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Role of Polyphenolic Compounds in Management of Oxidative Stress Associated With Glaucoma

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Abstract**: Glaucoma is a first rank common cause of irreversible vision loss. It is also recognized as a neurodegenerative disease which progress with age, results in optic neuropathy. The exact cause of glaucoma remains unclear although oxidative stress considered as one of the reasons for cell death in the retinal ganglion cell and retinal pigment epithelium. Oxidative stress could result after imbalance between formation and utilization of reactive oxygen species. Current pharmacotherapy of glaucoma includes lowering down of elevated level of IOP, which is not sufficient enough to retard irreversible vision loss in some instances. Hence, alternative neuroprotective therapy is warranted. Polyphenolic compounds possess antioxidant, anti-inflammatory properties and also show the neuroprotective effect in an experimental model. Amongst the natural polyphenolic compounds resveratrol, curcumin, rutin, quercetin, myricetin have been studied and showed potential as neuroprotection against cell apoptosis. Moreover, the extra supplement of a polyphenolic compound may also improve antioxidant status, which was underestimated in glaucoma disorder. Despite the potential, the polyphenolic compounds yet to explore for clinical use in ocular disorder. Hence it is an excellent opportunity for the future researcher to transform these substances from lab to clinic as neuroprotectants in glaucoma.

Keywords: Resveratrol, curcumin, quercetin, oxidative stress, glaucoma

1. INTRODUCTION:

Vision loss by eye disorders may affect healthy life and create a socioeconomic burden [1]. Worldwide, glaucoma is the first common cause of irreversible vision loss. [2, 3]. Glaucoma is an age-related eye disorder affecting around 60 million populations across the world. It is expected to affect over 110 million individuals by 2040 [4]. Glaucoma was considered a "sneak thief of life," and early diagnosis and treatment are needed to decrease its severity [5]. Glaucoma was considered a neurodegenerative disease due to the loss of RGC and nerve endings [6]. The process of degeneration usually progresses with age and responsible for the loss of vision [7]. Open-angle glaucoma (OAG) is the most common one;

it progresses slowly without any symptoms and detects in the latter stage; hence it is also termed chronic [8]. Another type of glaucoma that can be detected at an early stage is referred to as closed-angle (acute) glaucoma [2]. Elevation of ocular pressure (>21 mmHg) is the only measurable biomarker has been used for diagnosis of both acute and chronic type of glaucoma [9]. Other types of glaucoma, where cupping of nerve ending and death of RGC occurs without increasing eye pressure, are known as normal-tension glaucoma [10]. The exact cause of glaucoma is still unclear; however, oxidative stress is believed to be one reason for neurodegeneration. Mitochondrial damage and vascular dysfunction are also accounted for the possible cause of the disorder mentioned above [11].

The increase in eye pressure is one of the glaucoma problems, which occurs due to either overproduction of aqueous humour (AH) or impairment of drainage pathways. There are two pathways for AH drainage that is uveoscleral and trabecular TM outflow [12]. A study that has been performed recently on in vitro model (human TM cell) demonstrated that oxidative markers observed in the trabecular meshwork are associated with increased pressure (IOP) of the eye. The oxidative stress markers (biomarkers) accounted more with the glaucoma eye than the control eye. Furthermore, oxidative stress markers may worsen the process degeneration of TM cell, and hence outflow pathway may get disturbing results in a more elevated level of IOP, which could remain beyond the control [13,14,15,16,17]. Apart from oxidative stress, total antioxidant status (TAS) level in the glaucoma eye is underestimated compared with control [18,19]. All these factors need to be controlled to avoid neurodegeneration in cells of RPE, RGC, TM cell, etc.

Current pharmacotherapy of glaucoma is focused on targeting an elevated IOP of glaucoma. The therapeutic agent mainly includes alpha agonist (brimonidine), beta antagonist (levobunolol), carbonic anhydrase inhibitors (brinzolamide), and prostaglandin analogues (latanoprost). Eye drop of one of the anti-glaucoma drugs has been recommended for glaucoma treatment [20]. These agents can decrease the IOP 17-27% from the baseline [21]. However, some patients tolerated these drugs and could not achieve the target IOP level; hence, there is a need for a drug that works by a different mechanism. Although, treatment of glaucoma with the hypotensive drug could not be able to prevent possible neurodegeneration. Hence there is a need for an extra supplement of neuroprotective agents in combination with a hypotensive agent.

The polyphenolic compounds possess antioxidant and anti-inflammatory properties and could also perform the neuroprotective role [22]. Recent studies showed the role of some polyphenolic compounds (resveratrol) in controlling IOP in glaucoma [23]. Many studies have been carried out on polyphenolic phytoactive compounds like resveratrol, curcumin, quercetin, rutin, kaempferol, myricetin, and found effective in experimental glaucoma model. In this review, we will discuss the role of these polyphenolic compounds in the management of glaucoma.

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2. RELATION OF OXIDATIVE STRESS IN GLAUCOMA

2.1 ROS and oxidative stress

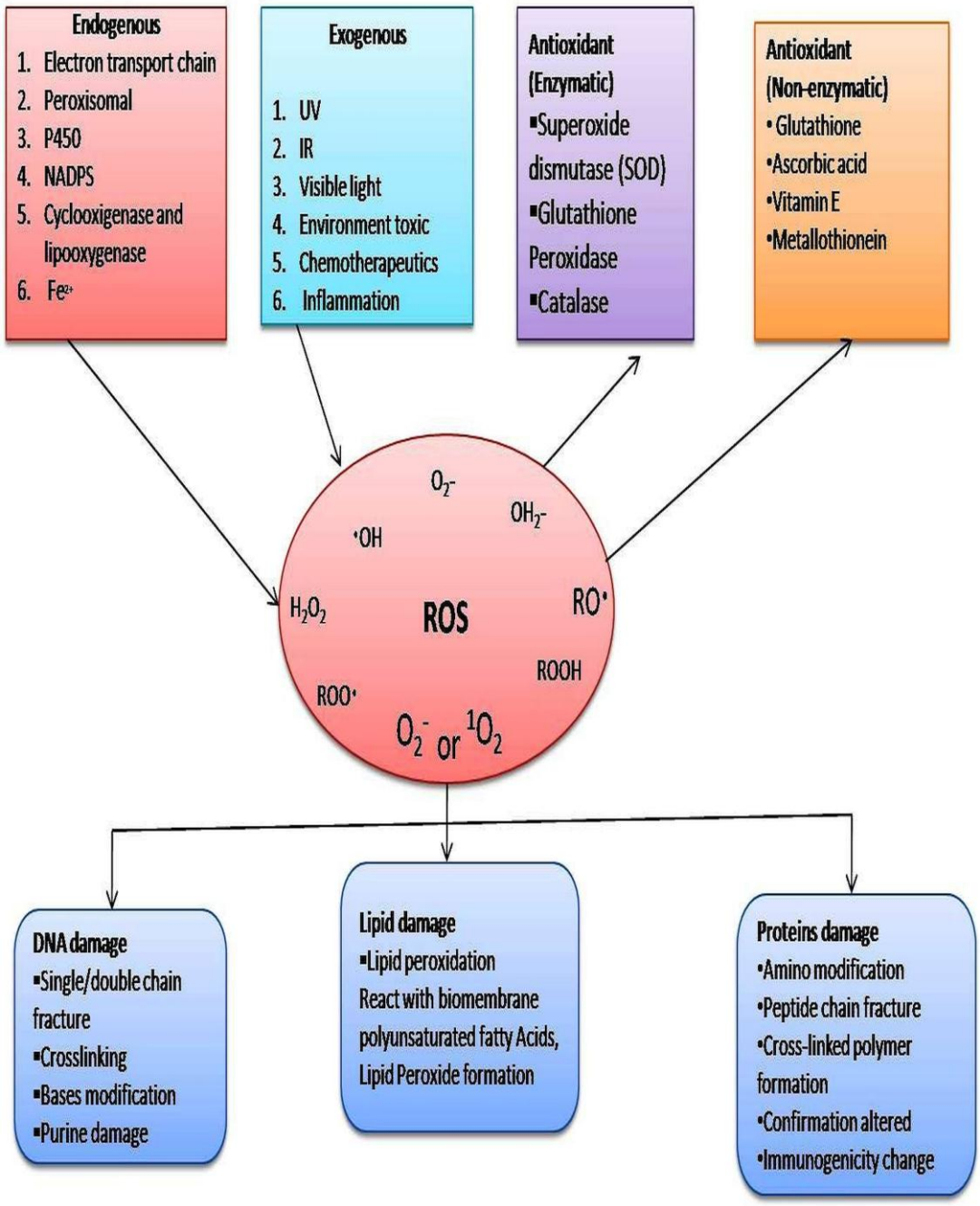

Figure 1. Process of production of ROS and its effect on biomolecules[24].

During the metabolic process, various moieties with unpaired electrons are produced are known as free radicals. They can be classified into two main types based on the presence of oxygen molecules. Oxygen-containing free radicals (> 95 %) and non-oxygen radicals [24]. Hydrogen peroxide, hydroxyl radicals, peroxide hydroxyl radicals, superoxide, and anionic

radicals are compositely called reactive oxygen species. These reactive species are generated due to internal stimuli such as growth factors and reactive cytokines with the aid of catalyst NADPH (a family of oxidase) [25,26]. Endogenous or exogenous factors can produce free radicals. Exogenous factors include environmental toxins such as tobacco smoke, the light of in the range of IR and UV. Endogenous factors are mitochondrial electron transport chain, peroxisome, endoplasmic reticulum [27]. The internal defence mechanism of the body and antioxidant compound controls the phenomenon of formation and utilization of reactive species. Any changes in the body may trigger imbalance between these two processes may cause oxidative stress. DNA damage cell apoptosis mutation and autophagy, which could cause age-related disorders like glaucoma [28].

2.2 TM oxidative stress and glaucoma

The patient suffers from glaucoma usually deficit with antioxidant capacity hence more susceptible to oxidative stress[29,30]. It has been found that depletion of an endogenous antioxidant, for instance, catalase, glutathione peroxidase, and superoxide dismutase has declined in glaucoma patients [31]. All these changes are responsible for the production of ROS and may cause cell apoptosis. TM cells are more susceptible to oxidation, which may alter their structure and cellularity. Oxidative stress causes a change in the extracellular matrix structure and results in accumulation, further affecting the trabecular meshwork's cellularity and functionality. The production of free radicals may also produce some inflammatory responses by forming cytokines, which are further responsible for TM cell death and apoptosis. All these may contribute to altering TM cells' structure and function, which further increases the IOP [24].

3. POLYPHENOLIC COMPOUNDS

Phenolic compounds were considered the metabolite of plants and generally obtained from various plants [32]. Phenolic compounds are classified into flavonoids, phenolic acid, tocopherols (vitamin E), and phenolic acid. (Fig.**2**)

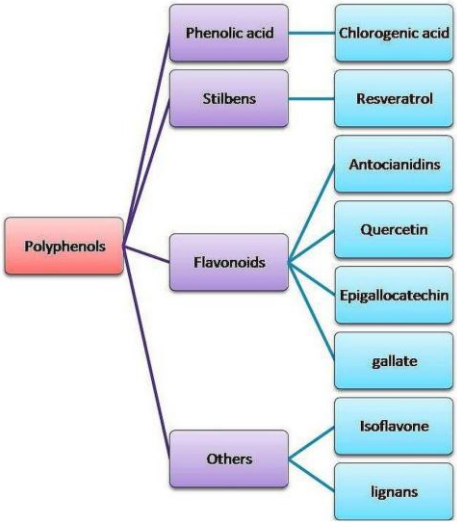

Figure 2 Classification of phytoactive polyphenolic compounds [33].

Most of the compounds in this class possess antioxidant (radical scavenger) and anti-inflammatory properties and found useful in various age-related disorders, including glaucoma [34]. The natural phenolic compounds can combat oxidative stress and inflammatory responses related to glaucoma [35]. Moreover, some phenolic compounds can also lower down IOP in the eye of the experimental glaucoma model [23]. Hence polyphenolic can be incorporated in drug delivery combined with glaucoma drugs for the effective management of glaucoma. The following equation can explain the mechanism of polyphenolic compounds. The OH group compounds can scavenge free radical (R) by accepting or transferring unpaired electron[31].

$R+ArOH \rightarrow RH+ArO$ ..... (1)

$R+ArOH \rightarrow R^{-} + ArOH^{+}$ ……. (2)

Where R= free radicals, ArOH = antioxidant compound, RH-radical hydrogen complex.

Equation 1, applicable for the antioxidant (ArOH) compounds, has weaker bond dissociation energy, while equation 2 represents intense bond dissociation energy, which may form unwanted free radicals ($ArOH^{+}$) [36,37]. Hence equation 1 is ideal for an antioxidant property, which is best suited for the polyphenolic compounds.

3.1 Role in antioxidation

The ROS and RNS are, in combination, could contribute to oxidative stress. The polyphenolic compound consists of a hydroxy (OH) group, which may contribute antioxidant role by scavenging free radicals. Besides, they may also inhibit enzymes that are responsible for the production of ROS [38]. In some instances, it works by upregulation of endogenous antioxidants. The enzyme involves in catalysis of ROS can also be degraded with natural polyphenolic compounds. Lastly, polyphenolics can scavenge free metal ions (heavy metals), which was also a contributor to a redox reaction [39].

3.2 Free radical bonding

The polyphenolic compound binds with the plasma membrane and alters biomolecules' properties, which reduces the incidences of oxidation. Binding of these compounds with an enzyme with nitric oxide synthase and xanthine oxidase inhibits various radicals' formation[38].

3.3 Role in ant- inflammation

Tumor necrosis factor-α can stimulate inflammatory responses through leukotriene (LT). Polyphenolic compounds can minimize the effect of TNF- α and endothelial growth factor. Hence it can decrease the production of leukotrienes IL-8, IL-6, and IL1a [33].

3.4 Effects of oxidation on enzymatic inhibition

Various studies have confirmed the activity of polyphenolic compounds through the arachidonic pathway (AA). The activity of enzymes like cyclooxygenase, nitric oxide synthase, and lipooxygenase has changed through this pathway. The elevated level of iNOS, NO, has been observed during the body's defence mechanism and is responsible for oxidative

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stress. The polyphenol containing substances can minimize oxidative stress by inhibiting COX and LOX. The effectiveness of the polyphenolic compounds was also studied and showed potential against AA related biomarkers. Inflammatory biomarkers are AP-1, NF-Kb, iNOS, COX-2, IL-1β, and TNF- α; all these may contribute to inflammation in the body. The approach of polyphenolic compounds can minimize their effect[40,41,42]. The mechanism of neuroprotection of polyphenolic compounds are given in Fig. **3**

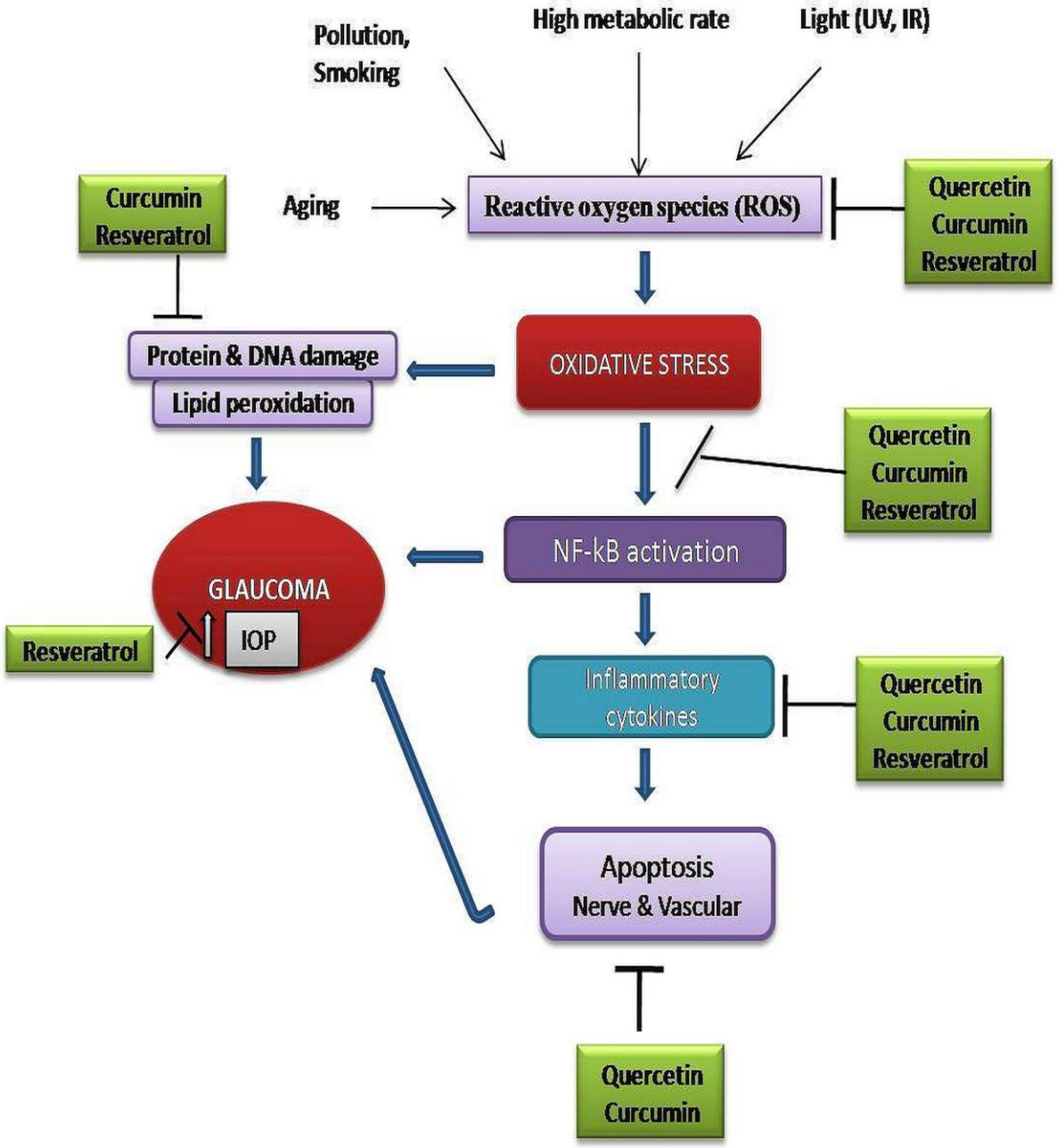

Figure 3 Protective effects of natural polyphenolic compounds on glaucoma[43].

4. CURCUMIN:

Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6- heptadien-3,5-dione) is a very important constituent of Curcuma *longa*. It has been using for a long year for different disorders like inflammation, wound healing, and management of diseases like cancer. Its

antioxidant properties and neuroprotective nature become more popular in treating neurodegenerative diseases like glaucoma. Despite the potential, its use is not approved clinically due to its less water solubility and available in very less amount systemically after administered orally [44,45]. The antioxidant and anti-inflammatory properties of curcumin are often necessary for glaucoma to exert a neuroprotective effect [46]. The mechanism of curcumin in neuroprotection are listed in Table **1**

Table 1 Mechanism of curcumin in neuroprotection

Role	Mechanism/Pathway/Enzyme	Reference
Rescue oxidative stress 	free radicals, DNA damage, production of ROS, Nitric oxide, Lipid peroxidation	[47]
	Catalase, Superoxide dismutase, Glutathione peroxidase, and HO-1	[48]
Anti-inflammatory response	↓(NF)-kB → TNF-a ↓cyclooxygenase (COX-2) an3 d lipoxygenase (5-LOX) ↓ IL1, IL-6, IL-8, and TNF	[49] [47]
	↑ peroxisome proliferator-activated receptor-γ (PPAR-γ)	[50]
Antiapoptosis	↓ BAX ↑ BCL-2	[51]
	↓ Fas pathway, Fas ligand receptor-interacting kinases	.[52]

This polyphenolic compound has been reported as an efficacious and safe compound in clinical trials and has been approved as a "generally regarded as safe" compound by the U.S. Food and Drug Administration [53].

Acute retinal ischemia is one of the eye disorders generally associated with glaucoma; reperfusion (I/R) also occurs in worse condition of glaucoma. In a study, curcumin was studied for neuroprotective effect on the I/R injury-induced rat model. Neurodegeneration in ischemia-reperfusion disease is typically associated with neuron death, glial activation, and vascular degeneration. Curcumin had shown a protective effect against these conditions by activating the NF-kB factor and regulating STAT3 and MCP-1. In a study, ischemic glaucoma produced by raising eye pressure for 1 hour. Degenerative effects were shown on the ganglion's cell layer and the retinal capillaries. The pre-treated animal studies group showed comparatively less damage in both the cells, suggesting a neuroprotective role of curcumin[46]. Awad et al., [51] have performed an *in vivo* study on the same experimental animal model and showed an anti-apoptotic effect on different cells.

Curcumin was reported to protect TM cells against oxidative stress associated with glaucoma. Hydrogen peroxide treated TM cell, in *vitro* model was selected for the study. Oxidative stress markers, like cell apoptosis, production of iROS, proinflammatory factors, were found to decrease, and their intensity is inversely proportional to curcumin concentration [45]. The study demonstrated neuroprotective effects on experimental animal glaucoma model (rat) and cell line (in vitro). In a curcumin-treated cell line analysis, decreased reactive species (ROS) and apoptosis showed improved cell viability. The experimental animal treated with curcumin exhibited inhibitory effects on biomarkers such as caspase 3, cytochrome c, and BAX, while stimulation effects on other oxidative biomarkers BCL2 were observed [54]. In another study, researchers had demonstrated the cytoprotective effect of curcumin on the RGC-5 cell line (in vitro) and in vivo mice model mice. In the analysis, the cell line exposed to staurosporine (cytotoxic agent) showed decreased RGC cell count due to inhibitory effects on MMP-9 and other activators (tissue plasminogen activator and urokinase plasminogen activator). Comparative less cell death was observed in the curcumin-treated population. Curcumin protects RGC cell death in an in vitro model while the in vivo analysis confirms the protective effect on both amacrine and RGC cells. Curcumin could restore the inhibitory effect of staurosporine by regulating the NF-κB factor [55].

Excitotoxicity is also one of the causes of neurodegeneration in glaucoma. NMDA is one of the excitotoxicity-related receptors responsible for cell death. Cell line (excitotoxicity model) showed increased cell loss, which was reversed by the supplement of curcumin. Curcumin has been reported to regulate Ca2+ through the NMDA-NR1 pathway[56]. Despite, the several neuroprotective, the curcumin has been restricted in therapeutics due to poor solubility and bioavailability. To improve the bioavailability, curcumin combined with nanomaterial showed an improved neuroprotective effect on cobalt chloride ($Cocl_2$) treated cell lines (*in vitro*) and glutamate toxicity. *In vivo* study carried out, the curcumin-treated experimental model showed more RGC cell viability than control [57]. So, curcumin could prove to be an effective treatment strategy for the neuroprotection in glaucoma.

5. RESVERATROL

Resveratrol is a phytoactive compound with a polyphenol structure, generally derived from various natural sources like red wine, grapes, groundnut, etc. [23]. Resveratrol composes a couple of aromatic rings joined together by a methylene structure, known as a stilbene. Resveratrol (3,5,4, 1 -trihydroxy-trans-stilbene) is a phytoalexin compound with significant properties, anti-oxidative, and anti-inflammatory; others are anti-apoptotic and anti-ageing [33,58]. These properties are often necessary for the management of glaucoma. The properties and its mechanism of neuroprotection are summarized in Table **2**

Table 2 Mechanism of action of resveratrol

S.N.	Property	Mechanism of action	Ref.
1	Antioxidant	Scavenging free radicals, hem	[59]
		Glutamate excitotoxicity, up-regulate (OH-1) heme oxygenase	[60]

		↓ROS production, inhibition of Quinone reductase-2	[61]
		Adenosine A1 receptor	[62]
2	Anti-inflammatory	COX-1, IL-8, prostaglandins, and leukotrienes.	[63]
		Blocking the release of cytokinins, mast cells, macrophages, and neutrophils	[63]
		Inhibition NFkB pathway	[64]
		Proinflammatory effect by Microglial cell Activation of SIRT1 Pathway ↓ TNF-α, IL-1β	[63] [65]
3	Anti-apoptotic	Inhibition mitochondrial apoptosis-inducing factor	[66]
		Inhibition of cytochrome-C, ↓ level of total and cleave CASPASE	[65]
		In Gene expression ↑ B-cell lymphoma 2	[67]
		Optic Nerve Head protection ↓ oxidative stress by activation of Caspase‑3	[68]
		Improvement of mitochondrial function ↑Ampk/Sirt1/Pgc1α, ↓Akt/mTOR pathway	[69]

Much work has been published recently to assess resveratrol's protective role in glaucomatous induce rabbits or human cells. Cao et al. performed an experiment using the IOP mice model that showed an increase in reactive species (ROS) and acetyl p53, which decreased with resveratrol therapy. Other oxidative markers, such as BDNF and TrkB, increased during glaucoma induction and dropped in the treatment group, results in reduced cell apoptosis [70]. In another study, combination therapy of crocin and resveratrol on photo-degraded cell (retinal pigment epithelium) was carried out. Significant rise in glutathione levels indicated a synergistic cytoprotective effect on RPE [71].

In a study, resveratrol has shown neuroprotective action in *in vivo,* using the optic nerve transaction (ONT) rat model. Intravitreal injection of resveratrol along with sirtinol showed improvement in RGC 5 cell viability through activation sirtuin pathway [72]. In another study, resveratrol showed decreased the expression of caspase-9 and caspase-3, which was unregulated in the glucose-deprived *in vitro* model. Another cell line triggered by photon showed decreased PARP-1 and AIF levels that were unregulated by resveratrol treatment. During the study, photo/ glucose deprived photoreceptor cell line; 661W vitro model was used, lowering ROS level while improvement in glutathione level, indicated a neuroprotective role in damaged cell line [73].

Ischemia-reperfusion (I/R) injury rat model produces by raising the IOP at a level of around 110 mg Hg for 60 min, was used to evaluate the potency of resveratrol in apoptosis and inflammation. In the treatment group, decreased the level of caspase-3, and gliosis was observed. These results indicate the potential of resveratrol in cell protection and reduce inflammation in RGC [74]. In another ischemic mice model, pretreatment with resveratrol injection (intravitreal) improved the viability of RGC cells by increasing SIRT1 through the Akt pathway[75]. In a similar kind of study, Ischemia (I/R) experimental animal model was developed by eye hypertension for 60 minutes. Results show lesser apoptosis by activating

caspase-8 and 3 in an experimental model with pretreated resveratrol injection[73]. In a recent study, resveratrol has found to be effective in preventing apoptosis of cell such as RGC and neuroprotective in experimental model ischemia I/R model. Administration of sirtinol causes loss of cell, including RGC; concurrent treatment decreases the cytotoxic effect by activating the SRT1-JNK pathway [76]. In another study, retinal damage including RGC-5, mitochondrial defect was experienced in *vitro* and *in vivo* chronic glaucoma, which can be avoided by the treatment of resveratrol. A significant decrease of biomarkers like ROS, MMP was observed during the treatment by AMPK/PGC pathway; these all indicate resveratrol's potential against mitochondrial damage and RGC apoptosis. In a study cytoprotective effect of resveratrol was studied on in vitro cell lines (RPE). The cell line treated with acrolein shows formation superoxide, whereas cellular toxics' intensity was less with the resveratrol treatment group. Resveratrol produces an antioxidant effect on RPE cells by mitochondrial bioenergetics through adenosine triphosphate activation [75].

Extracellular matrix deposition in human TM cells is one of the causes of impairment in AH flow and increases IOP in glaucoma. In the study dexamethasone-treated human trabecular meshwork cell, an *in vitro* model shows an increase in the extracellular matrix (ECM) level, which is associated with an increase in the level matrix metalloproteinase (MMP2 and MMP9). Resveratrol shows its potential in lowering down the IOP in the glaucomatous induced model; it decreases the ECM deposition matrix in dexamethasone-treated HTMC by inhibiting metalloproteinase through stimulation adenosine A1 receptors and NFkB pathway[78,79]. In another study, topical resveratrol (0.2%) was useful in decreasing IOP in a steroid-induced rat model. The instillation eye drop reduces about 15% IOP; resveratrol activates adenosine receptor is the possible mechanism had reported[80]. In another study by the same group, the application of the topical resveratrol eye drop treated for 21 days in steroid-induced rabbit and its effects on the internal environment had been studied. The result concluded that resveratrol's multiple dosing elevates MM2 concentration in aqueous humour and produces the ocular hypotensive effect [23]. In a similar study, researchers developed a rat-inducing hypertensive model, which was pretreated with adenosine (A1AR), PLC, and ERK1/2 inhibitors. The hypotensive effect was observed in the experimental model due to the pretreated inhibitor's effect after the treatment with resveratrol improves IOP by different mechanisms. From their finding, it was concluded that the IOP lowering effect of *trans*-resveratrol involves activation of the adenosine receptor, which further increases the level of MMP-2. Additionally, it also increases the expression of PLC and ERK1/2. Treatment with resveratrol also inhibits the TGF-β2 pathway, which was associated with activation of TGFβRI and inhibition of l of SMAD7 [81].

In a study, co-administration of quercetin and resveratrol in PEG-modified chitosan nanoparticle. Topical instillation of a novel formulation of resveratrol in experimental rabbit shows more reduction in IOP (5.5±0.5 mmHg) than dispersion [82]. In another study, a PEG-modified chitosan nanoparticle of resveratrol was developed and tested on a rabbit model. The result shows a sustained decrease in IOP of 4.3 ±0.5 mmHg in experimental rabbit [83].
In an experimental animal (rat), glaucoma induction was carried out by injecting hyaluronic acid in the frontal part of the eye injection for six weeks. The administration of resveratrol, either alone or in combination with riluzole, was effective in protecting RGC. Pretreatment

and of resveratrol shows more neuroprotection effect as compared with post IOP induction. The combination therapy of resveratrol with riluzole produces a synergistic effect on cell viability [84].

6. QUERCETIN

Quercetin is another polyphenol bioactive compound obtained from onion, red wines, berries, citrus fruits, broccoli, etc. It is categorized as flavonoids and possesses essential features of prevention from oxidation and relieving inflammation in various neurodegenerative disorders like glaucoma, AMD, cataract, and diabetic retinopathy. Flavonoids compounds have radical scavenging property and quercetin considered excellent antioxidant properties, which strong enough than ascorbic acid (vitamin C) and tocopherols (Vitamin E) compounds [85]. Quercetin has the potential to scavenge ROS (reactive oxygen species) and can increase the concentration of endogenous antioxidant compounds like glutathione. Quercetin can activate the phase-2 protein responsible for the natural defence and antioxidant property; hence it can also perform the function like antiapoptosis[86]. Quercetin can perform a different function like protecting various eye tissues like RGC, RPE, and trabecular meshwork cells from oxidative damage[87]. It is also used to improve the blood flow in choroids of the eye and perform vascular protective effects [88,89]. Oxidative stress takes part in the pathogenesis of many ocular diseases, including glaucoma. Quercetin can persuade antioxidant responsive elements as well as dependent gene expression by activating the Nrf2 pathway **(**Fig. **4)**.

In a study, the TM cell (in vitro model) was used to study quercetin's effect on oxidative stress. The result demonstrated the increased level of peroxiredoxin (PRDX3 and PRDX5) and nuclear factor (Nrf2 and NRF1) in the TM cell model[86]. In a study, cell death in hydrogen peroxide insulted RGC-5 (in vitro model cell) was minimized by treating with quercetin (isoquercetin). Moreover, it was demonstrated the up-regulation of PARP, AIF, p53 while decreasing the biomarkers Bcl-2. The supplement of quercetin (iso) also suppresses ROS in injured RGC cells, decreasing apoptosis [90]. In another study, the in vitro and in vivo model was developed to assess the effectiveness of quercetin cell apoptosis and quercetin's protective function. The result shows a surprising effect on RGC cell survival, which was treated with quercetin. It also prevents oxidation in experimental animal and helps to improve mitochondrial function [87].

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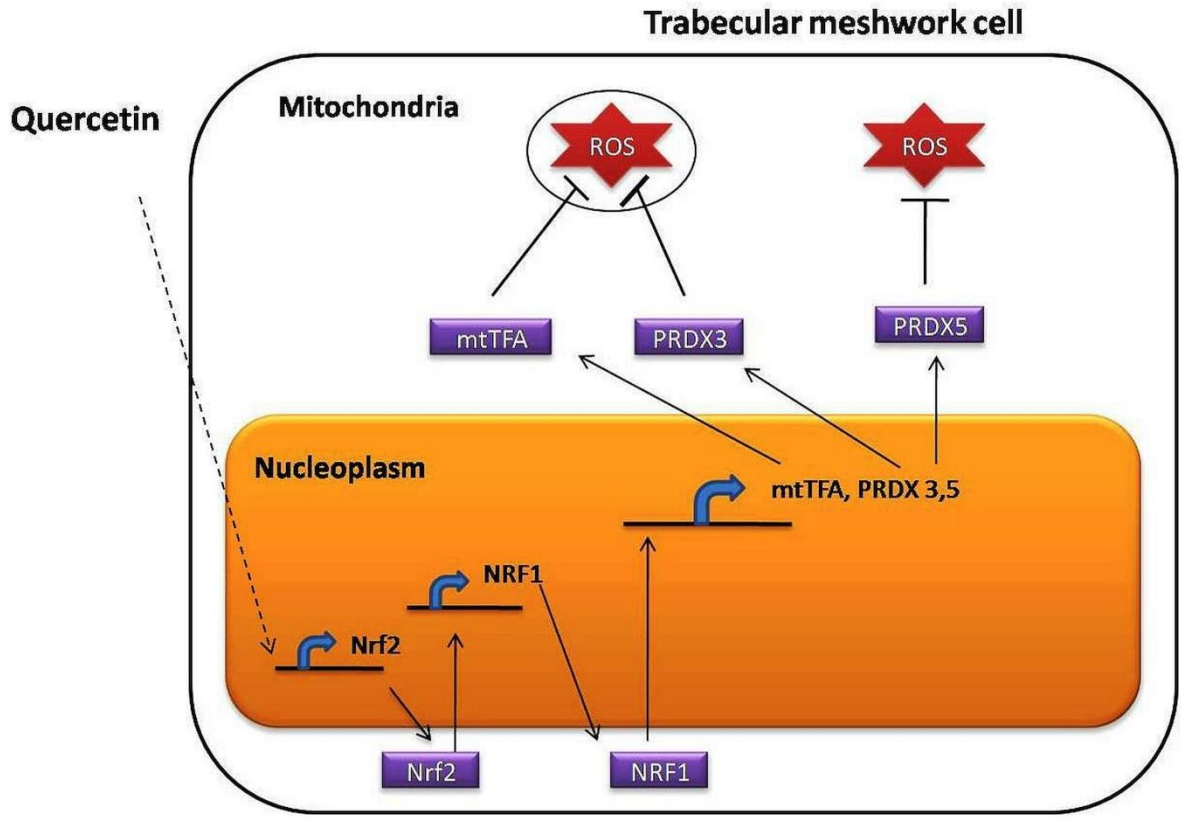

Figure 4 Mechanism of action of quercetin [85]

7. RUTIN

Rutin (3,3,4,5,7-pentahydroxyflavone-3-rhamnoglucoside) is a natural flavonoid that occurs in citrus fruits, buckwheat, apple, etc. Rutin is recognized by a different name like rutinoside, vitamin p, sophorin [91]. The chemical structure of rutin consists of two parts, i.e., quercetin and rutinose. The name rutin was originated from Ruta gravelolens, which contain the constituent's rutin. Rutin has become more prevalent in treating different disorders due to its properties like anticarcinogenic, neuroprotective, cytoprotective, cardioprotective, and antioxidant [91]. One of the essential features of rutin is to scavenge free radicals efficiently due to polyphenolic skeleton presence. Administration of rutin improves the eye's blood flow, includes choroidal and retinal [92]. Additionally, rutin can attenuate oxidative stress and neuroinflammation by upregulating Nrf2 [93]. Therefore rutin could be the drug of choice in the management of glaucoma. Various studies have been performed to prove the effectiveness of glaucoma. In a study, an experimental glaucoma model was developed using hypertonic saline injection, and a supplement of rutin was given orally (12.5 -50 mg/kg) for three weeks mg/kg orally and daily for 21 days orally to check the effectiveness of rutin in glaucoma. The result shows the significant decline of IOP and decreases the apoptosis level of RGC and TMC with the treated experimental model [94]. Rutin was found to effective in the glaucoma model by activating the pathway TGF-β Smad and Akt/PTEN pathway. Rutin can improve lachrymal dysfunction by increasing the capillary circulation and the metabolism of the eye and lachrymal glands. Dry eye disease is one of the causes during

treatment Hypotensive eye drop with benzalkonium chloride. In association with forskolin and vitamin B1 and B2, Rutin has shown effectiveness in dry eye disease in the glaucomatous eye[95]. The treatment of elevated IOP level in POAG, where patients have tolerated Hypotensive drugs and could not reach the target decrease in IOP [95]. To overcome this, rutin (improve ocular flow) can combine with forskolin (Hypotensive agent) to improve ocular blood flow. Clinical trials had been carried out by different groups using forskolin and rutin to study the effect on tolerated POAG patients. Oral supplement forskolin and rutin show a decrease in IOP level (>20%) from the baseline[95] https://clinicaltrials.gov/ct2/show/NCT00864578). In another trial, using the same combination suggested the effectiveness in lowering down of IOP in patients who remain unresponsive after laser iridology [96].

8. MYRICETIN

Myricetin is another polyphenolic phytoactive excellent antioxidant compound. The structure of myricetin is almost similar to quercetin and also possesses similar properties and functions to quercetin[97]. Flavonoids, Myricetin (3,5,7,3,4,5-hexahydroxyflavone) is found in most common fruits and vegetables like tomatoes, oranges, and other sources are tea, red wine. It is reported to have different properties, although antioxidant, neuroprotective, and anti-inflammatory are more important for glaucoma treatment [97,98]. Supplement of Myricetin produces a suppression of hyperglycemia and decreases lipid level in serum of the treated patient [98,99]. In this study, yang and coworkers have evaluated the effect of myricetin in a glaucomatous rat model. In study effectiveness of myricetin in POAG has been reported. Myricetin in different concentrations 25-100 mg/kg administered orally in glaucoma induced rat. Results show the decrease level of ROS and products of lipid peroxidation in the treated experimental animal. Myricetin down-regulates the cytokines (IL-6, IL-1α, TNF-α IL-1β, Il-8) in aqueous humour and TM cell, which increased glaucoma-induced animals. Additionally, Myricetin has also been reported to downregulate the factors like vascular endothelial growth factor, senescence biomarker like β galactoside [100].

9. KAEMPFEROL

Kaempferol is a natural polyphenolic flavonoid that occurs in common dietary vegetables and fruits. Kaempferol has been associated with the metabolic pathway of various to modulate signalling transduction pathways means in apoptosis, inflammation, angiogenesis, metastasis, and oxidative stress [101]. One of the important properties is an anti-inflammatory response, which can be processed through intermediate NF- κB [102]. It was also found to be effective in minimizing protein kinase[102]. stimulation of NLRP3 (inflammasome) [103]. Kaempferol has been reported to be effective in protecting the biomolecules from oxidations [104]. By these antioxidant and anti-inflammatory properties, kaempferol was considered effective in ischemic injury associated with glaucoma. In an ischemic study, the model was developed using mice, and the effect of kaempferol had been assessed. The result shows a decrease in cell death in RGC and reduces inflammatory response by downregulation of NLRP1/NLRP3 and caspase-8 as well as inhibition of pathway of NF-κB –JNK[103].

CONCLUSION

The current pharmacotherapy of acute and chronic type of glaucoma involves the use of pressure reducing agent. However, the loss of vision has continued even after the treatment of such agents. Oxidative stress could be one the cause of such neurodegeneration, which may progress after production of ROS. Hence there is a need for conjunctive neuroprotective therapy of antiradical and antioxidative substances. The polyphenolic compounds such as curcumin, rutin, quercetin, and kaempferol contain many phenolic groups in their structure and could scavenge ROS by accepting electrons from it. Resveratrol and rutin compound possess hypotensive property in glaucoma induce model. All the polyphenolic compounds described in this review have the potential to relieve oxidative stress associated with glaucoma. In the last decade, the polyphenolic compound had been studied and found useful in neuroprotection of eye diseases, including glaucoma. It could be an excellent choice to combine the polyphenolic substances and the FDA-approved hypotensive antiglaucoma drugs for effective management of glaucoma. However, due to less solubility and low bioavailability, their clinical use is restricted. Hence there is a need of biotechnology approaches to improve ocular bioavailability. Moreover, extensive clinical study is required to transform these compounds from lab to clinic.

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