**Advancements in Neuroprotection for Glaucoma: Insights into Genes, Mechanisms, Diagnosis, Chemical and Plant-Based Compounds for Therapies.**

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**Abstract:**

Glaucoma is one of the leading global causes of unreversible blindness. Estimates place the global prevalence of this condition at 450 million, 47 millions of whom are bilaterally blind. Glaucoma particularly targets the retinal ganglion cells (rgcs), the output neurons that transport visual information from the retina to the brain through their axons in the optic nerve, causing 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.

**Key Words: Glaucoma, gene in Glaucoma, Glaucoma Mechanism, Glaucoma diagnosis, Neuroprotective Drugs, Neuroprotective Plant compounds**

**Glaucoma:**

Glaucoma is the leading cause of irreversible blindness in worldwide. It has been estimated that 450 million people around the world are affected by this disease, with
47 million presenting bilateral blindness. Loss of vision due to glaucoma is caused by the selective death of retinal ganglion cells (RGCs) the output neurons that relay visual information from the retina to the brain through their axons in the optic nerve. Although the precise cause of RGC death in glaucoma is unknown, high intraocular pressure (IOP) is a major risk factor for developing this disease. Current treatments for glaucoma are limited to lowering IOP by medication or surgery, but a significant number of patients continue to experience visual loss despite responding well to pressure lowering therapies (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](http://www.webmd.com/heart/anatomy-picture-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

**Intraocular pressure (IOP):**

Intraocular pressure is the main indication of glaucoma. A change in the forces that act upon a contact lens can be correlated with IOP, hence contact lens sensors have utility in this application. Contact lens sensors that monitor analytes in tear fluid convert compositional information into signals that can be read optically by an obsever or by an instrument.
They may be classified according to their sensing principle: 1. Fluorescence, 2. Holographic, 3. Colloidal crystal array and 4. Electrochemical sensing. These sensors have been used to detect concentrations of glucose and lactate in tear fluid (Farandos *et al*., 2015).

**Aqueous humor production:**

The Ciliary Body Epithelia (CBE) in the eye, consisting of the Non-Pigmented (NPE) and Pigmented Epithelia (PE) are responsible for the production of the Aqueous Humor (AH). This includes passive diffusion, active transport and production of molecules from the CBE into the AH. Through the anterior chamber, the AH exits the eye through the trabecular meshwork (TM) and the canal of schlemm into the venous blood system. The balance between the production and outflow of AH ultimately determines the intraocular pressure (IOP) (Janssen *et al*., 2013).

**Types of Glaucoma:**

There are two main types of glaucoma 1. Open-Angle Glaucoma and 2. Angle Closure Glaucoma

 1. Open-Angle Glaucoma (Fig.1.) is caused by the slow clogging of the drainage canals, resulting in increased eye pressure and it has a wide and open angle between the iris and cornea. It develops slowly and is a lifelong condition. Open-angle glaucoma is also called primary or chronic glaucoma. POAG (Primary Open Angle Glaucoma) is now defined as significant optic nerve damage in an eye. It is the most prevalent type of glaucoma, affecting about three million Americans (Shahidullah *et al*., 2004).



**Fig.1. Open Angle Glaucoma**

2.Angle-closure glaucoma (Fig.2.) also called as acute or chronic angle-closure or narrow-angle glaucoma. Angle-closure glaucoma is a result of the angle between the iris and cornea. This type of glaucoma is less common in the West than in Asia and is caused by blocked drainage canals, resulting in a sudden rise in intraocular pressure and it develops very quickly. Primary angle closure glaucoma can be sub divided into subacute, acute, chronic, symptomatic, or asymptomatic according to the nature and severity of the onset (Shahidullah *et al*., 2004).



**Fig. 2. Primary Angle Closure Glaucoma**

There are some more types of glaucoma they are normal tension glaucoma, congenital glaucoma, secondary glaucoma, pigmentary glaucoma, pseudo exfoliative glaucoma, traumatic glaucoma, Neovascular glaucoma, Irido corneal endothelial syndrome (ICE).

**Symptoms** **of Glaucoma:**

In general glaucoma exhibits no symptoms early in the course of the disease.
The main symptoms of glaucoma are unusual trouble adjusting to dark rooms, difficulty focusing on near or distant objects, change in color of iris, recurrent pain in or around eyes, double vision, dark spot at the center of viewing, excess tearing or “watery eyes”, sudden loss of vision in one eye, sudden hazy or blurred vision, flashes of light or black sports and halos or rainbows around light.

**Diagnosis** **of Glaucoma:**

Screening for glaucoma is usually performed as part of a standard eye examination.

The following six important tests are used to diagnose the glaucoma

1. **Slit lamp examination:**

This is the first and basic examination

1. **Intraocular pressure (IOP):**

Measured by applanation tonometry, it has poor sensitivity and specificity for the detection of glaucoma and the normal range 10-20 mm Hg.

1. **Gonioscopy:**

This technique is dynamic gonioscopy with an indentation type lens like the
4-mirror susmann gonioscope.

1. **Disc and retinal nerve fibre layer examination:**

This imaging techniques are now available for documentation of the optic dics. This includes Heidelberg retinal tomogram (HRT), scanning laser polarimetry (GDX), and optical coherence tomography (OCT).

1. **Perimetry:**

This test is performed to preserve the patient’s visual function and quality of life. This test is mandatory to document functional damage.

1. **Torchlight examination:**

In the flashlight test a light is shone from the temporal side onto the cornea, parallel but anterior to the iris. This test is performed to find out the sensitivity and specificity of the eyes (Thomas and Parikh, 2006).

**Risk of Glaucoma:**

Glaucoma is the leading cause of blindness among African Americans.
There may be no single cause of glaucoma. Elevated intraocular pressure is the most important risk factor. Other risk factors are age, family history, ethnicity, genetic variation. Where age plays a significant role in the development of glaucoma. The phagocytosis of the trabecular meshwork is decreased or lost in older individuals leading to accumulation of toxic molecules within the drainage channels causing interference with Aqueous humor flow (Shahidullah *et al*.,2004).

**Glaucoma Treatment:**

 Glaucoma can be treated with eye drops, pills, laser surgery, traditional surgery or a combination of these methods. Most antiglaucoma drugs are delivered as eye drops, which may need to be used once or several times a day. The goal of any treatment is to prevent loss of vision, as vision loss from glaucoma is irreversible.
The good news is that glaucoma can be managed if detected early and that with medical and/or surgical treatment, most people with glaucoma will not lose their sight.Taking medications regularly, as prescribed is crucial in preventing vision-threatening damage. When medications do not achieve the desired results, or have intolerable side effects further treatment suggested will be surgery like laser surgery, laser trabeculoplasty and **Selective Laser Trabeculoplasty (for**open angle glaucoma***),*** Laser Peripheral Iridotomy (for angle closure glaucoma, Cycloablation) etc.,

**Gene in glaucoma:**

POAG (Primary Open Angle Glaucoma) is associated with mutations in different genes including MYOC, ASB10, WDR36, NTF4, TBK1 genes. A recent GWAS (Genome-Wide Association Study) identified two susceptibility loci for primary angle-closure glaucoma (PACG) like PLEKHA7, COL11A1.

Mutations in the CYP1B1 and LTBP2 genes cause primary congenital glaucoma with autosomal recessive inheritance. The GLC3B and GLC3C loci have also been linked to this form of glaucoma, although the normal genes at these loci are unknown. The CYP1B1 gene plays a role in oxidative and vascular homeostasis, whereas the LTBP2 gene functions in cell adhesion. Genetic testing for known disease-associated mutations is available for both CYP1B1 and LTBP2 (Aboobakar & Allingham, 2014).

Genes that cause early-onset forms of glaucoma are responsible for less than 5% of all POAG cases. Recent large-scale GWAS had identified several important POAG-associated genes and loci, including CDKN2B-AS, SIX1/SIX6, TMCO1, and CAV1/CAV2. Very recently, a common genetic variant in the SIX6 gene, rs33912345, was shown to reduce the size of the eye and optic nerve volume in an animal model (Aboobakar & Allingham, 2014).

**Glaucoma Mechanism:**

Glaucomas are characterized by a slow and progressive degeneration of retinal ganglion cells (RGCs) and their axons that carry information from eye to brain traveling through the optic nerve. This progressive degeneration results in a distinct appearance of the optic disc and a concomitant pattern of vision loss. Characteristic changes to the optic nerve in glaucoma include the enlargement and elongation of the optic nerve cup, the thinning and eventual notching of the neuroretinal rim, asymmetry in cup size between the two eyes and disc haemorrhages. Changes in the visual field with perimetric testing include scotomas that correspond to local and diffuse loss of nerve fibres within the retina. These characteristic changes consist of arcuate scotomas (depression vision), Nasal steps (Glucomatous effect) and paracentral scotomas (diminished vision). The disease involves the entire visual pathway, including the brainstem and the visual cortex (Zhang *et al*., 2012).

**Drugs used for Glaucoma:**

Intraocular pressure can be lowered with medication, usually eye drops. Several different classes of medications are used to treat glaucoma. Each of these medicines may have local and systemic side effects.

**Classification of antiglaucoma agents:**

Depending on their route of administration antiglaucoma agents may be classified as follows

**Topical drugs:**

1. Carbonic anhydrase inhibitors e.g. dorzolamide and brinzolamide.
2. Acetylcholinergic agents e.g., pilocarpine, carbachol, demecarium bromide.
3. NMDA inhibitors e.g., Memataine
4. Adrenergic agonists e.g., epinephrine, dipivefrin, brimonidine and apraclonidine.
5. Beta blockers e.g., timolol, carteolol, betaxolol, levobunolol and metoprolol
6. Prostaglandin analogs e.g., PGF2α, latanoprost, unoprostone and PHXA-85.

**Systemic drugs:**

1. Carbonic anhydrase inhibitors e.g., acetazolamide and Brinzolamide.
2. Osmotic agents e.g., glycerine, mannitol and urea.

Miscellaneous drugs include forskolin, ethacrynic acid, steroid antagonists, cannabinoids, angiotensin converting enzyme inhibitors and neuroprotective agents.

**Mechanisms of action of antiglaucoma agents:**

 The antiglaucoma agents act on the aqueous humor dynamics to reduce the intraocular pressure by three mechanisms.

1. Decrease aqueous production in the ciliary body
2. Increase aqueous humor outflow through the trabecular meshwork and
3. Increase aqueous humor outflow via the uveoscleral pathway. (Saxena *et al*., 2002).

**Table 1. Mechanism of action of Drugs**

|  |  |  |  |
| --- | --- | --- | --- |
| S.No. | Drug Name | Mechanism of action | 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, exacerbated asthma, bradycardis, increased heart block, systemic hypotension, reduced exercise tolerance, depression. |
| 2. | Prostaglandin analogues | Prostaglandin analogues increase aqueous outflow, increase uveoscleral pathway. | Local irritation, conjunctival hyperaemia(redness), growth of eyelashes, hyperpigmentation of light irises and skin, macular oedema, iritis, keratitis, blurred vision. | Headache, dysponoea, exacerbation of asthma. |
| 3. | Alpha agonists | Alpha-agonists reduce aqueous production as well as reduce apiscleral venous pressure and some improvement in outflow.  | Follicular conjunctivitis, contact blepharodermatitis. | Dry mouth, letharty/ headache. |
| 4. | Carbonic anhydrase | Carbonic anhydrase inhibitors decrease aqueous production, direct effect of cilary body. | Topical formulations blurred vision, ocular irritation, conjunctival hyperaemia. | Alteration of taste, headache, metabolic acidosis, polyuria, caution in diabetes, blood dyscrasia. |
| 5. | Cholinergic receptor | Cholinergics/ miotics improve outflow, specific in angle-closure glaucoma. | Blurred vision, miosis, lacrimation, local irritation, poorly tolerated by young. | Sweating, rhinitis, frequency of micturition, dizziness, flushing, abdorminal pain, hypertension. |
| 6. | Sympathomimetics | Sympathomimetics decrease aqueous production and increase aqueous outflow | Irritation, hyperaemia | Sympathomimetic side-effects, palpitations, tachycardia,cardiac arrhythmias, dizziness. |

**Neuroprotection in Glaucoma:**

Neuroprotection was initially investigated for disorders of the central nervous system such as amyotrophic lateral sclerosis, Alzheimer’s disease, Parkinson, and head trauma. Glaucoma neuroprotection must be considered independent of IOP lowering and the target neurons should be in the central visual pathway, including RGCs (retinal ganglion cells). Chronic progressive loss of retinal ganglion cells is thought to be biphasic; initiation of damage is caused by a primary injury associated to the 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 denegaration 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 death of RGC in presence of 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 fulfil these four criteria.

1. To have a specific target (receptors) in the retina.
2. To exhibit neuroprotective activity and have a measurable effect on RGC survival.
3. To reach the retina/vitreous in neuroprotective concentrations after clinical dosing.
4. Neuroprotective activity must be demonstrated in randomized, controlled, clinical trials in humans.

Glaucoma neuroprotection offers a potential complementary therapy to
IOP-lowering for patients with previous severe damage and for those in whom pressure-lowering agents are ineffective to stop progression (Pinar & Vecino, 2009).

**Neuroprotective Drugs in Glaucoma:**

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

**Dynacin:**

Dynacin hydrochloride is a second-generation tetracycline, commonly used in humans because of its beneficial antimicrobial and anti-inflammatory actions. Dynacin effectively crosses the blood-brain barrier. This drug also has remarkable neuroprotective qualities in animal models of cerebral ischemia, traumatic brain injury, Huntington disease and Parkinson disease (Pinar & Vecino, 2009).

**Doxycycline:**

 Doxycycline is another semisynthetic second-generation tetracycline. 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).

**Carbonic anhydrase:**

The carbonic anhydrases (CA), ubiquitous zinc enzymes present in *Archaea,* prokaryotes and eukaryotes are of three types. They are α-CAs- present in vertebrates, eubacteria, algae and cytoplasm of green plants, β-CAs- predominantly in eubacteria, algae and some eubacteria and γ-CAs- mainly in Archaea and some eubacteria. Basically, there are several cytosolic forms (CA I-III), four membrane bound isozymes, one mitochondrial form as well as secreted CA isozyme. These enzymes catalyse an amazingly simple physiological reaction, the interconversion between carbon dioxide and the bicarbonate ion and are thus involved in crucial physiological processes connected with respiration and transport of CO2-bicarbonate between metabolizing tissues and lungs. The Zinc (Zn) ion of CA is essential for catalysis. X-ray crystallographic data showed that the metal ion is situated at the bottom of a 15 Å deep active site cleft (Supuram *et al*., 2003a).

Systemic sulfonamide drugs have been used clinically, mainly as antiglaucoma agents for a long time. The drugs are Acetazolamide and Brinzolamide. Systemic inhibitors are useful in reducing elevated intraocular pressure (IOP) characteristic to this disease, as they represent the most efficient physiological treatment of glaucoma. This is because by inhibiting the ciliary process enzyme reduced rate of bicarbonate and aqueous humor secretion is achieved, which leads to a 25-30% decrease of IOP, but the inhibition of various CA isozymes presents in tissues other than that of the eye leads to an entire range of side effects (Supuram *et al*., 2003b).

Systemic carbonic anhydrase inhibitors have been an integral part of glaucoma medical therapy for the past 40 years. These are the reserved group of drugs and are given orally as an adjunct when IOP is not controlled adequately with topical medication. Approximately 50% patients have shown intolerable side effects with the use of systemic carbonic anhydrase inhibitors. Therefore, these drugs are currently used to control IOP in patients waiting for surgery (Supuram *et al*., 2003b).

1. **Acetazolamide:**

This is the most widely prescribed carbonic anhydrase inhibitor. However, approximately 50% patients stop treatment with acetazolamide as a consequence of intolerable side effects due to extraocular inhibition of carbonic anhydrase. It reversibly blocks the enzyme carbonic anhydrase in the ciliary body and thus suppresses aqueous humor production. The aqueous fluid rich in sodium and bicarbonate ions is hyperosmotic as compared to plasma. The usual oral dose is 125-250 mg four times daily. The effect of acetazolamide may be sustained by dispensing in coated granules form and using an osmotic pump delivery system. Gastrointestinal upset is the most frequent symptom of acetazolamide intolerance. Severe side effects include myopia, pulmonary failure, renal stones, aplastic anaemia, metabolic acidosis, hypersensitivity reactions and peripheral neuropathy (Saxena *et al*., 2002).

1. **Brinzolamide:**

It is also commercially available since 1998. Its 1% suspension is comparable to 2% dorzolamide in lowering IOP. It is administered three times daily. Though it has a lower incidence of burning and stinging, it elicits more blurred vision. One percent (1%) brinzolamide three times daily used adjunctively with timolol 0.5% twice daily produces a significantly additive IOP reduction in open angle glaucoma and ocular hypertensive patients with fewer side effects (Saxena *et al.,* 2002).

**Acetylcholinesterase:**

Acetylcholinesterase is involved in the termination of impulse transmission by rapid hydrolysis of the neurotransmitter acetylcholine in numerous cholinergic pathways in the central and peripheral nervous system.

Cholinesterase is a family of enzymes that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation.

It involves two types: 1. Acetylcholinesterase (AChE) is found in many types of conducting tissues like nerve and muscle, central and peripheral tissues, motor and sensory fibers and cholinergic and noncholinergic fibers. The activity of AChE is higher in motor neurons than in sensory neurons. AChE is also found in the red blood cell membranes, where it constitutes the Yt blood group antigen. The enzyme exists in multiple molecular forms, which possess similar catalytic properties but differ in their oligomeric assembly and mode of attachment to the cell surface (Colovic *et al*., 2013).

2. Pseudocholinesterase also known as plasma cholinesterase, butyrylcholinesterase or acylcholine acylhydrolase is found primarily in the liver.

AChE inhibitors inhibit the cholinesterase enzyme from breaking down ACh, increasing both the level and duration of the neurotransmitter action. According to the mode of action, AChE inhibitors can be divided into two groups: irreversible and reversible. Reversible inhibitors, competitive or noncompetitive, mostly have therapeutic applications, while toxic effects are associated with irreversible AChE activity modulators. Irreversible AChE inhibitors play an important role in pharmacological manipulation of the enzyme activity. These inhibitors include compounds with different functional groups, and have been applied in the diagnostic and/or treatment of various diseases such as glaucoma, myasthenia gravis, Alzhemir Disease (AD), postoperative ileus and bladder distention (Colovic *et al.,* 2013)

**Diisopropyl Flurophosphate:**

Carbamates are organic compounds derived from carbamic acid (NH2COOH). It is mainly used as therapeutic drug in human medicine like Myasthenia gravis, glaucoma Lewy bodies. These reversible AChE inhibitor have been applied as pesticides. The disease is associated with increased fluid pressure in the eye and can permanently damage vision in the affected eye(s) and lead to blindness if left untreated. Diisopropyl fluorophosphate is a parasympathomimetic drug, irreversible anti-cholinesterase and has been used Acute poisoning by a nerve agent leads to contraction of pupils, profuse salivation, convulsions, involuntary urination. Treatment of chronic glaucoma, an eye disease in which the optic nerve is damaged in a characteristic pattern (Colovic *et al.,* 2013).

**Echothiophate:**

Contraction of pupils, profuse salivation, convulsions, involuntary urination, Treatment of chronic glaucoma, an eye disease in which the optic nerve is damaged in a characteristic pattern. It exerts ocular side effects mainly associated with its AChE inhibitory properties and ability to induce delayed peripheral neuropathy. Echothiophate (phospholine) is a parasympathomimetic phosphorothioate, irreversible AChE inhibitor. It is used as an ocular antihypertensive in the treatment of chronic glaucoma and in some cases accommodative esotropia. Its application is local (eye drops) and the effects can last a week or more. The drug is available under several trade names such as phospholine iodide. Adverse effects include muscle spasm and other systemic effects (Colovic *et al*., 2013).

**NMDA (N-Methyl-D-Aspartate) Receptor:**

The NMDA receptor, a member of the glutamate receptor family, is an example of an ion channel coupled receptor with excitatory properties which have been implicated in the mechanism of general anaesthesia, analgesia and also in neurotoxicity. Ketamine is a non-competitive antagonist of the NMDA receptor Ca2+ channel pore. which interacts with the phencyclidine binding site leading to significant inhibition of NMDA receptor activity and this occurs only when the channel has been opened.

 Glutamate is an essential amino acid that is abundant in all cells and known to play a significant role as the main excitatory neurotransmitter in the CNS and retina. Glutamate release has been implicated as a mechanism of RGC death in glaucoma and inhibition or blockade of glutamate activity in particular, modulation of the N-methyl
D-aspartate (NMDA) type receptor has been advocated to be an important strategy for neuroprotection in glaucoma although its exact role is controversial. Glutamate is tightly regulated in the presynaptic cells as excessive expression of glutamate is potent and neurotoxic (Cheung *et al*., 2008).

 NMDA’s play a significant role in both the proper development of the central nervous system and the processes underlying functional and structural plasticity in the adult brain. They can perform the possess a combination of unique properties
1. High affinity for the excitatory transmitter L-glutamate, 2. Terribly slow kinetics of activation, 3. Pronounced voltage dependence due to external Mg block, 4. High permeability to Ca ions and 5. Large cytoplasmic domains that enable them to become part of and help organize large macromolecular synaptic signaling complexes (Blanke and Vandongen, 2009).

**Memantine:**

Memantine is currently available clinical glutamate modifier which was first synthesized in 1960s by Eli Lilly & Company and was patented in 1968. Memantine is aderivative of amantadine which was used as an anti-influenza compound. Memantine has been demonstrated to be effective in the treatment of AD and PD. It was believed that memantine was anticholinergic or dopaminergic and it was only relatively recently shown to be an NMDA-receptor antagonist. Memantine has been shown to be a highly effective neuroprotective agent in both acute and chronic animal models of RGC death. Daily administration of memantine (5 to 10 mg/kg) enhanced survival of RGCs in a laser-induced rat and primate model of chronic ocular hypertension and transgenic mouse model of glaucoma. In 2008 Memantine was in a phase IV clinical trial assessing its efficiency in glaucoma patients (Cheung *et al*., 2008).

**Neuroprotective Plant compounds:**

 **Artepillin:**

Artepillin was extracted from Brazilian propolis. The botanical origin of the propolis was *Baccharis dracunculifolia* plant resinous exudates. It was also observed that honeybee visited the leaf buds or unexpanded leaves of *Baccharis dracunculifolia* but rarely expanded leaves (Park *et al*., 2004). Artepillin propolis in *vitro* it was reported for their neuroprotective activity in PC12 cell culture and acted as an antioxidant against lipid peroxidation and free radical production. *In vivo* Artepillin propolis has neuroprotective activity against ischemic injury, also it has antioxidant properties (Shimazawa *et al*., 2005).

**Baicalin:**

 Baicalin, a flavonoid compound isolated from the Chinese medicinal herb *Scutellaria baicalensis*. It has been used to treat upper respiratory infections, diphtheris scarlet fever and viral hepatitis. Baicalin were having anticonvulsant and neuroprotective effect in the pilocarpine- induced epileptic model in rates (Liu *et al*., 2012). Baicalin provides a neuroprotective effect on permanent focal cerebral ischemia in rats, also the neuroprotective action of baicalin was demonstrated to be reducing HSP70 expression of hippocampal neurons in focal cerebral ischemia/reperfusion injury rats
(Tu *et al*., 2009) .

**Bilobalide:**

Bilobalide is a flavonoid extracted maily from the leaves of *Ginkgo biloba* plant and present in the phytopharmaceutical preparations containing ginkgo extracts
(Beek *et al*., 1991). The neuroprotective effect of bilobalide against ischemic injury had been demonstrated in animal models and find out the purified terpene lactone from EGb 761 and EGb 761 against ischemic injury (Chandrasekaran *et al*., 2001). Bilobalide has multiple mechanism of action that may associated with neuroprotection which include its preservation of mitochondrial ATP synthesis, its inhibition of apoptotic damage induced by staurosporine or by serum free medium, its suppression of hypoxia induced membrane deterioration in the brain (Defeudis, 2002).

**Caffeine:**

Around sixty plant species are known to contain caffeine. The genus Coffea is from Rubiaceae family. Caffeine is a psychoactive substance mainly extracted from the *Coffea Arabica* and *Coffea canephora* seeds. Coffee is the brewed beverages prepared from roasted seeds, it also known as coffee beans. It is the most frequently consumed stimulant drink all over the world (Yadav *et al*., 2012). The metabolites of caffeine provide a neuroprotective effect in mouse model of parkinson’s disease. Caffeine protects against putative toxin-induced dopaminergic neuron injury on human. The temporal pairing between caffeine and toxin exposures may not be critical because the duration of caffeine may be extended by protective effects of its major metabolites (Kachroo *et al* 2010).

**Carnitine:**

Carnitine are found in nuts, grains, seeds, legumes, pulses, fruits and vegetables.
The highest concentrations of carnitine are found in red meat. Carnitine status in human is reported to vary according to body composition, gender and diet. Carnitine biosynthesis requires pathways in different tissues and is and efficient system (Steiber *et al*., 2004). Carnitine is a natural compound which has an essential role in intermediary metabolism, but there is also proved experimental evidence that carnitine has neuroprotective action on both the central and peripheral nervous system (Ghirardi *et al*., 2005).

**Catechin:**

Catechin is a flavanoid compound isolated from the hooks and stem of *Uncaria sinenis* plant (Shimada, 2001). Flavanols of catechin are found in high concentration in cocoa, tea, red wine and fruits such as apples, grapes and strawberries. It differs in nature based on their constitutive units their sequence and the position of interflavanic linkages (Vauzour *et al*., 2008). Catechin contributes to the neuroprotective effects of both green and black tea. The protective effect of catechin is likely to be associated with its inhibitory action on Aβ fibrils or oligomers formation, this supports the view that not only green but also black tea may reduce age related neurodegenerative diseases (Yao *et al*., 2006).

**Epicatechin:**

Epicatechin is a flavanoid compound also isolated from the hooks and stem of *Uncaria sinenis* plant. It is having protective effects against glutamate induced neuronal death in cultured rat cerebellar granule cells (Shimada, 2001). The neuroprotective action of Epicatechin involves several effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation and the potential to promote memory learning and cognitive function (Vauzour *et al*., 2008).

**Folic acid:**

 Folic acid is a water-soluble B vitamin that was first isolated from *Avocado* later its presence was reported from spinach leaves and green leafy vegetables. It is essential for the maintenance of normal brain function and may also function as potential source for therapeutics against excitotoxicity (Ding *et al*., 2010). Folic acid had strong neuron protective effects and has been suggested to be a promising compound in the prevention of neurodegeneration. Neuroprotective effect of folic acid against induced oxidative damage in neurons and its mitochondria was demonstrated by Ding *et al.* ( 2010).

**Genipin:**

Genipin is extracted from the *Gardenia jasminoides* plant fruit. It has been used in traditional Chinese medicine as a treatment for various diseases. It is now commonly believed that genipin is multipotent ingredient. It has been reported to protect against amyloid β toxicity (Yamazaki and Chiba, 2005). Genipin is a natural compound with crosslinker properties in the cornea which was similar to crosslinking of porcine corneas in the model of whole eye (Nam *et al*., 2010). Genipin acts as a new neurotrophic factor like compound with both neuritogenic and neuroprotective effects on Neruro 2a cells (Fast growing mouse neuroblastoma cell line). Genipin has the potential to serve as a lead compound for the treatment of neurodegenerative disease (Yamazaki and Chiba, 2005).

**Genistein:**

 Genistein is a 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 posphatase, adenosine triphosphatase and 5’-nucleotidase (Pal and Tandon, 1998). Genistein is one of the nutraceutical molecules found in soybean seeds. The antioxidant activity of genistein has the beneficial effects such as protection against vascular dysfunction through the amelioration of oxidative modifications and upregulation of endogenous antioxidant signaling pathways (Qian *et al.,* 2012). Genistein has a neuroprotective effect in transient focal ischemia and it may involve regulation of mitochondria-dependent apoptosis pathways and suppression of ROS-induced NF-kB activation (Qian *et al*., 2012).

**Isorhamnetin:**

Isorhamnetin was isolated mainly from the *Tagetet lucida* plant leaves. It is an  O-methylated flavonol, a type of flavonoid. Isorhamnetin was shown to induce the expression of neuro filaments and to potentiate the neurite inducing activity of NGF (Normal Growth Factor) (Xu *et al*., 2012). Isorhamnetin was found to have a most evident effect in inducing the expression of neurofilaments in PC12 cells (Xu *et al*., 2006). Isorhamnetin is a flavonol aglycone is present in most neuroprotective plants. This is one of the constituents of *Ginkgo biloba* extract which has been used for brain disorder etc,. Isorhamnetin has potent neuroprotective effect against Amyloid beta induced neurotoxicity in rat (Asha and Sumathi, 2015).

**Kaempferol:**

Kaempferol is a natural flavonol mostly present in fruits such as apple, grape, tomato and in plants such as green tea, pine, *Angelica decursiva* and *Ginkgo* leaf. Kaempferol had shown to have an antioxidant activity and anti-imflammatory. Also, it reduces the risk of cardiovascular and neuroinflammatory disease (Kim & Choi, 2013). Kaempferol is a yellow crystalline solid with a melting point of 276–278 °C (529–532 °F).
It is slightly soluble in water and highly soluble in hot ethanol, ethers and DMSO.
(Kim & Choi, 2013). Kaempferol has neuroprotective effects in MPTP-induced PD mice, which may be attributed to its anti-oxidative capacity to scavenge free radicals and reported in the survival of more dopamine neurons (Shen and Xiao, 2011).

**Levodopa:**

Levodopa also known as L-DOPA (L-3,4-dihydroxyphenylalanine) is important for parkinson’s disease. Levodapa was isolated *Mucuna pruriens* plant in natural source (Brain, 1976). Levodopa having the protective action, whereas Emerging data regarding dopamine agonists have supported a neuroprotective action through antioxidant or antiapoptotic mechanisms that can be attributed to the protective action of Levodopa which is a neuroprotectant as dopamine receptor agonists has provide rationale for assessing the progression of dopamine neuronal degeneration (Shin *et al*., 2009).

**Liquiritin:**

Liquiritin is a flavanoid and the most extensively used medicinal herbs in Eastern and Western medicine. It was isolated from the *Glysyrrhiza uralensis* plant root.
This compound has a wide variety of pharmacological activities, including anti-viral,
anti-oxidant, anti-inflammatory, immunomodulatary and antiulcer (Shen *et al*., 2006). Liquiritin flavanoid has neuroprotective effect through modulation of multiple pathways associated with apotosis, also have protective effect against cerebral ischemia injury which might be due to the amelioration of cerebral energy metabolism and antioxidant activity (Sun *et al*., 2010).

**Melatonin:**

 Melatonin is found in many plants including *Tanacetum parthenium, Hypericum perforatum* etc., Apart from this melatonin present in rice, corn, tomato, grape and edible fruits. Melatonin has the Neuroprotective protective activity to maintain cell survival through the modulation of a wide range of physiological function. Melatonin has been proposed as a neuroprotective agent on the basis of its ability to function as a free radical scavenger, provided that lipoeroxidation and other free radical damage induced by reactive processes of ischemic neuronal damage.

**Minocycline:**

Minocycline is a semi synthetic product of chlortetracycline which is isolated from *streptomyces aureofaciens* (Chin *et al*., 2006)*.* Minocycline has been shown to have neuroprotective properties in different animal models of acute neurological injury. Minocycline exhibits neuroprotective effects against neuronal damage in animal models of focal and global brain ischaemia. Neuroprotective actions of minocycline effects to various intracellular signaling pathways, including antioxidant systems, nitric oxide synthase and blockade of inflammatory responses (Elewa *et al*., 2006).

**Nobiletin:**

Nobiletin is a powerful polymethoxylated flavonoid that found in the peel of citrus fruits of *Citrus reticulate* fruits (Cohen, 2015). Nobiletin is having antioxidant, anti-cancer, anti-inflammation, and cholesterol lowering activity. Nobiletin acts by its antiproliferative effect without being toxic to normal cells (Jasim, 2012). Neuroprotective mechanism of nobiletin has fully elucidated in anti-neuroinflamatory activity of suppression of brain insult induced excessive microglial activation (Cui *et al*., 2010). Recent evidence of citrus nobiletin active in the central nervous system and also its neurotrophic activity has been reported by Cui *et al*., (2010).

**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 an inhibitor of phosphodiesterase, however the precise mechanis, underlying the putative neuroprotective action of papaverine remains unclear. The effects of papaverine was observed on nerve growth factor (NGF) induced neurite outgrowth in PC12 cells (Itoh *et al*., 2011).

**Paraxanthine:**

Paraxanthine (7-methyl xanthine) is found in caffine, the main source of paraxanthine is *Coffea arabica* and *Coffea conephora* seeds(Ashihara, 2006). Paraxanthine can contribute to the pharmacological action of caffeine, especially during long-term caffeine consumption at higher doses when there is accumulation of paraxanthine in plama due to its saturable metabolism (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).

**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). Combined effects of piracetam and ginkgo biloba produced more significant effect. Piracetam has more efficient neuroprotection activity, it increases the lifetime of isolated neuron in higher concentration (Burov *et al*., 1999).

**Pramiracetam:**

Pramiracetam is a noortropic agents (memory enhancer / neuro enhancer). It is extracted from the *Bacopa monniera, Azadirachta indica, Withania sonmifera, and ocimum sanctum* plants. Although several plant products are traditionally used to treat the age-related neurodegenerative complication (Sridharamurthy *et al*., 2012). Pramiracetam reportedly improved cognitive deficits associated with traumatic brain injuries. Recent studies demonstrated its neuroprotective effect when during coronary bypass surgery (Malykh and Sadaie, 2010).

**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). Quercetin possesses neuroprotective effect and may be useful in preventing oxidative damage in the brain also it has strong antioxidant properties. It inhibits PGE2 production, inducible nitric oxide synthase expression and nuclear factor-kB activation (Pany *et al*., 2014).

**Resveratrol:**

Resveratrol is a type of natural phenol that occurs in  phytoalexin and phytoestrogen produced naturally by several plants like hellebore of roots. Food sources of resveratrol include the skin of grapes which was reported to have variety of biological and pharmacological actions (Kim *et al*., 2014). Many Resveratrol oligomers have been found in seven plant families, i.e., Dipterocarpaceae, Vitaceae, Cyperaceae, Genetaceae, Welwitschiaceae, Umbelliferae and Leguminosae and their antimicrobial and various physiological activities had been reported (Gonthier *et al*., 2012). The neuroprotective effect of resveratrol against Aβ (Amyloid beta) toxic effects could also be mediated by promoting the intracellular degradation of Aβ through the ubiquitin proteasome system (Calabrese *et al*., 2008).

**Tangeretin:**

Tangeretin is a flavonoid found in the peel of citrus fruits including mandarins, tangerines, grapefruits, and oranges. The dried and mature peel of *Citrus reticulate* fruits have been recorded in the Chinese pharmacopoeia as appropriate for medical use
(Jasim, 2012). Tissue distribution and neuroprotective effects of citrus flavonoid tangeretin in rat model of parkinson’s disease was demonstrated (Datla *et al*., 2011). Tangeretin increases the levels of dopamine and has potential neuroprotective activity.
It also has cholesterol lowering properties (Jasim,2012)

**Theobromine:**

Theobromine is flavonoids present in Cacao plant, with the chemical formulaC7H8N4O2 and it is found in chocolate (Xu *et al.*, 2006). It is classified as a xanthine alkaloid, which also include the similar compounds theophylline and caffeine.  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 exert a multiplicity of neuroprotective actions, including the capacity to protect neurons from damage induced by neurotoxins, reduce neuroinflammation and promote memory, learning and cognitive function.

**Theanine:**

Theanine is a flavorous component of green tea extracted from *Camellia sinensis* leaves and is characteristic component of tea. Theanine was reported to be biologically active in reducing systemic blood pressure, producing a relaxation effect, and suppressing the stimulatory action of caffeine (Sakato, 1949). Theanine is an ethylamide and glutamate analogue of the excitatory neurotransmitter glutamic acid. The actions of theanine which may compete with glutamic acid to bind the glutamate receptors, thereby suppressing glutamate toxicity and conferring a neuroprotective effect Cho *et al*., (2008) investigated the neuroprotective effect of theanine in both *in vitro* and *in vivo* studies, as well as the mechanisms of the posited neuroprotective effects.

**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). Theophylline cytoprotective capacity of the antioxidant would be critical to define a putative neuroprotective therapeutic activity (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).

**Trigonelline**

Trigonelline is a alkaloid, commonly found in *Trigonella foenum-graecum seeds* and known as fenugreek, is one of the oldest medicinal plants. Trigonelline is shown to be potent antidiabetic and antioxidant compound. Therefore, fenugreek extract standardized to bioactive marker compound, trigonelline can prove to be beneficial in management of neuropathic pain (Morani *et al*., 2012). Recent review proved that Trigonelline is a major ingredient of several traditional Chinese medicine with anti-diabetic and neuroprotective effect, has a hypoglycemic effect both in rats and human (Yin and Wen, 2012).

**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). Ubiquinone is an essential biological cofactor of the electron transport chain that serves as an important antioxidant in mitochondrial and lipid membranes. Ubiquinone can penetrate blood brain barrier and can modulate the mitochondrial electron transport chain, modulate mitochondria. Because of these functions, ubiquinone has attracted attention as a neuroprotective agent in neurodegenerative disorders linked to mitochondrial defects or oxidative stress, such as Parkinson’s desease (Kabel *et al*., 2013).

**Wogonin:**

Wogonin (5,7-dihydroxy-8-methoxyflavone) is a flavonoid derived from the root of *Scutellaria baicalensis*. It a medicinal plant traditionally used in Oriental medicine (Lee *et al*., 2003). Based on the known anti-inflammatory activity of wogonin in macrophages and other cell types in periphery. Wogonin may tested for exertion of a similar anti-inflammatory effect in brain microglia and for neuroprotection against brain injury where microglia-mediated inflammatory responses play an important pathogenic role (Lee *et al*., 2003). Trigonelline mechanisms of these flavones was reported in animal models of ocular disease (Xiao, 2014).

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