ADVANCEMENTS IN NEUROPROTECTION FOR GLAUCOMA: INSIGHTS INTO GENES, MECHANISMS, DIAGNOSIS, CHEMICAL AND PLANT-BASED COMPOUNDS FOR THERAPIES.

Abstract

One of the main global causes of irreversible blindness is glaucoma. Estimates place the global prevalence of this condition at 450 million, 47 million of whom are bilaterally blind. Retinal ganglion cells (rgcs), the output neurons that transmit visual data from the retina to the brain via their axons in the optic nerve, are specifically targeted by glaucoma, which results in vision loss. This chapter will go in-depth on the diverse types of glaucoma, its symptoms, and diagnosis, the glaucoma gene, the glaucoma mechanism, the different medications used to treat glaucoma, the mechanisms of action of antiglaucoma medications, neuroprotective chemicals-based drugs, and plant-based neuroprotective compounds for medications in glaucoma.

Keywords: Glaucoma, gene in Glaucoma, Glaucoma Mechanism, Glaucoma diagnosis, Neuroprotective Drugs, Neuroprotective Plant compounds

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I. GLAUCOMA

The primary factor in permanent blindness worldwide is glaucoma. Around the world, 450 million people are thought to be impacted by this illness, with 47 million showing bilateral blindness. The selective death of retinal ganglion cells (RGCs), the output neurons that transmit visual information from the retina to the brain through their axons in the optic nerve, results in glaucoma-related vision loss. High intraocular pressure (IOP) is a significant risk factor for developing glaucoma, despite the fact that the exact mechanism of RGC mortality in this condition is uncertain. The only available treatments for glaucoma are medications or surgery to lower IOP, however, although many patients respond successfully to pressure-lowering medicines, many still incur vision loss. (Almasieh *et al*., 2010).

Glaucoma usually occurs when pressure in the eye increases. This can happen when eye fluid isn't circulating normally in the front part of the eye. Normally, this fluid, called aqueous humor, flows out of the eye through a mesh-like channel. If this channel becomes blocked, fluid builds up, causing glaucoma. The direct cause of this blockage is unknown, but doctors do know that it can be inherited. Less common causes of glaucoma include a blunt or chemical injury to the eye, severe eye infection, blockage of blood vessels in the eye, inflammatory conditions of the eye and occasionally eye surgery to correct another condition. Glaucoma usually occurs in both eyes, but it may involve each eye to a different extent (Daniel and Amit,2023)

he primary glaucoma indicator is intraocular pressure. Contact lens sensors are useful in this application because a change in the forces acting on a contact lens can be associated with IOP. Analyte-tracking contact lens sensors transform compositional data into signals that may be read optically by an observer or by a device. They can be categorized based on their sensing methodology: Fluorescence, holography, colloidal crystal array, and electrochemical sensing are the first four technologies. These sensors have been utilized to find levels of lactate and glucose in tear fluid. (Farandos *et al*., 2015).

1. **Aqueous Humor Production:** Aqueous Humor (AH) is produced by the Ciliary Body Epithelia (CBE) in the eye, which consists of the Non-Pigmented (NPE) and Pigmented Epithelia (PE).This comprises the generation of molecules from the CBE into the AH as well as passive diffusion and active transport. The AH leaves the eye through the anterior chamber and enters the venous bloodstream through the trabecular meshwork (TM) and canal of Schlemm. The intraocular pressure (IOP) is ultimately determined by the equilibrium of AH generation and outflow. (Janssen *et al*., 2013).

2. **Types of Glaucoma:** There are two primary glaucoma categories. 1 Open-Angle Glaucoma and 2. Angle Closure Glaucoma.

    - Open-Angle Glaucoma (Figure 1) has a large and open angle between the iris and cornea and is brought on by the slow blockage of the drainage canals, which causes an increase in ocular pressure. It takes a while to develop and lasts a lifetime. Primary or chronic glaucoma is another name for open-angle glaucoma. Significant optic nerve damage in the eye is now considered a symptom of POAG (Primary Open Angle Glaucoma). About three million Americans are affected by it, which makes it the most common type of glaucoma. (Shahidullah *et al*., 2004).

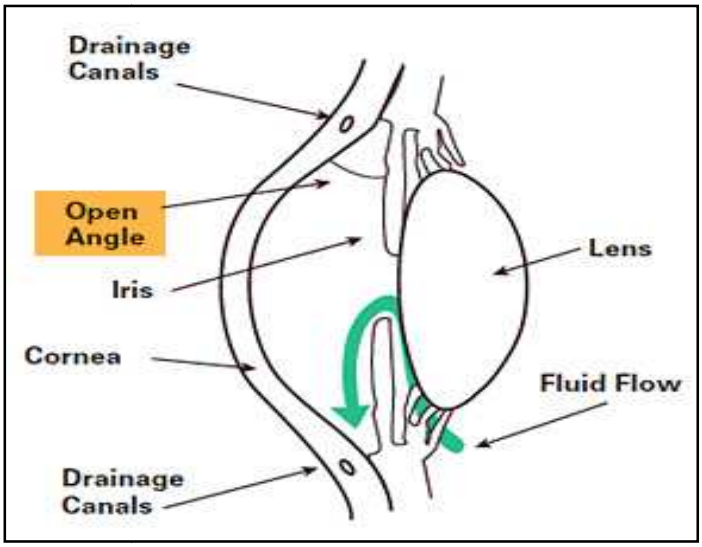

Figure 1: Open Angle Glaucoma

- Angle-closure glaucoma, also known as acute, chronic, or narrow-angle glaucoma, is shown in Figure 2. The angle formed by the iris and cornea leads to angle-closure glaucoma. The blocked drainage channels that produce this type of glaucoma, which is less frequent in the West than it is in Asia and develops very quickly, induce an abrupt increase in intraocular pressure. According to the kind and severity of the onset, primary angle closure glaucoma can be further classified as subacute, acute, chronic, symptomatic, or asymptomatic. (Shahidullah *et al*., 2004).

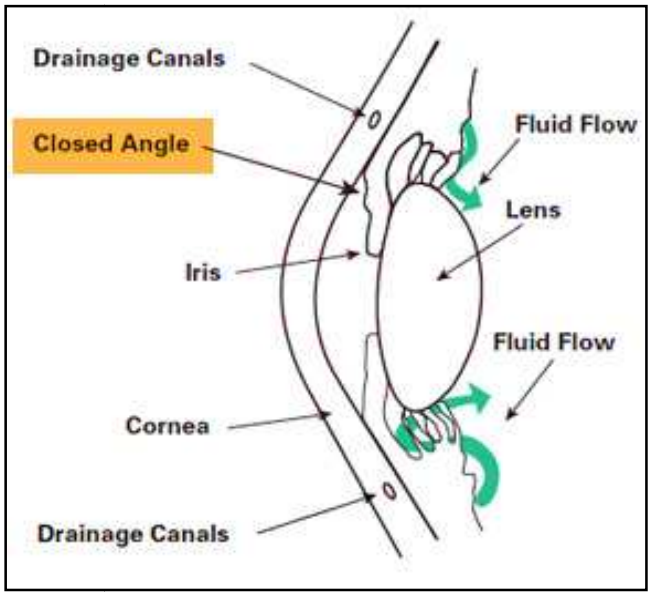

Figure 2: Primary Angle Closure Glaucoma

Additional glaucoma forms include normal tension, traumatic, neovascular, pigmentary, congenital, secondary, pseudo-exfoliative, and iris corneal endothelial syndrome (ICE).

3. **Symptoms of Glaucoma:** Typically, glaucoma develops without any symptoms at the beginning of the condition. The most common glaucoma symptoms include unusual difficulty adjusting to darkness, difficulty focusing on close-up or distant objects, change in iris color, recurrent eye pain, double vision, a dark spot in the center of vision, excessive tearing or "watery eyes," sudden loss of vision in one eye, sudden hazy or blurry vision, flashes of light or black spots, and halos or rainbows around light.

4. **Diagnosis of Glaucoma:**Usually, glaucoma screening is done as part of a routine eye exam. The following six important tests are used to diagnose the glaucoma

    - **Slit Lamp Examination:** This is the first and basic examination
    - **Intraocular Pressure(IOP):** For the identification of glaucoma and the normal range of 10–20 mm Hg, applanation tonometry has poor sensitivity and specificity.
    - **Gonioscopy:** This method uses a lens with an indentation, similar to the 4-mirror Susmann gonioscope, to do dynamic gonioscopy.
    - **Disc and Retinal Nerve Fibre Layer Examination:** Now that imaging techniques are accessible, optic disc may be documented. This comprises optical coherence tomography (OCT), the Heidelberg retinal tomogram (HRT), and scanning laser polarimetry (GDX).
    - **Perimetry:** The purpose of this examination is to maintain the patient's quality of life and visual function. For functional damage to be documented, this test is required.
    - **Torchlight Examination:** In the flashlight test, a light is flashed onto the cornea from the temporal side, parallel to the iris but anterior to it. This examination is carried out to determine the eyes' sensitivity and specificity.(Thomas and Parikh, 2006).

5. **Risk of Glaucoma:** The main cause of blindness in African Americans is glaucoma. Glaucoma may have multiple causes. High intraocular pressure is the main cause of danger. Age, family history, ethnicity, and genetic diversity are other risk factors. Age is a significant influence on glaucoma prevalence when compared to other factors.. In older people, the trabecular meshwork's phagocytosis is reduced or absent, which causes harmful compounds to build up in the drainage channels and obstruct the flow of aqueous humor. (Shahidullah *et al*.,2004).

6. **Glaucoma Treatment:** Eye drops, medications, laser surgery, conventional surgery, or a combination of these treatments can be used to treat glaucoma. The majority of antiglaucoma medications are administered as eye drops, which may need to be applied once or many times each day. Any treatment should aim to avoid vision loss since glaucoma is an irreversible cause of vision loss (Alexander *et al*., 2020).

    The good news is that with medication and/or surgical treatment, the majority of glaucoma sufferers will not lose their vision. Glaucoma can be controlled if discovered early.Regular medicine use as directed is essential for avoiding damage that could result in visual loss. When drugs do not work as intended or have unpleasant side effects, surgery such as laser surgery, laser trabeculoplasty, and selective laser trabeculoplasty (for open angle glaucoma) will be considered as an additional treatment (Alexander *et al*., 2020).

7. **Gene in Glaucoma:** POAG (Primary Open Angle Glaucoma) has been linked to mutations in the MYOC, ASB10, WDR36, NTF4, and TBK1 genes, among others. PLEKHA7 and COL11A1 are two susceptibility loci for primary angle-closure glaucoma (PACG) that have recently been discovered by a GWAS (Genome-Wide Association Study) (Kapetanakis *et al*., 2016).

Autosomal recessive primary congenital glaucoma is brought on by mutations in the CYP1B1 and LTBP2 genes. Although the normal genes at these loci are unknown, the GLC3B and GLC3C loci have also been connected to this kind of glaucoma.The LTBP2 gene is involved in cell adhesion, whereas the CYP1B1 gene is involved in oxidative and vascular homeostasis. For both CYP1B1 and LTBP2, genetic testing for known disease-associated mutations is available. (Aboobakar &Allingham,2014).

Less than 5% of POAG cases are brought on by early-onset glaucoma-causing genes. Several significant POAG-associated genes and loci, including CDKN2B-AS, SIX1/SIX6, TMCO1, and CAV1/CAV2, have been discovered by recent large-scale GWAS. Very recently, it was shown that an animal model's optic nerve volume and eye size were reduced by the common genetic variant rs33912345 in the SIX6 gene. (Aboobakar & Allingham, 2014).

II. GLAUCOMA MECHANISM

Retinal ganglion cells (RGCs) and their axons, which transmit information from the eye to the brain via the optic nerve, gradually deteriorate in glaucomas. The optic disc takes on a distinctive appearance as a result of this gradual degeneration, and a pattern of vision loss follows. The growth and lengthening of the optic nerve cup, the thinning and eventual notching of the neuroretinal rim, the asymmetry in cup size between the two eyes, and disc hemorrhages are typical changes to the optic nerve in glaucoma. Scotomas, which represent the local and generalized loss of nerve fibers inside the retina, are among the changes in the visual field observed during perimetric testing. Arcuate scotomas (depression vision), Nasal steps (glucomatous effect), and paracentral scotomas (diminished vision) are some of these distinguishing alterations. The entire visual pathway, including the brainstem and the visual cortex, is affected by the condition. (Zhang *et al*., 2012).

Drugs used for Glaucoma: Drugs, mainly eye drops, can reduce intraocular pressure. The pharmaceutical classes used to treat glaucoma are numerous. These medications all have potential local and systemic side effects.

1. **Classification of Antiglaucoma Agents:** The following categories may apply to antiglaucoma medications depending on how they are administered.

- **Topical Drugs:**

  - Carbonic anhydrase inhibitors e.g. dorzolamide and brinzolamide.
  - Acetylcholinergic agents e.g., pilocarpine, carbachol, demecarium bromide.
  - NMDA inhibitors e.g., Memataine
  - Adrenergic agonists, such as apraclonidine, brimonidine, dipivefrin, and epinephrine.

- Beta blockers such as metoprolol, timolol, carteolol, betaxolol, and betaxolol
- Prostaglandin analogs, such as PHXA-85, latanoprost, and PGF2.

- **Systemic Drugs:**

  - Inhibitors of carbonic anhydrase, such as acetazolamide and brinzolamide.
  - Osmotic substances, such as urea, mannitol, and glycerine.

Forskolin, ethacrynic acid, steroid antagonists, cannabinoids, angiotensin converting enzyme inhibitors, and neuroprotective medicines are examples of other medications.

2. **Mechanisms of Action of Antiglaucoma Agents:** The dynamics of the aqueous humor are affected by the antiglaucoma medications in three different ways, lowering intraocular pressure. Decrease aqueous production in the ciliary body

- Increase trabecular meshwork aqueous humor outflow and
- Increase uveoscleral route aqueous humor outflow. (Saxena *et al*., 2002).

Table 1. Mechanism of Action of Drugs

S. No	Drug Name	Mechanism ofaction	Side-effects	
			Topical	Systemic
1.	Beta - Blocker	Beta-blockers reduce aqueous secretion (Reduce inflow)	Local irritation, corneal anaesthesis, punctuate keratitis, conjunctival dryness.	All beta-blockers, worsened asthma, bradycardia, elevated heart block, systemic hypotension, decreased capacity for exertion, and depression.
2.	Prostaglandin analogues	Prostaglandin analogues increase aqueous outflow, increase uveoscleral pathway.	Local irritation, conjunctival hyperaemia(redness), growth of eyelashes, Iris, keratitis, macular oedema, hyper pigmentation of light-colored skin, and hyper pigmentation of theirises.	Headache, dysponoea, exacerbation ofasthma.
3.	Alpha agonists	Aqueous production, apiscleral venous pressure, and	Contact blepharodermatitis with follicular conjunctivitis.	Dry mouth, letharty/ headache.

		certain outflow improvements are all decreased by alpha-agonists.		
4.	Carbonic anhydrase	As a direct result of the cilary body, carbonic anhydrase inhibitors reduce the generation of aqueous.	Topical remedies visual haze, ocular discomfort, and conjunctival hyperemia.	Topical remedies visual haze, ocular discomfort, and conjunctival hyperemia.
5.	Cholinergic receptor	Miotics and cholinergics increase outflow, especially in angle-closure glaucoma.	visual haziness, miosis, lacrimation, local irritability, and low tolerance in children.	Dizziness, flushing, abdominal pain, sweating, rhinitis, frequent urination, and hypertension.
6.	Sympathomimetics	Sympathomimetics increase aqueous outflow while reducing aqueous production.	Hyperaemia, Irritation	Side effects of sympathomimetic drugs include palpitations, tachycardia, cardiac arrhythmias, and vertigo.

III. NEUROPROTECTION IN GLAUCOMA

For conditions of the central nervous system such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and head trauma, neuroprotection was initially researched. Target neurons for glaucoma neuroprotection, including RGCs (retinal ganglion cells), should be in the central visual pathway and should not depend on IOP reduction. Chronic progressive loss of retinal ganglion cells is thought to be biphasic; initiation of damage is caused by a primary injury associated withthe main risk factors of glaucoma and there is a delayed (secondary) degeneration of neurons that either escaped the injury or only partially damaged. The secondary degeneration may be an outcome of a hostile environment created by damaged neurons.

Some factors which have been identified as mediators of this secondary neuronal degeneration are high levels of potassium and calcium ions, nitric oxide, amounts of free radicals and excitatory aminoacids such as glutamate and aspartate. Neuroprotection in glaucoma consists of the prevention of the death of marginally damaged neurons and the secondary degeneration of those undergoing the hostile environment created by the initial damage. In other words, neuroprotection attempts to provide protection to such retinal ganglion cells that continue to remain at risk (Pinar & Vecino, 2009).

A neuroprotective drug is expected to prevent the death of RGC in presence of the chronic stress by attenuating the hostility of the environment or supplying the cells with the tools to deal with those chances.

The pharmacological profile of neuroprotective drugs should fulfill these four criteria.

- To have a particular retinal target (receptors).
- To demonstrate neuroprotective properties and to significantly impact RGC survival.
- To reach neuroprotective concentrations in the retina and vitreous after clinical dosage.
- Clinical trials in humans that are randomized, controlled, and evaluated for neuroprotective efficacy are required.

For patients who have had substantial damage in the past and for whom pressure-lowering medications are unable to stop the progression of their glaucoma, glaucoma neuroprotection offers a potential additional therapy to IOP-lowering. (Pinar & Vecino, 2009).

IV. NEUROPROTECTIVE DRUGS IN GLAUCOMA

Some agents have been reported as having neuroprotective activity for RGCs in experimental research as well as clinical studies.

1. **Dynacin:** A second-generation tetracycline known as dynacin hydrochloride is frequently utilized in humans due to its advantageous antibacterial and anti-inflammatory properties. The blood-brain barrier is efficiently crossed by dynacin. In animal models of cerebral ischemia, traumatic brain injury, Huntington's disease, and Parkinson's disease, this medication exhibits exceptional neuroprotective properties as well. (Pinar & Vecino, 2009).

2. **Doxycycline:** Another semi-synthetic second-generation tetracycline is doxycycline. It also penetrates the blood-brain barrier, with well-known effects of neuroprotection (Gabler *et al*., 1992; Smith and Gabler, 1994). However, it didn't exhibit as much neuroprotective effect as minocycline in most studies (Pinar & Vecino, 2009).

3. **Carbonic Anhydrase:** There are three different forms of carbonic anhydrases (CA), which are common zinc enzymes found in Archaea, Prokaryotes, and Eukaryotes. They are -CAs found in vertebrates, eubacteria, algae, and the cytoplasm of green plants; -CAs found primarily in some eubacteria and archaea; and -CAs found in eubacteria, algae, and some algae. Basically, there are four membrane-bound isozymes, four cytosolic forms (CA I–III), one mitochondrial form, and one secreted CA isozyme. These enzymes play an essential role in respiration and the transport of CO2-bicarbonate between metabolizing tissues and the lungs by catalyzing the remarkably straightforward physiological reaction of interconversion between carbon dioxide and the bicarbonate ion.For catalysis, the zinc (Zn) ion in CA is necessary. The metal ion was found to be located at the bottom of a 15-deep active site cleft according to X-ray crystallographic data. (Supuram *et al*., 2003a).

   Drugs that are systemic sulfonamides have long been utilized in medicine, primarily as antiglaucoma medications. The medications are Brinzolamide and Acetazolamide. Systemic inhibitors are helpful in lowering the increased intraocular pressure (IOP) associated with this condition because they are the most effective physiological glaucoma treatment. This is due to the fact that blocking the ciliary process

enzyme reduces the rate of bicarbonate and aqueous humor secretion, which results in a 25–30% reduction in IOP, but blocking the numerous CA isozymes found in tissues other than the eye has a wide range of negative side effects. (Supuram *et al*., 2003b).

For the past 40 years, systemic carbonic anhydrase inhibitors have been a crucial component of glaucoma medical therapy. These medications belong to the restricted class and are taken orally as a supplement when topical therapy does not sufficiently control IOP. Systemic carbonic anhydrase inhibitor usage has resulted in unacceptable adverse effects in about 50% of patients. As a result, these medications are currently utilized to manage IOP in patients awaiting surgery. (Supuram *et al*., 2003b).

- **Acetazolamide:** This is the carbonic anhydrase inhibitor that is most frequently administered. However,50% of patients cease taking acetazolamide because of unpleasant adverse effects brought on by the extraocular suppression of carbonic anhydrase. It inhibits the ciliary body's carbonic anhydrase enzyme in a reversible manner, preventing the generation of aqueous humor. In comparison to plasma, the aqueous fluid that is high in sodium and bicarbonate ions is hyperosmotic. 125–250 mg are typically taken orally four times a day. By using an osmotic pump delivery method with coated granule dispensing, the effect of acetazolamide may be maintained. The most typical sign of acetazolamide sensitivity is digestive discomfort. Myopia, respiratory failure, kidney stones, aplastic anemia, metabolic acidosis, hypersensitivity responses, and peripheral neuropathy are severe adverse effects. (Saxena *et al*., 2002).

- **Brinzolamide:** Additionally, it has been offered for sale since 1998. Its 1% suspension lowers IOP similarly to 2% dorzolamide. It is given three times each day. It causes greater impaired vision even though burning and stinging are less common side effects. Patients with open-angle glaucoma and ocular hypertension who take one percent brinzolamide three times per day in addition to timolol 0.5% twice a day see a considerably additive IOP reduction with fewer side effects. (Saxena *et al.,* 2002).

4. **Acetylcholinesterase:** Numerous cholinergic routes in the central and peripheral nervous systems use acetylcholinesterase to quickly hydrolyze the neurotransmitter acetylcholine to stop impulse transmission.

The hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid, which is required for cholinergic neurons to revert to their resting state following activation, is catalyzed by the cholinesterase family of enzymes.

It includes two categories;

- Many different types of conducting tissues, including nerve and muscle, central and peripheral tissues, motor and sensory fibers, and cholinergic and noncholinergic fibers, contain acetylcholinesterase (AChE). In motor neurons as opposed to sensory neurons, AChE activity is higher. The Yt blood group antigen, which is comprised of AChE, is also present in the red blood cell membranes. The enzyme is found in several molecular forms that share catalytic capabilities but differ in how they oligomerize and how they adhere to the cell surface. (Colovic *et al*., 2013).

- The liver is the main location of pseudocholinesterase, also known as plasma cholinesterase, butyrylcholinesterase, or acylcholine acylhydrolase.

AChE inhibitors prevent the cholinesterase enzyme from degrading ACh, hence extending the neurotransmitter action's level and duration. AChE inhibitors can be categorized into two groups: irreversible and reversible, depending on how they work. While irreversible AChEactivity modulators are linked to harmful consequences, reversible inhibitors, whether competitive or noncompetitive, typically have therapeutic benefits. Irreversible AChE inhibitors are crucial for controlling the activity of the enzyme pharmacologically. These inhibitors, which include substances with diverse functional groups, are used in the diagnosis and/or therapy of a number of illnesses, including glaucoma, myasthenia gravis, Alzheimer Disease (AD), postoperative ileus, and bladder distention. (Colovic *et al.,* 2013)

5. **Diisopropyl Flurophosphate:** Carbamic acid (NH2COOH) is the source of carbamates, which are chemical molecules. In human medicine, it is mostly utilized as a therapeutic medication for conditions including glaucoma and Lewy bodies. As pesticides, these reversible AChE inhibitors have been used. The condition, which is characterized by elevated fluid pressure in the eye, can permanently impair vision in the affected eye or eyes and if ignored, result in blindness. A parasympathomimetic medication called diisopropyl fluorophosphate has been utilized as an irreversible anti-cholinesterase. The symptoms of acute nerve agent poisoning include pupil constriction, excessive salivation, convulsions, and involuntary urine. Treatment for persistent glaucoma, a condition of the eyes where the optic nerve is harmed in a recognizable pattern. (Colovic *et al.,* 2013).

6. **Echothiophate:** Pupil constriction, excessive salivation, convulsions, and involuntary urination treatment for persistent glaucoma, a condition of the eyes in which the optic nerve suffers a specific pattern of damage. Its capacity to cause delayed peripheral neuropathy and its AChE inhibitory capabilities are primarily responsible for its eye side effects. An irreversible AChE inhibitor, echothiophate (phospholine) is a parasympathomimetic phosphorothioate. It is used to treat chronic glaucoma and, in rare situations, accommodate esotropia as an ocular antihypertensive. Its effects can last a week or longer and are applied locally (through eye drops). The medication is sold under a number of trade names, including phospholine iodide. Muscle spasms and other systemic symptoms are among the negative consequences. (Colovic *et al*., 2013).

7. **NMDA (N-Methyl-D-Aspartate) Receptor:** An example of an ion channel coupled receptor with excitatory features that has been linked to the mechanism of general anesthesia, analgesia, as well as neurotoxicity, is the NMDA receptor, a member of the glutamate receptor family. Ketamine interacts with the phencyclidine binding site, inhibiting the NMDA receptor's ability to function significantly only after the channel has been opened. Ketamine is a non-competitive antagonist of the NMDA receptor Ca2+ channel pore.

As the primary excitatory neurotransmitter in the central nervous system (CNS) and the retina, glutamate is an essential amino acid that is present in large amounts in all cells. Although its precise function is debatable, modulating the N-methyl D-

aspartate (NMDA) type receptor has been suggested as a key strategy for neuroprotection in glaucoma. Glutamate release has been implicated as a mechanism of RGC death in glaucoma, and inhibition or blockade of glutamate activity in particular, has been advocated. Due to glutamate's intense and damaging overexpression, glutamate is strictly controlled in presynaptic cells (Cheung *et al*., 2008).

Both the processes underpinning the healthy development of the adult brain's functional and structural plasticity as well as the normal development of the central nervous system depend heavily on NMDAs. They are capable of doing so and have a variety of special qualities.

High permeability to Ca ions, high voltage dependence caused by external Mg block, extremely slow kinetics of activation, high affinity for the excitatory transmitter L-glutamate, and large cytoplasmic domains allow them to join and organize large macromolecular synaptic signaling complexes (Blanke and Vandongen, 2009).

8. **Memantine:** Memantine, a therapeutic glutamate modulator that was developed by Eli Lilly & Company in the 1960s and patented in 1968, is currently accessible. Memantine is a derivative of amantadine, a drug that was once used to treat influenza. Memantine has been shown to be successful in treating AD and PD. Memantine was only recently discovered to be an NMDA-receptor antagonist; it was previously thought to be anticholinergic or dopaminergic. In both acute and long-term animal models of RGC mortality, memantine has been demonstrated to be a highly effective neuroprotective drug. In a transgenic mouse model of glaucoma and a laser-induced rat and primate model of chronic ocular hypertension, memantine (5 to 10 mg/kg) daily dosing improved RGC survival.Memantine was in a phase IV clinical trial in 2008. (Cheung *et al*., 2008).

V. NEUROPROTECTIVE PLANT COMPOUNDS

1. **Artepillin:** Brazilian propolis was used to make apepillin. The resinous exudates of the Baccharis dracunculifolia plant were the propolis' botanical source. Additionally, it was noted that honeybees rarely visited the enlarged leaves of Baccharis dracunculifolia and only occasionally visited the leaf buds. (Park *et al*., 2004). *in vitro* artepillin propolis Its neuroprotective effects in PC12 cell culture wasdocumented, and it also served as an antioxidant to prevent lipid peroxidation and the formation of free radicals. In addition to having antioxidant capabilities, artepillin propolis exhibits neuroprotective effects against ischemia injury in vivo. (Shimazawa *et al*., 2005).

2. **Baicalin:** A flavonoid chemical known as baicalin was discovered in the Chinese plant Scutellaria baicalensis. Upper respiratory infections, diphtheria scarlet fever, and viral hepatitis have all been treated with it. In the pilocarpine-induced epileptic model, baicalin had anticonvulsant and neuroprotective effects at varying rates. (Liu *et al*., 2012).Baicalin has been shown to have a neuroprotective effect in focal cerebral ischemia/reperfusion injury mice with permanent focal cerebral ischemia and to reduce the expression of HSP70 in hippocampus neurons (Tu *et al*., 2009).

3. **Bilobalide:** In phytopharmaceutical formulations containing ginkgo extracts, bilobalide, a flavonoid mostly derived from the leaves of the Ginkgo biloba plant, is also present. (Beek *et al*., 1991).Finding the pure terpene lactone from EGb 761 and EGb 761 against ischemia injury helped researchers determine the neuroprotective impact of bilobalide against ischemic injury in animal models. (Chandrasekaran *et al*., 2001).The preservation of mitochondrial ATP synthesis, inhibition of apoptotic damage brought on by staurosporine or serum free medium, and suppression of hypoxia-induced membrane deterioration in the brain are just a few of the multiple ways that bilobalide's actions may be associated with neuroprotection(Defeudis, 2002).

4. **Caffeine:** Caffeine is found in about sixty different plant species. *Coffea* is a member of the Rubiaceae family. *Coffea Arabica* and *Coffea canephora* seeds are the primary sources of the stimulant chemical known as caffeine. Coffee, usually referred to as coffee beans, is a brewed beverage made from roasted seeds. It is the stimulant beverage that is most regularly eaten worldwide (Yadav*et al*., 2012). In a mouse model of Parkinson's disease, caffeine metabolites have a neuroprotective effect. Caffeine shields humans from alleged toxin-induced damage to dopaminergic neurons. Because the duration of caffeine may be prolonged by the protective effects of its primary metabolites, the timing of caffeine and toxin exposures may not be crucial. (Kachroo*et al.*,2010).

5. **Carnitine:** Nuts, seeds, grains, legumes, pulses, fruits, and vegetables are all sources of carnitine. Red meat contains the highest levels of carnitine. According to body composition, gender, and food, human carnitine status reportedly varies. Carnitine biosynthesis is a productive process that requires pathways in several organs. (Steiber *et al*., 2004). In addition to playing a crucial part in intermediate metabolism, carnitine is a naturally occurring substance that has been shown in studies to protect both the central and peripheral nervous systems. (Ghirardi *et al*., 2005).

6. **Catechin:** A flavonoid substance called catechin was discovered in the hooks and stem of the *Uncariasinensis*plant. (Shimada, 2001).Cocoa, tea, red wine, and fruits including apples, grapes, and strawberries are high in flavanols of catechin. Based on their constituent parts, their arrangement, and the placement of inter flavanic links, they differ in nature. (Vauzour *et al*., 2008).Both green and black tea have neuroprotective properties that are aided by catechin. Inhibiting the development of a fibrils or oligomers is likely how catechin exerts its protective effects, which supports the idea that both black and green tea may delay the onset of age-related neurodegenerative disorders. (Yao *et al*., 2006).

7. **Epicatechin:** A flavonoid component known as epicatechin was also discovered in the hooks and stem of the *U. sinensis*plant. In cultured rat cerebellar granule cells, it is preventsthe neuronal death brought on by glutamate (Shimada, 2001).Epicatechin's ability to inhibit neuroinflammation, protect neurons from damage brought on by neurotoxins, and perhaps enhance memory and cognitive function are just a few of the effects that make up its neuroprotective impact (Vauzour *et al*., 2008).

8. **Folic Acid:** A water-soluble B vitamin called folic acid was originally discovered in avocados, and then it was discovered in spinach leaves and other green leafy foods. It is necessary for the preservation of healthy brain function and may also serve as a source of possible treatments for excitotoxicity. (Ding *et al*., 2010). Folic acid has been touted as a

promising substance for preventing neurodegeneration because of its potent neuron-protective actions. Ding et al. (2010) showed that folic acid has a neuroprotective effect against induced oxidative damage in neurons and their mitochondria.

9. **Genipin:** The fruit of the *Gardenia jasminoides* plant is where genipin is derived. It has been utilized as a therapy for several illnesses in traditional Chinese medicine. Genipin is now well acknowledged to be a strong ingredient. It is said to offer protection from the toxicity of amyloid (Yamazaki and Chiba, 2005).According to Namet al. (2010), genipin is a natural substance having crosslinker capabilities in the cornea that are comparable to crosslinking porcine corneas in a model of the entire eye. On Neruro 2a cells (a rapidly expanding mouse neuroblastoma cell line), genipin has both neurotrophic factor-like and neuroprotective properties. The key drug candidate for the treatment of neurodegenerative diseases may be genipin. (Yamazaki and Chiba, 2005).

10. **Genistein:** Genistein is an isoflavone present in the crude peel extract of *Flemingia vestita* Fruit (Das *et al*.,2007). Genistein exerts its effect on the activity of acid phosphatase, alkaline phosphatase, adenosine triphosphatase and 5’-nucleotidase (Pal and Tandon, 1998).Genistein is one of the nutraceutical molecules found in soybean seeds. The positive effects of genistein's antioxidant activity include protection against vascular dysfunction by reducing oxidative alterations and activating endogenous antioxidant signaling pathways. (Qian *et al.,* 2012).In transient focal ischemia, genistein has a neuroprotective effect that may include controlling mitochondria-dependent apoptotic pathways and preventing ROS-induced NF-kB activation (Qian *et al*., 2012).

11. **Isorhamnetin:** The Tagetet lucida plant's leaves were primarily used in the isolation of isorhamnetin. It is a flavonoid called an O-methylated flavonol. It has been demonstrated that isorhamnetin increases the production of neurofilaments and enhances NGF's ability to produce neurites. (Normal Growth Factor) (Xu *et al*., 2012). It was discovered that isorhamnetin significantly increased the expression of neurofilaments in PC12 cells. (Xu *et al*., 2006).The majority of plants that provide neuroprotection include isorhamnetin, a flavonol aglycone. This is a component of the Ginkgo biloba extract that has been used to treat brain disorders and other conditions. Isorhamnetin effectively protects against the neurotoxicity caused by amyloid beta in rats. (Asha and Sumathi, 2015).

12. **Kaempferol:** A naturally occurring flavonol called kaempferol is mostly found in plants like green tea, pine, *Angelica decursiva*, and Ginkgo leaf as well as in fruits like apples, grapes, and tomatos. Kaempferol has demonstrated anti-inflammatory and antioxidant properties. It also lessens the risk of developing cardiovascular and neuroinflammatory conditions. (Kim & Choi, 2013). The melting point of kaempferol, a yellow crystalline solid with a 529–532 °F melting range, is 276-278 °C.In heated ethanol, ethers, and DMSO, it is extremely soluble and only mildly soluble in water.(Kim & Choi,2013). Due to its ability to scavenge free radicals and anti-oxidative properties, kaempferol has been shown to have neuroprotective benefits in MPTP-induced PD rats. These effects have been shown to increase the lifespan of dopamine neurons. (Shen and Xiao, 2011).

13. **Levodopa:** Parkinson's disease involves levodopa, also known as L-DOPA (L-3,4-dihydroxyphenylalanine). Mucuna pruriens plant, a natural source of levodapa (Brain, 1976).Levodopa has a protective effect, although Levodopa, a neuroprotectant and

dopamine receptor agonist, has a protective effect that can be attributed to antioxidant or antiapoptotic mechanisms. New information about dopamine agonists has provided justification for assessing the progression of dopamine neuronal degeneration.(Shin *et al*., 2009).

14. **Liquiritin:** The most widely utilized medicinal herb in both Eastern and Western medicine is liquiditin, a flavonoid. It was taken out of the root of the *Glysyrrhiza uralensis* plant. Numerous pharmacological effects of this substance include antiviral, antioxidant, anti-inflammatory, immunomodulatory, and antiulcer effects. (Shen *et al*., 2006).Liquiritin flavanoid has neuroprotective effects via altering a number of apotosis-related pathways. It also has anti-ischemic effects, which may be attributable to improved brain energy metabolism and antioxidant activity. (Sun *et al*., 2010).

15. **Melatonin:** Numerous plants, such as *Tanacetum parthenium, Hypericum perforatum*, etc., contain melatonin. In addition to this, melatonin is found in edible fruits including grapes, tomatoes, rice, corn, and corn. Through the control of a variety of physiological functions, melatonin has the neuroprotective protective action to maintain cell life. On the basis of its capacity to operate as a free radical scavenger, melatonin has been recommended as a neuroprotective drug, given that lipoeroxidation and other free radical damageare generated by reactive processes of ischemia neuronal injury.

16. **Minocycline:** Minocycline is a semi synthetic product of chlortetracycline which is isolated from *streptomyces aureofaciens* (Chin *et al*., 2006).It has been demonstrated that minocycline has neuroprotective qualities in many animal models of acute brain damage. In animal models of focal and generalized brain ischaemia, minocycline displays neuroprotective properties against neuronal injury. Minocycline's neuroprotective properties have an impact on a number of intracellular signaling pathways, such as antioxidant systems, nitric oxide synthase, and the inhibition of inflammatory reactions. (Elewa*et al*., 2006).

17. **Nobiletin:** Nobiletin is a powerful polymethoxylated flavonoid that is found in thepeel of citrus fruits of*Citrus reticulate* fruits (Cohen, 2015). Nobiletin is hasantioxidant, anti-cancer, anti-inflammation, and cholesterol lowering activity. Nobiletin acts by its antiproliferative effect without being toxic to normal cells (Jasim, 2012).The neuroprotective mechanism of nobiletin has been fully elucidated in anti-neuroinflamatory activity of suppression of brain insult induced excessive microglial activation (Cui *et al*., 2010). Citrus nobiletin has recently been shown to have neurotrophic and central nervous system activities, according to Cui et al. (2010).

18. **Papaverine:** Papaverine is an alkaloid, and it is found in Indian and Netherlands poppy seeds and it was obtained from*papaver somniferum*plant seeds. This compound was detected by GC/MS technique (Paul *et al*., 1996).Papaverine is a phosphodiesterase inhibitor, however, the specific mechanism underlying its purported neuroprotective effects is still unknown. In PC12 cells, papaverine had an impact on the nerve growth factor (NGF)-induced neurite outgrowth (Itoh *et al*., 2011).

19. **Paraxanthine:** Paraxanthine (7-methyl xanthine) is found in caffeine, the main source of paraxanthine is *Coffea arabica* and *Coffea conephora* seeds (Ashihara, 2006). Due to its saturable metabolism, paraxanthine can accumulate in the plama during long-term, higher dosages of caffeine consumption and contribute to the pharmacological effects of caffeine. (Guerreiro*et al*., 2008). Paraxanthine has found the neuroprotective effect to be a dimethylxanthine metabolite of caffeine but only modestly to caffeine's neuroprotective effect in C57B1/6 mice (Xu *et al*., 2010).

20. **Piracetam:** Piracetam is one of the natural nootropics (memory enhancers or neuro enhancer) which is present in the *Huperzia serrata, Bacopa monnieri, Lions's mane mushroom* and *Ginkgo biloba and* also isolated from the Chinese club moss plant. Piracetam correlated to inhibit γ-aminobutyric acid (GABA) neurotransmitter (Alkuraishy *et al*., 2014). The effects of piracetam and ginkgo biloba taken together were more powerful. Piracetam has more efficient neuroprotection activity, it increases the lifetime of isolated neurons in higher concentrations (Burov *et al*., 1999).

21. **Pramiracetam:** Pramiracetam is a noortropic agent (memory enhancer / neuro enhancer). It is extracted from the *Bacopa monniera, Azadirachta indica, Withania somnifera,* and *Ocimum sanctum* plants. Although several plant products are traditionally used to treat the age-related neurodegenerative complications (Sridharamurthy *et al*., 2012). According to reports, pramiracetam helped with the cognitive problems brought on by traumatic brain injury. Recent research has shown that it protects the brain following coronary bypass surgery (Malykh and Sadaie, 2010).

22. **Quercetin:** Quercetin is a flavonoid found in onion leaves widely distributed in nature and it was isolated from the dried leaves of *Ginkgo biloba.*Quercetin is also found in many fruits, vegetables, leaves and grains (Wadsworth and Koop, 2001). Due to its potent antioxidant capabilities and neuroprotective effects, quercetin may be helpful in reducing brain oxidative damage. It prevents nuclear factor-kB activation, inducible nitric oxide synthase expression, and PGE2 synthesis (Pany *et al*., 2014).

23. **Resveratrol:** Resveratrol is a type of natural phenol that occurs in phytoalexin andphytoestrogen produced naturally by several plants like hellebore of roots. Food sources of resveratrol include the skin of grapes which was reported to have a variety of biological and pharmacological actions (Kim *et al*., 2014).Seven plant groups, including Dipterocarpaceae, Vitaceae, Cyperaceae, Genetaceae, Welwitschiaceae, Umbelliferae, and Leguminosae, have been shown to contain many Resveratrol oligomers, and their antibacterial and physiological effects have been documented. (Gonthier *et al*., 2012). Resveratrol's ability to shield neurons against the toxic effects of A (Amyloid beta) may also work by accelerating the intracellular breakdown of A through the ubiquitin proteasome system (Calabrese et al., 2008).

24. **Tangeretin:** Mandarins, tangerines, grapefruits, and oranges all contain the flavonoid tangeretin in their peels.The dried and mature peel of *Citrus reticulate* fruits have been recorded in the Chinese pharmacopoeia as appropriate for medical use (Jasim, 2012).In a rat model of Parkinson's disease, the tissue distribution and neuroprotective effects of the citrus flavonoid tangeretin were shown (Datla *et al*., 2011).

Tangeretin increases the levels of dopamine and has potential neuroprotective activity. It also has cholesterol reducingproperties (Jasim,2012)

25. **Theobromine:** Theobromine is flavonoids present in Cacaoplant, with the chemical formula$C_7H_8N_4O_2$ and it is found in chocolate(Xu *et al.*, 2006).It is categorized as a xanthine alkaloid, along with theophylline and caffeine and other related substances. Xanthine derivative of theobromine was recently introduced as a drug with neuroprotective properties for treatment of brain dementia (Zlatkov *et al*., 2000). *Cacao* beans are a concentrated source of antioxidants, Theobromine, another methylxanthine present in high concentrations.Theobromines have the ability to protect neurons from damage brought on by neurotoxins, lessen neuroinflammation, and enhance memory, learning, and cognitive function, among other neuroprotective effects.

26. **Theanine:** Green tea's flavorful theanine, which is derived from Camellia sinensis leaves, is a distinctive element of tea. According to studies, theanine is biologically capable of lowering systemic blood pressure, promoting relaxation, and inhibiting caffeine's stimulatory effects (Sakato, 1949). The excitatory neurotransmitter glutamic acid has an ethylamide and glutamate counterpart in theanine. Theanine may compete with glutamic acid for glutamate receptor binding, which would reduce glutamate toxicity and have a neuroprotective effect. Theanine's potential for neuroprotection was studied by Cho et al. (2008), along with the processes underlying the effects in both in vitro and in vivo experiments.

27. **Theophylline:** Theophylline is naturally found in *Cocoa* beans, and it is a flavonoid compound. The quality of the Coco beans on many factors such as genotype, soil factor, the climate conditions and most important the post-harvest technology (Brunetto *et al*., 2005). To characterize a possible neuroprotective therapeutic effect, the antioxidant's theophylline cytoprotective capacity would be crucial (Dajas *et al*., 2003). Numerous studies support that neuroprotective activity present flavonol theophylline in experimental focal ischemia and models of neurogeneration (Dajas *et al*., 2013).

28. **Trigonelline:** Trigonelline is an alkaloid, commonly found in *Trigonella foenum-graecum seeds* and known as fenugreek, is one of the oldest medicinal plants. Trigonelline has been found to be a powerful antioxidant and anti-diabetic molecule. As a result, fenugreek extract that has been standardized to the bioactive marker component trigonelline may be useful in the treatment of neuropathic pain. (Morani *et al*., 2012). Recent research demonstrated that trigonelline, a key component of various traditional Chinese medicines, has anti-diabetic and neuroprotective effects and lowers blood sugar levels in both rats and people (Yin and Wen, 2012).

29. **Ubiquinone:** Ubiquinone or coenzyme Q10 is isolated from the plant mitochondria of the potato tubers (*Solanum tuberosum*), spinach leaves (*Spinacia oleracea*) and daffodil petals (*Narcissus pseudonarcissus*) (Brinkhaus *et al*., 2005).The biological cofactor ubiquinone is crucial for the electron transport chain and a vital antioxidant in lipid and mitochondrial membranes. Ubiquinone can cross the blood-brain barrier and affect mitochondria and the mitochondrial electron transport chain. Due to these properties, ubiquinone has gained interest as a neuroprotective drug in neurodegenerative diseases

like Parkinson's disease that are connected to mitochondrial abnormalities or oxidative stress (Kabel et al., 2013).

30. **Wogonin:** A flavonoid called wogonin (5,7-dihydroxy-8-methoxyflavone) is found in the roots of *Scutellaria baicalensis*. It is a herb that has long been utilized in traditional Oriental medicine (Lee et al., 2003). based on wogonin's recognized ability to reduce inflammation in macrophages and other peripheral cell types. In brain microglia, where microglia-mediated inflammatory responses play a significant pathogenic role, wogonin may be evaluated for exerting a comparable anti-inflammatory effect as well as for neuroprotection against brain injury (Lee et al., 2003). In animal models of ocular illness, trigonelline mechanisms of these flavones were reported (Xiao, 2014).

VI. CONCLUSION

Finally, there are numerous plant natural compounds that can effectively treat Glaucoma. The selected compounds which are better than the drugs suggesting its efficacy as a drug with multi- targeting potential or as a lead compound for synthesizing a multi-targeting drug to combat glaucoma.

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