The balance between secretion of aqueous humor by the ciliary body and its drainage through 2 independent pathways—the trabecular meshwork and uveoscleral outflow pathway—determines the intra-ocular pressure. In patients with open-angle glaucoma, there is increased resistance to aqueous outflow through the trabecular meshwork. In contrast, the access to the drainage pathways is obstructed typically by their is in patients with angle-closure glaucoma (Weinreb, 2014).Intraocular pressure can cause mechanical stress and strain on the posterior structures of the eye, notably the lamina cribrosa and adjacent tissues(Quigley, 1981). The sclera is perforated at the lamina where the optic nerve fibers (retinal ganglion cell axons) exit the eye. The lamina is the weakest point in the wall of the pressurized eye. Intraocular pressure–induced stress and strain may result in compression, deformation, and remodeling of the lamina cribrosa with consequent mechanical axonal damage and disruption of axonal transport(Fechtner, 1994).Primary neural pathological processes may cause secondary neurodegeneration of other retinal neurons and cells in the central visual pathway by altering their environment and increasing susceptibility to damage (Almasieh, 2012).Systemic application of mineralocorticoids to glaucoma patients shows no changes in the IOP in most of the cases(May, 2012).However, single individuals react with a high increase in intraocular pressure (Frenkel, 1964).Points to a possible role of mineralocorticoids for glaucoma therapy but not for general glaucoma pathophysiology. The narrowed role is also supported by the negative findings in the animal models and the various

human conditions described in **Fig. (2)**. The therapeutic effect of mineralocorticoid antagonists seems mainly mediated by a decrease of aqueous humour formation (Mirshahi, 1996).

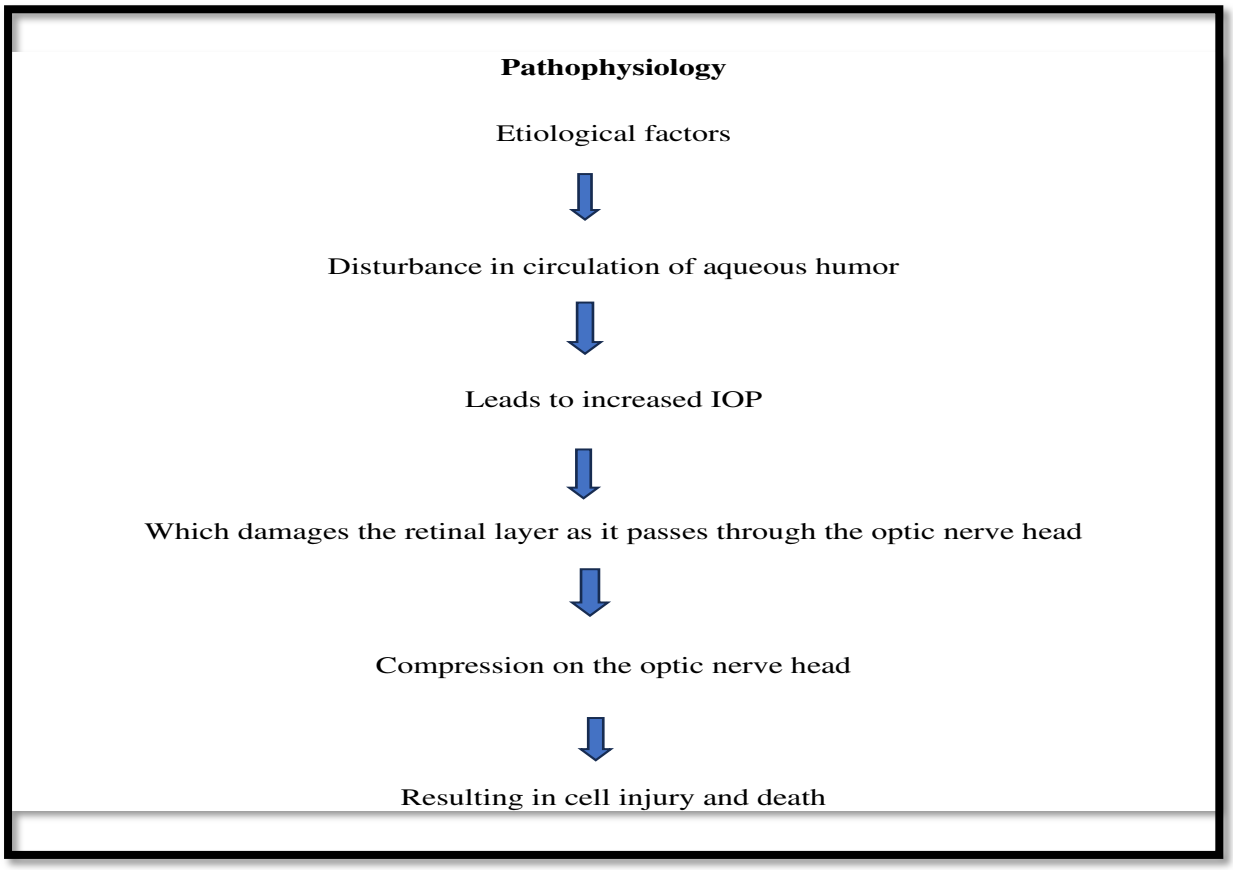


Fig. (2). General pathophysiology of glaucoma

Pathogenesis

Elevated IOP causes changes locally in the eye, so it would logically follow that retrobulbar areas would be less affected and would therefore show fewer changes. Examinations of retrobulbar areas in elevated IOP models support this assumption and have not shown similar extracellular accumulations that are seen in the eye (Morrison, 2003).Elevated IOP has been suspected to induce negative effects by the formation of a hypoxic environment in the eye following a reduction in ocular blood flow (Williams, 2017). Glaucomatous neurodegeneration is often preceded by a reduction of ocular perfusion due to decreased blood flow. Additionally, not all patients with glaucoma have elevated intraocular pressure, exemplified by normal tension glaucoma. Ischemia and histopathological glaucomatous abnormalities may occur in conditions of elevated IOP as well as in normal IOP conditions (Macanian, 2022).Conversely, early changes are often seen in the lamina cribrosa, a structure in the optic nerve head that is responsible for supporting the axons exiting the eye. The

lamina cribrosa (LC), the mesh-like connective tissue in the optic nerve head, contains a meshwork of pores through which RGC nerve fibers pass through before converging to form the optic nerve. Along the optic nerve, supportive glial cells are present to provide cellular support for RGCaxonsandmaintain communication between these cells. Astrocytes are commonly found in these locations and maintain RGC axon health by functioning in the extracellular space to maintain ion balances and, along with other maintenance functions, remodel the extracellular environment. In glaucomatous eyes, astrocyte function around the lamina cribrosa decreases which results in pathogenic remodeling of the extracellular matrix. These abnormalities, including extracellular depositions of collagens and basement membrane components, have been noted in pathologic studies of glaucomatous optic nerve heads in humans and monkeys(Hernandez, 2000) as mentioned in **Fig. (3)**.Retinal ganglion cell axons in the glaucomatous ONH exhibit several abnormalities which result in the degeneration of these axons. Studies have shown that in both ani mal models and humans, RGCaxons in the ONHexhibit swelling. This axonal swelling has been proposed to represent the accumulation of transport vesicles, thereby demon strating the dysfunctional retrograde and anterograde transport occurring in the ONH axons .Inhibited transport may have many complications, including the prevention of neurotrophic factors from reaching the RGCs. Retinal ganglion cell axons eventually synapse on other neurons which release neurotrophic factor, indicating that the connection between these neurons is stable and therefore maintains the health of the neuronal connection. When such connections are disrupted, retinal ganglion cell axons and somas begin to degenerate. Morgan et al. showed that of all RGC axons passing through the lamina cribrosa, approximately 8–12% deviated to travel through a tight space between the collagenous plates (Hernandez, 2000; Morgan, 1998).Furthermore, normal function of signal transduction of RGCs is not affected, as retinal ganglion cell soma produces both brain-derived neurotrophic factor and TrkB receptors themselves (Vecino, 2002).The exact pathogenesis of glaucoma is complex and has not yet been fully eluci dated. The potential mechanism involved in the neurodegeneration of glaucoma has been postulated to involve an amalgamation of mechanical, vascular, genetic and immunological factors (Sim, 2022).The mechanical hypothesis explains the relationship between the IOP and RGC pathphysiology. The perforated lamina cribrosa (LC) is the weakest part of the sclera, and it is where the RGC axons pierce through the minute perforations to form the optic nerve, while the central retinal artery and vein pass through the LC via a larger central aperture (Standring, 2022). Optic nerve cupping is characterized by the remodeling of the extracellular matrix (ECM) and fibrosis in the LC. Glaucomatous LC cells showed increased ECM gene expression and elevated intracellular calcium, which is known to promote proliferation, activation and contractility in fibroblasts via the nuclear factor of activated T cells/calcium signalling pathway . This deformation damages the optic nerve and capillaries passing through the LC, disturbing the anterograde axonal

transportation of RGCs, which then ultimately triggers visual field defects in glaucoma(Irnaten, 2018).This study also demonstrated upregulation of hypoxia-inducible enzyme heme oxygenase-1 (HO-1) and the anaerobic glycolytic enzyme lactate dehydrogenase, and increased generation of superoxide radicals in the retina and ONH, as well as the active subunit of the superoxide-generating enzyme NADPH oxidase, suggesting the involvement of oxidative stress(Irnaten, 2018).The blood flow of the ONH was significantly reduced in the eyes of pre-perimetric glaucoma patients, where there are characteristic glaucomatous changes in the optic disc, but without the presence of visual field defects(Shiga, 2016).In accordance with animal studies, numerous studies have provided evidence of in creased oxidative stress in glaucoma patients. In addition, blood and aqueous humor levels of oxidative stress-related molecular biomarkers, i.e., protein carbonyls and advanced glycation end products, significantly increased in glaucomatous samples compared with healthy controls (Hondur, 2017).Similarly, PACG patients presented with decreased serum levels of total antioxidant status (TAS) and superoxide dismutase (SOD), as well as increased levels of malondialdehyde (MDA), compared to healthy controls . A meta-analysis further indicated that POAG patients had lower TAS in the blood and higher levels of SOD, glutathione peroxidase (GPX) and catalase (CAT) in the aqueous humour(Tang, 2019).Systemic inflammatory status markers, i.e., the neutrophil-to lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune inflammation index, weresignificantly increased in POAG patients compared with the control group. POAG patients exhibited a significant increase in various cytokines, i.e., serum interleukin (IL)-4,-6 and-12p70 and tumor necrosis factor-alpha (TNF-), compared with the controls (Rudnicka, 2006). Similarly, elevated plasma TNF-levels in patients with POAG and pseudo exfoliation glaucoma were detected (Kondkar, 2018).In addition to the inflammatory response, glial cells in the retina also play a vital role in the function of the retina by providing homeostatic and metabolic support to the photoreceptors and retinal neurons.Glaucomatous eyes have been shown to have decreased levels of EAAT-1, and the glutamate receptor subunit N-methyl-d-aspartate (NMDA)-R1 (Naskar, 2000).

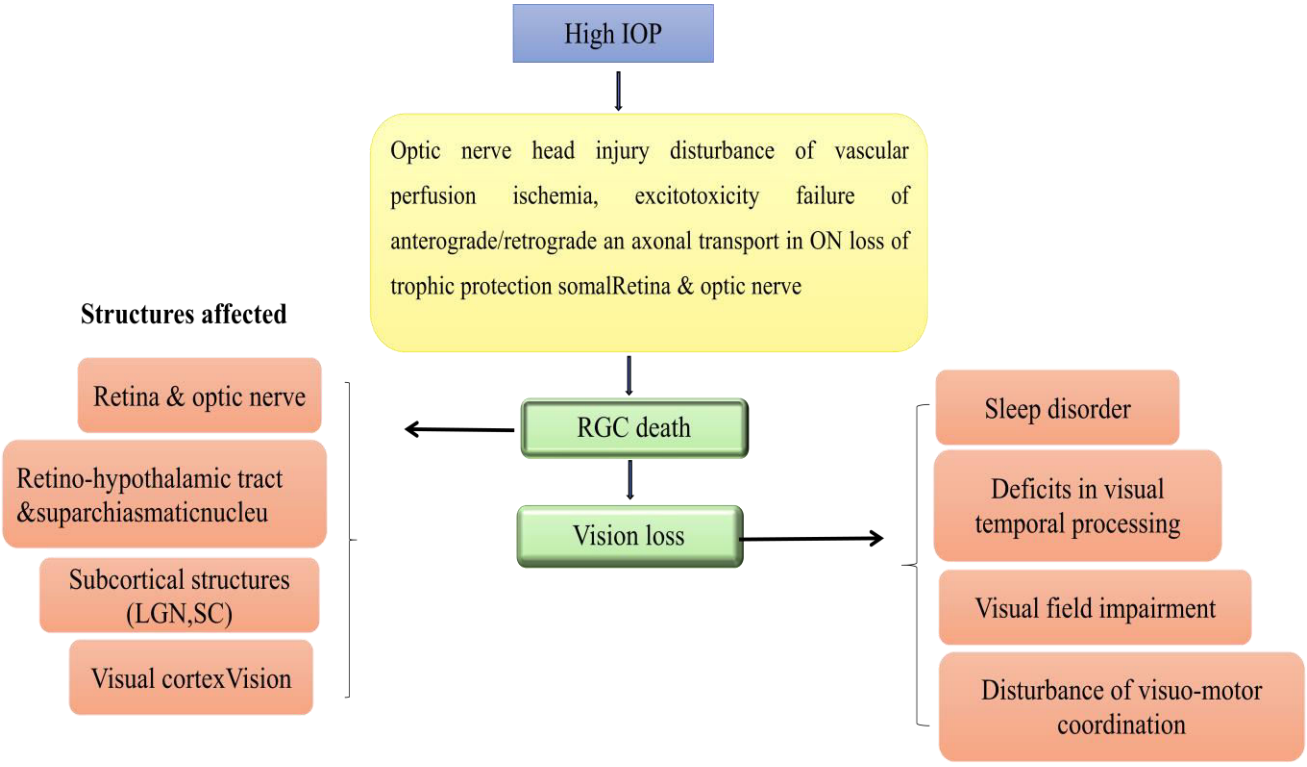


Fig. (3). Pathogenesis and problems associated with glaucoma

Diagnosis

The retinal ganglion cell death and optic nerve fiber loss in glaucoma, characteristic changes in the appearance of the optic nerve head and retinal nerve fiber layer occur. These changes are the most important aspect of a glaucoma diagnosis and can be identified during ophthalmoscopic examination of the optic nerve head(Weinreb,2014).The importance of conducting an appropriate ophthalmologic examination of the eye cannot be overstated with respect to early detection of glaucoma. Retinal ganglion cell loss causes progressive deterioration of visual fields, which usually begins in the midperiphery and may progress in a centripetal manner until there remains only a central or peripheral island of vision as shown in **Fig. (4)**.Because there is no single perfect reference standard for establishing the diagnosis of glaucoma, early diagnosis can be challenging. Although examination of the optic nerve head can reveal signs of neuronal loss, wide variability of its appearance in the healthy population makes identification of early damage challenging. Presence of characteristic visual field defects can confirm the diagnosis, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing(Harwert,2010). Longitudinal evaluation and documentation of structural damage to the optic nerve is, therefore, a critical component of the diagnosis of the disease,Such an evaluation may be performed by observing the optic nerve head using an ophthalmoscope or by obtaining optic nerve head photographs. However, subjective identification of optic disc damage from glaucoma can be

challenging, with large disagreement in grading observed even among glaucoma specialists (Jampel,2009).Primary care physicians have an important role in the diagnosis of glaucoma by referring patients with a family history of glaucoma to undergo a complete ophthalmologic examination. Anyone with a family history of the disease and who has not had a dilated,funduscopic examination of the optic nerve head in the past 2 years should be referred for examination. In addition, evaluation of the optic nerve with direct ophthalmoscopy performed by primary care physicians during a routine clinical visit may reveal signs suspicious for optic nerve damage that should prompt referral to an ophthalmologis(Hollands,2013).With biomicroscopy, one is able to visualize posteriorly located structures such as the ciliary body, lens zonules, and the anterior choroid, making it useful for identifying specific causes of angle closure. Biomicroscopic imaging requires a skilled operator and cooperation from patients during the imaging. Anterior segment optical coherence tomography is a noncontact imaging device that acquires high-resolution cross-sectional images of the anterior chamber. The incorporation of automated image analysis software allows for rapid measurement of anterior segment parameters. Comparison studies found a higher rate of diagnosis of closed angles with tomography than with gonioscopy (Wong,2009).In the early stages, the NVI may be unnoticeable, so it can be detected by iris fluorescein angiography (FAG). FAG is considered to be the gold standard in identifying NV and ischemic areas in the eye blood circulation . This method is used to determine retinal and choroidal blood flow with fluorescein dyes. FAG evaluates the blood vessels, the presence of NV, circulatory disorders, or increased vascular permeability. The early sign of NV in the iris is the leakage of intravenously injected sodium fluorescein dye from vessels at a pupillary margin(Urbonavičiūtė,2022).

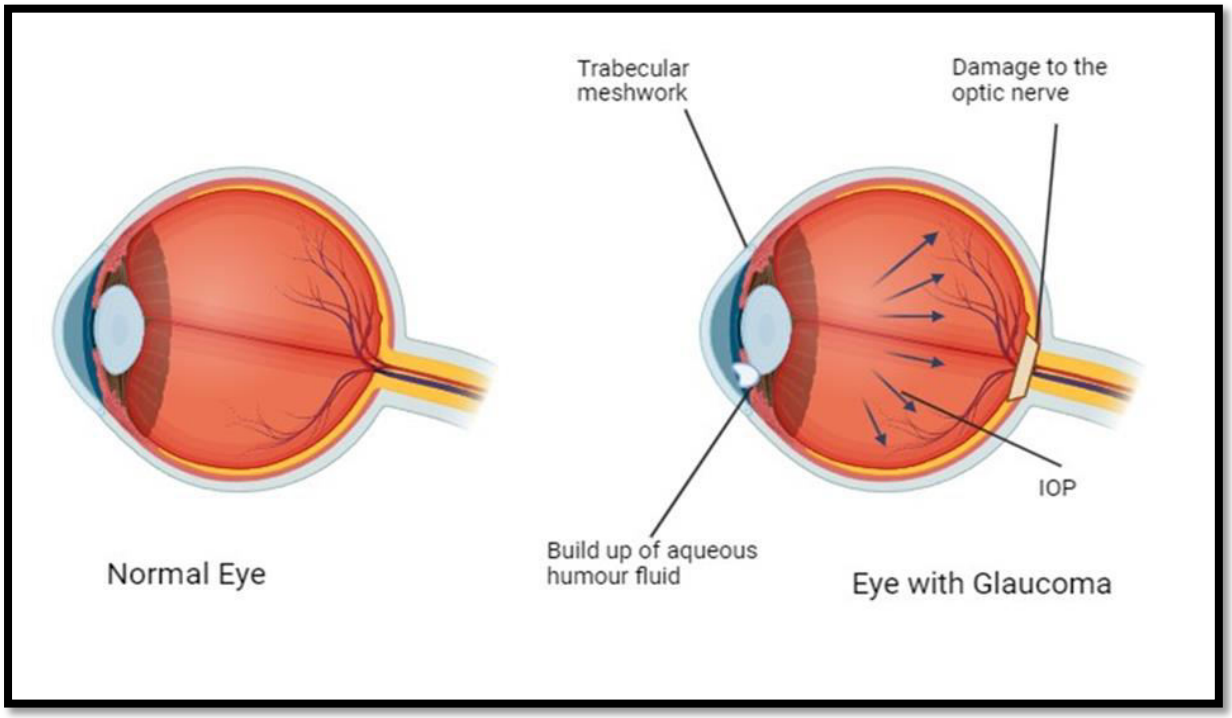


Fig. (4). Comparison of normal and glaucoma eye.

Novel approaches

Nanoparticle

Multiple studies have attempted to develop drug encapsulated NPs for the delivery to anterior and posterior segments of the eye. Conjugating ocular drugs onto NPs has been shown to boost eye permeation, particularly pass through the precorneal barrier.NPs made of natural or synthetic polymers and proteins [e.g., chitosan, polyethylene glycol (PEG), polycaprolactone, sodium alginate, and albumin] usually take the form of finely dispersed latexes (Kaminskas,2011). Due to their optimal size for the penetration of ocular barriers, NPs usually do not impose eye irritation, thereby limiting the frequency of drug administration as well as maintaining sustained drug release(Grefi1995). The same features were observed for human serum albumin NPs, where the conjugated drug molecules successfully infiltrated the retina layers through specific pathway in the Müller cells, relying on endocytosis and exocytosis (Talevi,2014). By controlling properties of NPs, it is possible to achieve maximal therapeutic effects, minimal side effects as well as highest solubility for targeted drugs. Engineered NPs may be created to help the molecule to find its target. For instance, docetaxel and ketoconazole loaded in solid lipid nanoparticles had their surface modified with folic acid to improve brain targeting (Venishetty,2013). Nanoparticles may generate cellular toxicity through oxidative stress, interaction with the cell membrane, and inflammation. Plants such as ginkgo biloba, saffron, and phytochemicals such as epigallocat echin-3-gallate and resveratrol are known as traditional remedies used in glaucoma pathology(Al Owaifeer,2018). The beneficial component of this living fossil tree is found in the ginkgo extract, which contains polyphenolic flavonoids that stabilize the mitochondria at organelle level, and also exerts multiple therapeutic properties, including the antioxidant, antimicrobial, neuroprotective and antiapoptotic effects , Extract 761 (EGb761), obtained from leaves of the ginkgo plant, has been effective in treat ing Alzheimer's dementia and cognitive impairment. T herefore, researchers attempted to use EGb761 in the treatment of glaucoma due to the analogous biological and mechanistic features between these two chronic disorders (Birks,2009). In previous studies, both short- and long-term effects of the Ginkgo biloba extract were tested and the extract was used to treat pre-existing patients with normal tension glaucoma, often resulting in a significant improvement of visual acuity, In a similar study, the standardized EGb761 extract demonstrated a progressing pharmacological effect on the oxidative stress with improved vascular circulation in both in vitro and in vivo experiments, highlighting the neuroprotective effect of the drug against the hypoxic injury of RGCs(Cho,2019). Saffron, the dried stigmas originating from the Crocus sativus flower of the Iridaceae family in Greece, has been commonly used in cooking as an aromatizing and coloring seasoning, The major constituents in saffron are natural carotenoid compounds, namely crocin and crocetin (Bathaie,2014) . Both saffron compound extracts, crocin and crocetin, showed an enhanced neuroprotective effect through repression of activated microglia

neurotoxicity. The development of intracellular ROS and nitric oxide is inhibited with a slower release of TNF-α and IL-1β In a pilot study, Bonyadi et al. investigated the influence of an aqueous saffron extract on the IOP in the eyes of POAG patients and showed that the treatment significantly decreased the mean base line IOP compared to the control group by the end of the therapy (JabbarpoorBonyadi, 2014).In a pilot study, Bonyadi et al. investigated the influence of an aqueous saffron extract on the IOP in the eyes of POAG patients and showed that the treatment significantly decreased the mean base line IOP compared to the control group by the end of the therapy(JabbarpoorBonyadi,2014).Epigallocatechin-gallate (EGCG) is a type of catechin mainly found in green tea. It is well known as a robust antioxidant with multifunctional properties and has been investigated for its contribution to neuroprotection in human corneal epithelial cell culture models and ani mal models of glaucoma (Falsini,2009). Earlier findings not only demonstrated its therapeutic effect on the axon and the bodies of RGCs in optic nerve crush and N-methyl d-aspartate (NMDA) toxicity studies, but also showed an elevation in the survival rates of RGCs via oral administration(Shen,2015). In a similar study, which also used oral EGCG, the drug was shown to be a potent penetrator into the retina, where it reduced both the injury caused by ischemia and in vitro white light-induced apopto sis in RGC-5 cells (Zhang,2008). Resveratrol (RSV), also known as 3,5,4′-trihydrocystil bene, a nonflavonoid polyphenol compound derived from plant sources such as grapes, blueberries and apples, has been developed into an effective phytoalexin (Harikumar,2008). It has diverse roles in relation to the well-being of humans, by virtue of biological attributes including antioxidant, ant inflammatory and neuroprotective functions, In POAG patients, RSV was shown to interrupt intracellular ROS, inhibit the release of inflammatory cytokines and slow down the accretion of carbonylated proteins, hence supporting the neuroprotective action of the drug against the RGC apoptosis and the ability to slow down the progression of glaucoma (Luna,2009). Moreover, researchers have suggested the induction of mitochondrial biogenesis by RSV to alleviate glaucomatous retinopathy. This is due to the efficiency of RSV in reducing derivative-serum in the RGC-5 cell line by subcellular translocation of SIRT1 dependent proliferator-activated receptor-gamma coactivator 1 alpha(Liu,2012). In addition, Shamsher et al. studied the in vitro and in vivo neuroprotective effects of RSV and curcumin nanoparticle formulations with ~ 70% encapsulation efficiency (Shamsher,2021). One of the examples of long-standing, well-conducted research and development of an anti-inflammatory agent comes from curcumin, a major active compound of turmeric, Curcuma longa(Dong,2012). The chemical properties in curcumin with anti-inflamma tory and antioxidant functions have been suggested to be associated to its hydroxyl and methoxy group, which deregulates TNF-α and pro-inflammatory interleukins which lead to the downregulation of STAT pathways. In both in vitro and in vivo experimental glaucoma stud ies, curcumin has shown antioxidant effects, as demon strated by the improved

cell viability of microglial cells, reduced intracellular ROS and apoptosis of RGCs(Yue,2014). One of the promising drug carriers for the delivery of curcumin has been the amphiphilic polymer polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, Soluplus (Chen,2020). Generally, in the drug delivery field for neurodegenerative and ocular diseases, NPs are most commonly made of soft carbonaceous materials, such as polymers and/or lipids, Both lipid and polymeric NPs have success fully delivered drugs for several therapeutic purposes, while protecting the encapsulated drugs from enzymatic degradation and controlling their release. NPs made of natural or synthetic polymers and proteins [e.g., chitosan, poly(ethylene glycol) (PEG), polycaprolactone, sodium alginate, and albumin] usually take the form of finely dis persedlatexes(Souto,2010). However, compared to nanomicelles, a type of nanocarrier, polymeric-based NPs have been unable to escape the rapid loss of the instilled solution from the precorneal integument and the nasolacrimal drainage system. To overcome this limitation, NPs with mucoadhesive properties (i.e., chitosan and hyaluronic acid) were developed (Silva,2017). Polysaccharides (components of the vitreous body) have also been proven safe for incorporation into ophthalmic solutions. Other NPs composed of polymeric-based materials have also improved the drug delivery interaction with the cornea, and thus allowed for the controlled drug release and the treatment of the ocular disease of the outer segment. It was postulated that nanocarriers coated with bioadhesive polymers (e.g., PACA and cyclosporine-A) can enhance the penetration of the embedded drug and improve the stability in the lacrimal fluid, which has been shown to prevent the enzymatic degradation of the delivered drug (Swetledge,2021). One example is lectin, a glycoprotein that exhibits extremely high binding affinities for specific car bohydrate groups present on the surface of corneal epithelial cells, Lately, there has been an increased emergence of reports on NPs (Manchester,2018).Polymeric NPs can form nanocapsules (surface vesicular systems) or nanospheres (matrix systems) depending on their internal structure and preparation method. While the former systems contain a drug encapsulated within a liquid core cavity, the latter ones contain a structural polymeric matrix where the drug is physically and uniformly dispersed (Gentile,2014) and many more reported in **Table 1.**

Table 1. List of natural product reported in nanoparticle.

S. No	**Natural product**	**Extract**	**M.O.A**	**Ref**
1.	Ginkgobiloba	polyphenolic flavonoids	degeneration and deposition of	(Birks,2009)

		egb761	extracellular f ibrils in the exfoliation syndrome, indicating that both are likely derived from similar misfolding mechanisms	
2.	Saffron	crocin and crocetin	therapeutic spectrum, including neuroprotective, anti-inflammatory, anti-oxidant and anti-genotoxic activity, Both saffron compound extracts, crocin and crocetin, showed an enhanced neuroprotective effect through repression of activated microglia neurotoxicity. T he development of intracellular ROS and nitric oxide is inhibited with a slower release of TNF-α and IL-1	(Bathaie,2014; (JabbarpoorBonyadi, 2014))
3.	Epigllacotechin-3galcate	catechin	It is well known as a robust antioxidant with multifunctional properties and has been investigated for its contribution to neuroprotection in human corneal epithelial cell culture models and ani mal	(Falsini,2009)

			models of glaucoma	
4.	Resveratrol	Phytoalexin.	In POAG patients, RSV was shown to interrupt intracellular ROS, inhibit the release of inflammatory cytokines and slow down the accretion of carbonylated proteins, hence supporting the neuroprotective action of the drug against the RGC apoptosis and the ability to slow down the progression of glaucoma	(Harikumar,2008; (Luna,2009))
	Curcuma longa	Curcumin	reduced intracellular ROS and apoptosis of RGCs	(Yue,2014), (Chen,2020)]

Liposomes

Many ophthalmic drugs, such as citicoline, are considered to have pharmacological activities against glaucoma, as already demonstrated in various experimental in vitro and in vivo studies. Nevertheless, low aqueous solubility and poor oral bioavailability limit the use of these compounds as effective therapeutic agents. Liposomes represent a category of vesicles that can act as nanocarriers for drug delivery and increase the solubility and stability of drugs, thereby improving their bioavailability and therapeutic potential. Although the entrapment efficiency of citicoline is still relatively low, the improved solubility and optimized efficiency of the encapsulated biomolecules could lead to the development of efficient clinical products(Bonechi,2023).Citicoline(cytidine-5-diphosphocholine) is an endogenous molecule essential to synthesizing membrane phospholipids and acetylcholine and increasing neurotransmitter levels in CNS. The neuroprotective properties of citicoline in glaucoma have been defined; in particular, it induces antiapoptotic effects, increases retinal dopamine levels, and counteracts thinning of the retinal nerve fiber layer (Parisi,2018).Recently, liposomal ophthalmic formulations have been widely

applied for drug-delivery applications, offering various advantages over the other ophthalmic delivery systems due to their biodegradability and nontoxicity. Also, their employment in ophthalmic drug forms enhances the bioavailability of loaded-molecule formulations against enzymes present on the surface of the corneal epithelium, while conventional ophthalmic formulations such as solutions lack bioavailability features(Garrigue,2017).The presence of cholesterol, a rigid and almost planar molecule, enhances the fluidity of the bilayer membrane and reduces the leakage of water-soluble molecules,Water soluble drugs like citicoline are capsulated into the inner aqueous part. The thin-film hydration method has been considered the most widely used technique(Jaafar-Maalej,2010). The aim of the present research study was to encapsulate citicoline in a liposomal carrier with two different molar ratios, which is expected to improve the efficiency of drug delivery for possible ophthalmic applications. These vesicles are composed of 1,2-dioleoyl-sn-glycerol 3-phosphocholine (DOPC) and cholesterol (Chol) in two different molar ratios, (1:1) and (2:1), respectively(González-Cela-(Casamayor,2022). The formulation DOPC:Chol, Cit (1:1), 1 reaches a high value of release faster than the formulation DOPC:Chol, Cit (2:1), 1. Cholesterol concentration affects the release process of citicoline in physiological fluid. In particular, a higher cholesterol concentration accelerates the release of the drug. This behavior is directly influenced by the increase in fluidity of the lipid bilayer, which increases with cholesterol concentration (Bonechi,2021). The potential of liposomes as drug delivery systems for ocular surface isenormous and increasingly evident. They are investigated to treat pathologies of the ocular surface itself, as is the case for numerous ocular surface infections, as well as for anesthesia (Gonzalez,2022). In therapeutics, there are many ocular antihypertensive drugs available in chronic topical treatments, such as the 2-adrenergic receptor agonist brimonidine and prostaglandin PGF2 analogue travopros(Whitson,2002).In the case of ocular topical administration, previous studies on corneal cells have shown that liposomes are able to penetrate into the cells of the ocular surface,Furthermore, the lipid bilayer of liposomes is mainly composed of phospholipids, widely presented in the tear film composition(Gonzalez,2022) [104]. Studies carried out with liposomal formulations containing HPMC(hydroxypropyl methylcellulose) have shown an improvement on the loaded drug efficacy after ocular instillation,In addition, previous studies carried out in our research group showed that the inclusion of HPMC in the eye-drops has a beneficial effect on their tolerance on the ocular surface, Synthetic phospholipids 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPM)were purchased from Lipoid GmbH (Ludwigshafen, Germany). The other lipid components of liposomes, Cholesterol (99%),-Tocopherol acetate (96%), and Ubiquinol (USP reference standard)(Gonzalez,2022).Our liposomal formulations were composed by several components with antioxidant and osmoprotective activity. Antioxidant compounds were included in the lipid bilayer, in addition to cholesterol, this last one providing rigidity to liposomes(Biruglia,2015).The

combination of acetazolamide-loaded nano-liposomes and Hydroxypropyl methylcellulose (HPMC) with similar components to the preocular tear film in an osmoprotectant media (trehalose and erythritol) is proposed as a novel strategy to increase the ocular bioavailability of poorly soluble drugs.The inclusion of HPMC produced an increment in viscosity (from 0.9 to 4.7 mPas. 64.9 2.6% of acetazolamide initially included in the formulation was retained in vesicles (Gomez,2019).Acetazolamide (ACZ) is a carbonic anhydrase inhibitor with a potent specific effect in reducing aqueous humour production and, therefore, intraocular pressure (Sugrue,1997).Timolol maleate (TM) is a non-selective beta-blocker drug used in the treatment of glaucoma for more than three decadesC. cicadae mycelia extract in a steroid-induced rat model of glaucoma. The aqueous extract and ethanolic extract of the mycelia were obtained through lyophilization (Homog,2021). Herbal medicines have become a prominent global field of research for health care. C. cicadae have long been used as a Chinese herbal medicine since ancient times. It belongs to the Clavicipitaceae family, and is also known as cicadae flower or Chan-hua. It parasitizes the larvae or nymphs of cicadas (Cicada flammate) and formsa biological complex of larva and fungus(Chiu,2016). The polysaccharide content in CCM was estimated using the phenol-sulfuric acid method and expressed as galactose equivalents (Homg,2014).Scutellariabaicalensis is a medicinal herb widely available in several East Asian countries and in China. Since ancient times, its dried root, known as Scutellariae radix.Baicalin (5,6-dihydroxy-7-O-glucuronide), wogonin (5,7-dihydroxy-8-methoxyflavone), and baicalein (5,6,7-trihydroxyflavone) are the principal bioflavones extracted from this radix. They have a broad spectrum of bioactivity, including antioxidant, anticancer, anti-inflammation effects, and neuroprotection (Vitiello,2023). Particularly, they are capable of reducing interleukin-8 (IL-8), which is generally increased in POAG patients(Takai,2012). The neuroprotective effects against oxidative stress of both baicalin and baicalein have been proved in RGCs. An in vitro study carried out in an immortalized RGC line (RGC-5) demonstrated that baicalein effectively rescued RGCs in three different oxidative stress models(Maher,2005). Regarding the role of wogonin in preventing RGC loss in glaucoma, a study by Xu et al. Finally, although the bioflavones extracted from the ScutellariabaicalensisGeorgi have proven their ability in preventing RGC loss in glaucomatous animal models in vitro, they have not been used yet in vivo glaucoma patients, and, consequently, their efficacy in the glaucoma management in human subjects needs to be further demonstrated (Xu, 2016).Coleus forskohlii has been used in Ayurvedic and Hindu traditional medicine for a very long time. Its root, which has historically been used in medicine, includes forskolin, the active constituent. Through the activation of the enzyme adenylatecyclase, forskolin's main mechanism of action is to enhance cyclic adenosine monophosphate (cAMP) and cAMP-mediated activitie(Metzger, 1981).Several studies using topical forskolin applications to decrease IOP have been carried out, with contrasting results. IOP was significantly reduced in a dose-

dependent manner in the eyes of normal rabbits using solutions of 2%, 1%, and 0.5% forskolin. These effects peaked in 2-3 hours and lasted up to 10 hours (Satriano, 2023).Clinical research on the use of forskolin in glaucoma patients is scarce, despite its topical use in healthy humans and animals that seems promising. Mutolo et al. studied twenty-two POAG patients already under treatment with IOP-lowering medications to determine the effects of a food supplement containing forskolin; homotaurine; carnosine; folic acid; vitamins B1, B2, and B6; and magnesium over the course of a 12-month period. They found a further IOP decrease and a foveal sensitivity and pattern electroretinogram amplitude improvement in treated patients with this food supplement, also showing a short-term neuroactiveeffect(Mutolo, 2016).Vacciniummyrtillus (Bilberry). Anthocyanins derived from Vacciniummyrtillus or bilberry are increasingly being used in ophthalmology. In fact, vascular tissues and eyes are particularly responsive to flavonoid anthocyanosides,Strong antioxidant properties (Head, 2001). Ribesnigrum L. (Black Currant Fruits). As bilberry, black currant fruit is rich in anthocyanins and is commonlyconsumed worldwide too. Black currants contain only four different anthocyanins, a simpler composition than bil berries. We found some published papers about black cur rant anthocyanin intake related to glaucoma progression. (Ohguro, 2012).Erigeron breviscapus.Erigeron breviscapus is an herbal medicine spread in Yunnan Province, well known as a Chi nese medicinal plant for heart disease. Several studies have shown that it can improve blood circulation and reduce thrombotic events (Wang, 1993). Salvia miltiorrhiza a traditional botanical Chinese medicine that, when administered intra venously, seems to improve microcirculation . For this reason, this extract may have neuroprotective effects on the retina in progressive glaucoma (Cheng, 2007). List of natural product reported in lipsomes in **Table 2**.

Table 2. List of natural product reported in lipsomes.

Herbal Compound	**Family**	**Exrtact**	**Biological Properties**	**Ref**
Scutellariabaicalensis	Lamiaceae	Dried root	Blood pressure, Capillary permeability, and serum cholesterol level reduction Antitumor capacities Anti-inflammatory effect Neuroprotection	(Xu, 2016)
Salvia miltiorrhiza	Lamiaceae	Leaf , Root	Vascular microcirculation improvement	(Cheng, 2007
Ribesnigrum	Grossulariaceae	Leaf	Antioxidant properties Capillary permebility and fragility	(Ohguro , 2012)

			reduction Collagen fiber stabilization and collagen biosynthesis promotion Anti-inflammatory inhibition Blood glucose level reduction Platelet aggregation inhibition	
Erigeron breviscapus	Asteraceae	Flower	Blood circulation improvement Antithrombotic effects	(Wang, 1993)
Vacciniummyrtillus	Ericaceae	Fruit	Strong antioxidant properties Capillary permeability and fragility reduction Collagen fiber stabilization and collagen biosynthesis promotion Anti-inflammatory effects Platelet aggregation inhibition Blood glucose level reduction	(Head, 2001)

Microsphere

To replace the need for eye drops, in this study we tested the hypothesis that IOP can be reduced for one month after a single targeted injection using a microneedle for administration of a glaucoma medication (i.e., brimonidine) formulated for sustained release in the supraciliary space of the eye adjacent to the drug's site of action at the ciliarybody.To test this hypothesis, brimonidine-loaded microspheres were formulated using poly(lactic acid) (PLA) to release brimonidine at a constant rate for 35 days and microneedles were designed to penetrate through the sclera, without penetrating into the choroid/retina, in order to target injection into the supraciliary space .A single administration of these microspheres using a hollow microneedle was performed in the eye of New Zealand White rabbits and was found to reduce IOP initially by 6 mmHg and then by progressively smaller amounts for more than one month (Horng, 2021).Brimonidine tartrate, poly-lactic acid (PLA) with an inherent viscosity (i.v.) of 0.20 dL/g (free acid terminated, RESOMER® 202H), and polyvinyl alcohol (PVA, 80% hydrolyzed, MW ~9000–10,000) were purchased from Sigma-Aldrich (St. Louis, MO). PLGA (75:25, i.v. = 1.13 dL/g, ester terminated) was purchased from Durect (Cupertino, CA). All solvents used were HPLC grade and were purchased from Fisher Scientific (Waltham, MA), and unless otherwise noted, all other chemicals were purchased from Sigma-Aldrich,In this study, we hypothesize that IOP can be reduced for one month after a single microneedle injection of brimonidine formulated for sustained release using PLA into the supraciliary space of the eye. Brimonidine was chosen because it is an FDA-approved IOPlowering agent currently prescribed to glaucoma patient (Chiang, 2016).As discussed in **Table 3**

Table 3. List of natural product reported in microsphere.

Compound	Polymer	Release type	Ref.
Brimonidine	Polylactic acid	Sustained release	(Horng, 2021)
Brimonidine tartrate	Poly-lactic acid	Sustained release	(Chiu, 2016)
Pilocarpine	Poly-lactic acid	Sustained release	(Chiang, 1995)

Conclusion

Glaucoma is a chronic, diverse set of illnesses that is not always well treated with medications that are already on the market. Many medicinal herbs used to treat glaucoma since long time, some of them can preserve retinal ganglion cells from damage. New drug delivery methods for eye medications can lead to more therapy options and vision conservation basically By modifying medication solubility and hence improving bioavailability, nanoparticle, microsphere and liposomes may improve the present therapeutics.To fully understand the advantages of medicinal products in the management of glaucoma, greater, deeper investigations comparing the impact of these remedies to the prevailing standard therapies are required.

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