

## REVIEW ARTICLE

# Rational Basis for Nutraceuticals in the Treatment of Glaucoma

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**Abstract: Background:** Glaucoma, the second leading cause of blindness worldwide, is a chronic optic neuropathy characterized by progressive retinal ganglion cell (RGC) axons degeneration and death.

Primary open-angle glaucoma (OAG), the most common type, is often associated with increased intraocular pressure (IOP), however other factors have been recognized to participate to the pathogenesis of the optic neuropathy. IOP-independent mechanisms that contribute to the glaucoma-related neurodegeneration include oxidative stress, excitotoxicity, neuroinflammation, and impaired ocular blood flow. The involvement of several and diverse factors is one of the reasons for the progression of glaucoma observed even under efficient IOP control with the currently available drugs.

**Methods:** Current research and online content related to the potential of nutritional supplements for limiting retinal damage and improving RGC survival is reviewed.

**Results:** Recent studies have suggested a link between dietary factors and glaucoma risk. Particularly, some nutrients have proven capable of lowering IOP, increase circulation to the optic nerve, modulate excitotoxicity and promote RGC survival. However, the lack of clinical trials limit their current therapeutic use. The appropriate use of nutraceuticals that may be able to modify the risk of glaucoma may provide insight into glaucoma pathogenesis and decrease the need for, and therefore the side effects from, conventional therapies.

**Conclusion:** The effects of nutrients with anti-oxidant and neuroprotective properties are of great interest and nutraceuticals may offer some therapeutic potential although a further rigorous evaluation of nutraceuticals in the treatment of glaucoma is needed to determine their safety and efficacy.

**Keywords:** Glaucoma, retinal ganglion cells, neurodegeneration, oxidative stress, nutraceuticals, neuroprotection.

## 1. INTRODUCTION

Glaucoma is a neurodegenerative disease characterized by retinal ganglion cells (RGC) death, typical visual field defect and eventual blindness [1]. Elevated intraocular pressure (IOP), aging, genetic, epigenetic and environmental factors are among a number of recognized risk factors for glaucoma [2, 3]. Glaucoma is thus a progressive optic neuropathy with complex pathophysiology and RGC loss in glaucoma remains incompletely understood [4]. Several mechanisms have been suggested to play a role in RGC damage including oxidative stress, excitotoxicity and neuroinflammation [5-7]. Particularly, excitotoxicity through the overactivation of N-methyl-D-aspartate (NMDA) and

non-NMDA glutamate receptors [8, 9] has been proposed as one of the determinants involved in RGC damage [5]. Furthermore, several studies demonstrate that mitochondrial perturbations are among the very first changes occurring within RGCs during glaucoma [7, 10-12] suggesting that oxidative stress is also a key mechanism of excitotoxic, glutamate induced RGC loss [8, 13, 14]. Several studies have shown that free radical species can cause RGC death by inhibition of key enzymes of the tricarboxylic acid cycle, the mitochondrial electron transport chain, and mitochondrial calcium homeostasis, leading to defective energy metabolism [15, 16]. Interestingly, increased levels of oxidative stress markers were observed in aqueous humor of patients with primary open-angle glaucoma (POAG) [17, 18] and with primary angle closure glaucoma (PACG) [19]. Accordingly, a recent meta-analysis by Benoist d'Azy and Colleagues reported that oxidative stress increased in glaucoma patients, both in serum and aqueous humor [20]. In addition to its detrimental effect on the optic nerve, oxidative stress

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has also been suggested to damage the trabecular meshwork (TM) [21-23] resulting in an increase in the IOP. Incidentally, recent experimental data revealed that autophagy modulation occurs in RGC under glaucoma-related stressing conditions supporting the hypothesis that dysfunctional autophagy might participate to the process leading to RGC death [24]. Despite accumulating evidence of pressure-independent causes of glaucomatous optic neuropathy has led to the recognition that lowering IOP alone may often be insufficient for the long-term preservation of visual function [25], most of the current treatment modalities are based on lowering the IOP and a need exists for novel therapies able to save RGCs from injury or to repair damaged neurons. Interestingly, several studies have suggested a link between dietary factors, now named “nutraceuticals” [26, 27] and glaucoma risk [28, 29]. Deficiencies of specific nutrients have been found in patients with glaucoma and supplementation may play a role in treatment [28]. Interestingly, some nutraceuticals have shown their ability to lower IOP [30-32], increase circulation to the optic nerve [28], modulate excitotoxicity and promote RGC survival [14, 33-36]. In this respect, a prospective study for ten years revealed an association between low intake of antioxidant nutrients and a higher risk of open angle glaucoma [37]. On the contrary, Kang and Colleagues reported no strong associations between antioxidants intake and primary open-angle glaucoma (OAG) risk [38]. Likewise, more recently, a two-year follow-up of oral antioxidants supplementation in OAG did not demonstrate beneficial short-term effects [39]. This apparent discrepancy could be explained by considering the sample size estimate and the different features of clinical trials. In fact, although some nutraceuticals have been described as neuroprotective, the lack of clinical trials examining their benefits for glaucoma limits their current therapeutic use [1, 40] suggesting that well designed clinical trials are needed to assess their efficacy and tolerability in glaucoma treatment. Therefore, appropriate use of nutraceuticals with anti-oxidant and neuroprotective properties may be able to modify the risk of glaucoma, provide insight into glaucoma pathogenesis and decrease the need for, and therefore the side effects from, conventional therapies.

This review discusses the most current knowledge on the neuroprotective effects of a number of nutraceuticals in RGC damage and their potential benefit in glaucoma treatment.

## 2. VITAMINS

Considering the key role played by oxidative stress in RGC damage, antioxidant vitamins have been suggested as potential neuroprotective agents [41, 42]. However, although their deficiency may be linked to symptoms of optic-nerve dysfunction, the association between serum vitamin levels and glaucoma prevalence in humans remains controversial. For example, in 2003, the Nurses’ Health Study and Health Professionals Follow-up Study reported no strong association between the risk of primary open-angle glaucoma and vitamin C, vitamin E, and vitamin A consumption [38]. Accordingly, a recent meta-analysis by Li and Colleagues reported that normal-tension glaucoma (NTG) risk is not associated with serum vitamin B6, vitamin B12, or folic acid levels [43]. Moreover, another meta-analysis reported no association between serum vitamin B6, vitamin B12, or vi-

tamin D levels and the different types of glaucoma [44]. On the contrary, the Rotterdam Study, a prospective study on a glaucoma cohort of 3500 Individuals, revealed an association between low intake of antioxidant nutrients, including retinol equivalents and vitamin B1, and a higher risk of open angle glaucoma [37]. Yuki and Colleagues investigated the levels of antioxidants as vitamins A, C, E, folic acid in the serum of Japanese patients with normal-tension glaucoma compared with normal controls. Interestingly, they found lower serum levels of vitamin C in glaucoma patients [45]. Furthermore, Asregadoo reported a statistically significant lower thiamine blood level in 38 glaucoma patients than in 12 controls [46]. Moreover, Turgut and Colleagues reported that plasma levels of vitamin B6 increase in NTG or POAG patients [47]. Conversely no statistical differences were observed in serum vitamin B12 and folate levels among control subjects and glaucoma groups. In addition, the plasma level of homocysteine was found to be increased only in patients with pseudo-exfoliative glaucoma (PXG) [47]. Similar results were observed by Cumurcu and Colleagues [48] and Xu and Colleagues [49]. Moreover, Kang and Colleagues investigated the association between B vitamins (folate, vitamin B6, and vitamin B12) intake and exfoliation glaucoma (EG) or suspected EG (SEG) risk and reported that higher folate, but not vitamin B6 and vitamin B12 intake, was associated with a lower risk for EG/SEG [50]. Wang and Colleagues also investigated, in a cross-sectional study included 2912 participants, the potential association between glaucoma prevalence and supplemental intake, as well as serum levels of vitamins A, C and E. The authors reported no association between vitamins with glaucoma prevalence, however supplementary consumption of vitamin C was found to be associated with decreased odds of glaucoma [51]. Interestingly, Xu and Colleagues reported that vitamin C shows a dose-dependent effect against oxidative insult by modulation of iron homeostasis and intracellular ROS formation and, in addition, elicits the activation of the autophagic lysosomal pathway in TM cells [52]. Moreover, Lee and Colleagues reported a correlation of aqueous humor ascorbate concentration with intraocular pressure as well as outflow facility in hereditary buphthalmic rabbits [53] but found no correlation in OAG patients [54]. Vitamin C has also been found, *in vitro*, to stimulate synthesis of hyaluronic acid in trabecular meshwork from glaucomatous eyes [55] and to reduce the viscosity of hyaluronic acid and increase outflow through the trabeculum [56]. More recently, Goncalves and Colleagues reported vitamin D insufficiency is associated with POAG [57]. Interestingly, topical administration of 1 $\alpha$ ,25-dihydroxyvitamin D(3) or its analog, 2-methylene-19-nor-(20S)-1 $\alpha$ ,25-dihydroxyvitamin D(3) (2MD), markedly reduced IOP in non-human primates [58]. However, Krefting and Colleagues reported that the administration of vitamin D3 to healthy volunteers with low levels of 25(OH)D does not affect IOP [59]. In 2010, Ko and Colleagues reported that vitamin E deficiency increased RGC loss in a rat model of glaucoma [60]. Particularly, the Authors found that vitamin E deficiency alone for ten weeks did not increase RGC death. However, when vitamin E deficiency was combined with IOP elevation for five weeks, there was a significant increase in RGC death and higher levels of retinal lipid peroxidation. Interestingly, vitamin E deficiency did not change the activities of superoxide dismutase (SOD) and catalase in

the rat retina after IOP elevation [60]. Moreover, Yu and Colleagues demonstrated that vitamin E is able to reduce the transforming growth factor-beta2 (TGFb2)-induced cellular changes in cultured human trabecular meshwork cells, suggesting that increasing the antioxidative capacity may help to lower the incidence of characteristic glaucomatous changes in TM [61]. Interestingly, more recently, Williams and Colleagues, demonstrated that oral administration of vitamin B3 (nicotinamide) a precursor of nicotinamide adenine dinucleotide (NAD) or Nmnat1 (nicotinamide/nicotinic acid mononucleotide adenylyltransferase 1) gene therapy reduces mitochondrial vulnerability and prevents glaucoma in aged mice [11].

### 3. COENZYME Q

Coenzyme Q is an essential cofactor of the electron transport chain, a membrane stabilizer, and a cofactor in the production of adenosine triphosphate (ATP) by oxidative phosphorylation [36, 62]. Coenzyme Q is endowed with potent antioxidant properties that have been shown to mediate its neuroprotection [63-65]. Interestingly, several studies demonstrated that the compound protects retinal cells against oxidative stress *in vitro* and *in vivo*, as well as prevents retinal damage induced by acute IOP elevation or excitotoxicity *in vivo* [14, 62, 66, 67]. In this respect, Nucci and Colleagues reported that intraocular administration of coenzyme Q affords neuroprotection in the retina of rats subjected to ischemia/reperfusion preventing glutamate increase observed by microdialysis and this was accompanied by minimization of cell death [66]. Accordingly, Lee and Colleagues reported that the compound also inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in glaucomatous DBA/2J mice [36]. Particularly, coenzyme Q promoted RGC survival, preserved the axons in the optic nerve head and inhibited astroglial activation [36]. Moreover, it prevented the upregulation of NMDA receptor subunit 1 and 2A, SOD2 and heme oxygenase-1 (HO1), and also prevented the apoptotic cell death by decreasing Bax and increasing pBad expression. Lee and Colleagues also reported that coenzyme Q preserved mitochondrial DNA content and mitochondrial transcription factor A/oxidative phosphorylation complex IV protein expression in the retina [36]. Furthermore, Noh and Colleagues demonstrated that coenzyme Q protects optic nerve head (ONH) astrocytes against oxidative stress-mediated mitochondrial dysfunction or alteration in glaucoma and other optic neuropathies [68]. Particularly, coenzyme Q decreased SOD2 immunoreactivity in the ONH astrocytes exposed to H<sub>2</sub>O<sub>2</sub> and promotes mitofilin and peroxisome-proliferator activated receptor- $\gamma$  coactivator-1 (PGC-1 $\alpha$ ). Interestingly, Nakajima and Colleagues reported that in cultured retinal ganglion cells (RGC-5), a combination of coenzyme Q and trolox, a water-soluble vitamin E analogue, prevented cell damage more effectively than either agent alone [62]. Accordingly, Parisi and Colleagues reported that administration of coenzyme Q associated with vitamin E in open-angle glaucoma patients shows a beneficial effect on the inner retinal function with consequent enhancement of the visual cortical responses [69]. Concerning the mechanism underlying neuroprotection afforded in glaucoma models by coenzyme Q it is conceivable that a free radical scavenging mechanism is only one of the determi-

nants. In fact, neuroprotection afforded by the compound was far greater than that provided by treatment with vitamin E [66]. The Authors hypothesized that coenzyme Q reduces the detrimental action of ischemia/reperfusion on mitochondrial energy metabolism and, consequently, on the function of glutamate transporters, thus limiting accumulation of extracellular glutamate and preventing apoptotic death of RGC [66]. More recently, in agreement with the latter result, Lulli and Colleagues reported that coenzyme Q increases RGC viability and inhibits apoptosis in response to different apoptotic stimuli such as glutamate, chemical hypoxia and serum withdrawal by preventing mitochondrial depolarization [67]. The opening of the mitochondrial permeability transition pore (PTP) followed by extrusion of apoptogenic molecules to the cytoplasm [70] is recognized as the main trigger of apoptosis. Incidentally, coenzyme Q has been shown to inhibit apoptosis by maintaining PTP in the closed conformation *via* a mechanism independent from free radical scavenging [71].

### 4. FLAVONOIDS

Flavonoids are a large family of phytonutrient compounds widely distributed in fruits and vegetables as well as in chocolate and red wine [72-74]. These compounds have been shown to demonstrate anti-inflammatory and neuroprotective effects that may reduce damage from oxidative stress [75, 76]. Flavonoids exert beneficial effects on multiple disease states, including cancer, cardiovascular disease, and neurodegenerative disorders [73, 77-79]. Interestingly, several studies *in vivo* and *in vitro* also reported the beneficial effects of flavonoids in ocular diseases [80-84], however, a recent meta-analysis showed no statistically significant effect of flavonoids on lowering intraocular pressure [85]. Nakayama and Colleagues [86] investigated the neuroprotective potential of three types of flavonoid compounds—kaempferol 3-O-rutinoside (nicotiflorin), quercetin 3-O-rutinoside (rutin), and quercetin 3-Orhamnoside (quercitrin)—using rat primary-isolated RGCs cultured under three kinds of stress conditions: hypoxia, excessive glutamate levels, and oxidative stress. Under these conditions all compounds significantly increased the RGC survival rate but nicotiflorin and rutin were more active than quercitrin [86]. Moreover, rutin significantly inhibited the induction of caspase-3 under both hypoxia and excessive glutamate stress, as well as blocking the induction of calpain during oxidative stress [86]. Interestingly, resveratrol, a naturally occurring polyphenol found in berries, nuts, and red wine, can enhance stress resistance and exerts antiinflammatory, anti-oxidant, and anti-apoptotic effects [87-89]. In this respect, Luna and Colleagues investigated the effects of chronic administration of resveratrol on the expression of markers for inflammation, oxidative damage, and cellular senescence in primary TM cells subjected to chronic oxidative stress [90]. Interestingly, resveratrol treatment prevented increased production of intracellular ROS, IL1 $\alpha$ , IL6, IL8, and ELAM-1 [90]. Moreover, it reduced expression of the senescence markers sa- $\beta$ -gal, lipofuscin, and accumulation of carbonylated proteins. In addition, the compound, exerted antiapoptotic effects that were not associated with a decrease in cell prolifer-

eration [90]. Moreover, Chen and Colleagues investigated the role of peroxisome proliferator activated receptor- $\gamma$  co-activator 1 $\alpha$  (PGC-1 $\alpha$ ) in resveratrol-triggered mitochondrial biogenesis for preventing apoptosis in a retinal ganglion cell line RGC-5 [91]. The Authors reported that resveratrol promoted the protein expression of SIRT1, facilitated PGC-1 $\alpha$  translocation from the cytoplasm to the nucleus and up-regulated NRF1 and TFAM [91]. More recently, Lindsey and Colleagues, using an optic nerve crush model, reported that long-term dietary resveratrol treatment delays RGC dendrite remodeling and loss after optic nerve injury and alters the expression of the unfolded protein response BiP, CHOP, and XBP [92]. A number of studies also investigated the potential effects of epigallocatechin-3-gallate (EGCG), the major catechin found in green tea. For example, Zhang and Colleagues reported that EGCG attenuates damaging influences to the retina caused by ischemia/reperfusion and significantly reduced the apoptosis induced by H<sub>2</sub>O<sub>2</sub> in cultured RGCs [82]. In addition, Xie and Colleagues reported a neuroprotective effect of EGCG in an optic nerve crush model in rats [93]. Moreover, Peng and Colleagues demonstrated that administration of EGCG prior to axotomy promotes RGC survival in rats [94]. The neuroprotective capacity of EGCG appears to act through nitric oxide, anti-apoptotic, and cell survival signaling pathways [94]. More recently, Jin and Colleagues reported that key bioactive compounds in green tea leaves (EGCG, theanine and caffeine), attenuate the injury of retinal ganglion RGC-5 induced by H<sub>2</sub>O<sub>2</sub> and ultraviolet radiation [95]. Interestingly, the Authors reported that caffeine and theanine both protected RGC-5 cells from injury as well as enhanced their recovery, while EGCG only protected the cells from injury and did not help them to recover [95].

*Ginkgo biloba* (Ginkgoaceae) is an ancient species of tree similar to plants which were living 270 million years ago. *Ginkgo biloba* leaves also contain many different flavonoids, including polyphenolic flavanoids which have been proven to exert antioxidative properties by delivering electrons to free radicals [96]. The extract from the leaves of *ginkgo biloba*, named as *ginkgo biloba* extract 761 (EGb761), has been shown to be beneficial for cognitive impairment and dementia [97]. Interestingly, a number of studies suggested a helpful effect of *ginkgo biloba* for the treatment of glaucoma [98-100]. For example, Hirooka and Colleagues reported RGC neuroprotection by *ginkgo biloba* extract in rats after IOP elevation [101]. In addition, Ma and Colleagues reported that intraperitoneal injections of *ginkgo biloba* extract given prior to and daily after an experimental and standardized optic nerve crush in rats were associated with a higher survival rate of retinal ganglion cells [102, 103]. However, it has remained unclear how *ginkgo biloba* may help RGC to survive after the optic nerve crush. In addition, in contrast to previous studies, recently, Guo and Colleagues, reported no significant improvements in visual field defects and contrast sensitivity in Chinese patients with normal tension glaucoma after four weeks of oral treatment with *ginkgo biloba* extract [104]. Nevertheless, Shim and colleague reported that systemic administration of Bilberry anthocyanins and *Ginkgo biloba* extract improves visual function in some individuals with NTG [105].

## 5. CITICOLINE

Citicoline is a natural constituent of all cells, where it serves as the intermediate in phosphatidylcholine synthesis [106]. Citicoline attenuates free fatty acids release and re-establishes levels of cardiolipin phospholipid component of the inner mitochondrial membrane [107]. Citicoline also increase neurotransmitters levels in the central nervous system [108] and in retina [109]. Interestingly, a number of studies reported citicoline may induce an improvement of the retinal and of the visual pathway function in patients with glaucoma [110-114]. Neuroprotective properties of citicoline have been shown in various experimental model of glaucoma. For example, in partial crush injury of the rat optic nerve model, citicoline was found effective in rescuing RGC and their axons *in vivo* against delayed degeneration triggered by optic nerve crush [115]. Particularly, the Authors reported that citicoline increased retinal expression of the apoptotic regulating protein Bcl-2, indicating one of the mechanisms which may be engaged in the neuroprotective effect of the compound [115]. Moreover, after intravitreal injection of kainic acid (KA), citicoline counteracted increased expression of NOS isoforms [116] and decreased ERK1/2 kinase activation [117] caused by KA. Using murine retinal explants Oshitari and Colleagues have shown that citicoline can rescue damaged RGCs through an anti-apoptotic effect probably acting as a BDNF mimic [118, 119]. This effect was correlated with the reduction of the expression of active forms of caspases-9 and -3 [119].

## 6. POLYUNSATURATED FATTY ACIDS

Omega 3 ( $\omega$ -3) and omega 6 ( $\omega$ -6) are polyunsaturated essential fatty acids (PUFAs). Both fatty acids are concentrated in the phospholipids of cell membranes throughout the human body, but especially in the brain, heart, retina, and testes [120]. Essential fatty acids omega 3 and omega 6 are of special interest due to their reported anti-inflammatory, antithrombotic, hypolipidemic, and vasodilatory capacities [121, 122]. Interestingly, recent studies suggest a key role for PUFAs also in neurodegeneration and neuropsychiatric diseases [123, 124]. Dietary deficiencies in  $\omega$ -3 polyunsaturated fatty acids are also known to effect retinal function including RGC activity whereas a diet rich in  $\omega$ -3 PUFA helps to reduce vulnerability of RGCs to dysfunction induced by IOP stress [125]. Nguyen and Colleagues demonstrated that an increased consumption of omega-3 fatty acids leads to decreased IOP through an increased aqueous outflow facility via prostaglandins (PGs) [126]. In fact, PGs, are metabolites of omega-3 fatty acids [127] and reduce IOP by enhancing uveoscleral and trabecular outflow via direct effects on ciliary muscle relaxation and remodeling of extracellular matrix [128]. Cod liver oil that contains vitamin A and both the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been demonstrated to lower IOP in experimental animals [129]. Moreover, a number of studies reported that omega-3 fatty acids prevented retinal cell structural degradation and counteracted glial cell activation induced by the elevation of IOP [130]. Accordingly, Nguyen and Colleagues, also reported that dietary  $\omega$ -3 deficiency and repeat acute IOP insult are additive risk factors for RGC dysfunction [131]. Interestingly, a diet with increased omega-3 and

decreased omega-6 could favor an increase in IOP reducing synthesis of PG-F2, leading to a decrease in uveoscleral outflow [132]. Conversely, a diet high in omega 6 and low in omega 3 to be associated with a reduced occurrence of POAG [133]. Therefore, it is important to have an appropriate balance between these fatty acid families [130, 134]. Accordingly, Pérez de Arcelus and Colleagues, in a prospective cohort study found that a diet with a high omega 3:6 ratio intake, thus low in omega 6, was associated with a higher occurrence of glaucoma [134]. Interestingly, Tourtas and Colleagues, reported in cultivated human TM cells, that  $\omega$ -6 was efficient in preventing H<sub>2</sub>O<sub>2</sub> mediated anti-proliferative effects, but displayed a repressive effect on mitochondrial activity and proliferation [135]. For  $\omega$ -3, the Authors observed no negative side effects but an effective potential to prevent H<sub>2</sub>O<sub>2</sub> mediated anti-proliferative/-metabolic effects [135]. Nevertheless, Schnebelen and Colleagues demonstrated that a 6-month supplementation with a combination of omega-3 and omega-6 PUFAs is more effective than single supplementations, since the EPA plus DHA plus gamma-linolenic acid dietary combination prevented retinal cell structure and decreased glial cell activation induced by the elevation of IOP in rats [130].

## 7. TAURINE

Taurine (2-aminoethylsulfonic acid) is a “semi-essential” sulfur amino acid structurally similar to the neurotransmitters glycine and gamma aminobutyric acid (GABA) [136, 137]. Taurine is the most abundant free amino acid in mammalian retina after glutamate [138, 139]. The source of taurine is mostly exogenous and meats, seafood and fish are the major sources of this amino acid [140]. Taurine intake from dietary sources is highly dependent on taurine transporter expression in tissues exhibiting a high retinal uptake index (26.6 % in serum) [141]. In retinal cells, taurine uptake was demonstrated in photoreceptors, retinal ganglion cells, retinal glial cells and in the retinal pigment epithelium cells [142-145]. Though the exact role of taurine in the retina is not fully understood, several studies have reported that taurine had a protective effect on cells from neuroretina [146] and retinal pigment epithelium [147]. The exact mechanism of this protective effect is still unknown. Taurine is considered to be an antioxidant, but the mechanisms underlying its antioxidant properties have never been clearly characterized, particularly in retinal cells [137].

However, activation of GABA<sub>A</sub> receptors through taurine binding may decrease neuronal vulnerability to excitotoxic damage [146]. Moreover, Bulley and Shen found that taurine reduces glutamate-induced Ca<sup>2+</sup> influx *via* ionotropic glutamate receptors and voltage-dependent Ca<sup>2+</sup> channels in the neurons, and the effect of taurine was selectively inhibited by strychnine and picrotoxin, but not GABA receptor antagonists, although GABA receptors were present in the neurons [136]. Interestingly, taurine supplementation in rats has demonstrated to reduce neuronal and glial cell death in different pathological conditions [148-150]. In cats, taurine supplementation has been found to prevent the progressive degeneration of retinal photoreceptors seen in retinitis pigmentosa [151]. In the retina, decreased taurine uptake was also found to induce retinal degeneration [152-159]. Retinal degeneration has been extensively investigated in taurine

free-diet fed cats [152-156, 159] and monkeys [157]. The taurine depletion was also induced in cats and rats by treatments with taurine transport inhibitors, such as  $\beta$ -alanine or guanidoethane sulfonate (GES) [158, 160]. At the level of RGCs, Gaucher and Colleagues observed a significant loss induced by the GES treatment [161]. This retinal ganglion cell degeneration in GES-treated mice was very similar to that obtained in vigabatrin-treated neonatal rats [150], which was already attributed to the taurine depletion. Accordingly, taurine supplementation prevented vigabatrin-induced RGC degeneration [150]. Moreover, Froger and Colleagues demonstrated that taurine can improve RGC survival in culture or in different animal models of RGC degeneration [162]. Particularly, taurine effect on RGC survival was assessed *in vitro* on primary pure RGC cultures under serum-deprivation conditions, and on NMDA-treated retinal explants from adult rats [162]. *In vivo*, taurine was administered through the drinking water in two glaucomatous animal models (DBA/2J mice and rats with vein occlusion) and in a model of retinitis pigmentosa with secondary RGC degeneration (P23H rats). Taurine significantly enhanced RGCs survival and partly prevented NMDA-induced RGC excitotoxicity [162]. Moreover, taurine supplementation increased RGC densities both in DBA/2J mice, in rats with vein occlusion and in P23H rats [162]. This study indicates that enriched taurine nutrition can directly promote RGC survival and provides evidence that taurine can positively interfere with retinal degenerative diseases. More recently, Han and Colleagues suggested that taurine neuroprotection may result from inhibition of NADPH oxidases, the primary source of superoxide induced by NMDA receptor activation, probably in a calcium-dependent manner [163].

## 8. ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA), also known as thioctic acid, is a naturally occurring compound synthesized enzymatically in the mitochondrion but commonly found in dietary components such as vegetables and meats [164]. ALA is a necessary cofactor for mitochondrial  $\alpha$ -ketoacid dehydrogenases, and thus serves a critical role in mitochondrial energy metabolism [164, 165]. ALA and its reduced form DHLA, are considered powerful antioxidant agents with a scavenging capacity for many ROS [166, 167] and appears to regenerate other endogenous antioxidants (*e.g.* vitamins C and E) [164]. In addition, the compounds elicited several cellular actions ranging from metal chelator to a mediator of cell signaling pathways to an insulin mimetic to a hypotriglyceridemic agent, *etc.* [164, 165]. Although ALA has been mainly studied in diabetic polyneuropathies, it showed beneficial properties for the prevention of vascular disease, hypertension, and inflammation [164, 165]. ALA is currently being tested as a treatment for neurodegeneration and neuropathy in several clinical trials. ALA has been also investigated in glaucoma. For example, Filina and Colleagues reported beneficial properties by ALA in correcting glutathione deficiency, detected in OAG patients by increasing lacrimal SH group level [168]. Particularly, some studies reported that supplementation of lipoic acid can increase glutathione in red blood cells [169] and lacrimal fluid [170] of patients with glaucoma. More recently, using a DBA/2J mouse model of glaucoma, Inman and Colleagues reported that addition of ALA to the diet increased antioxidant gene and protein expression and

improved RGC survival without significant IOP changes [35]. Interestingly, Koriyama and Colleagues demonstrated that ALA exerts a neuroprotective effect against oxidative stress in retinal neurons *in vitro* and *in vivo* by inducing the expression of heme oxygenase-1 through Kelch-like ECH-associated protein (Keap1) / NF-E2-related factor 2 (Nrf2) signaling [171].

## 9. FORSKOLIN

Forskolin is a diterpenoid isolated from plant *Coleus forskohlii* (Lamiaceae). Forskolin can penetrate cell membranes and stimulates the enzyme adenylate cyclase [172] decreasing IOP by reducing aqueous humor inflow in animals [173-176] and humans [173, 177-179] suggesting potential use for glaucoma treatment. Interestingly, oral administration of forskolin in association with rutin or with rutin and vitamins B1 and B2 contributed to IOP control [180] and could act in synergy with topical pharmacological treatments in POAG patients [181]. Interestingly, a number of studies suggested that forskolin promotes neuronal survival by stimulating neurotrophin activity in models of RGC death [182, 183]. Particularly, Intravitreal injection of forskolin with brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) contributed to survival and axonal regeneration of RGCs in adult cats [184]. Recently, Russo and Colleagues reported that forskolin prevents RGC loss induced by ischemia-reperfusion in rats and homotaurine and L-carnosine potentiate forskolin neuroprotection [185]. The treatment with forskolin/ homotaurine/ L-carnosine reduced calpain activation and increased Akt activation and GSK-3 $\beta$  phosphorylation in the retina subjected to ischemia/reperfusion [185]. The observed neuroprotection it was independent from PKA activation and distinct from the hypotensive effects of forskolin. Interestingly, Mutolo and Colleagues reported that a combined administration of forskolin, homotaurine, carnosine, and folic acid in POAG patients with their IOP compensated by topical drugs, induced a significant further decrease of IOP and an improvement of Pattern Electroretinogram (PERG) amplitude [186].

## 10. CURCUMIN

Curcumin is a polyphenol isolated from the plant *Curcuma Longa* (Zingiberaceae) and is the principal curcuminoid of the popular spice turmeric. Curcumin, has been widely used in many countries for centuries both as a spice and as a medicine [187]. In the past decade, several biofunctions of curcumin have been identified, including its anti-inflammatory effects, antitumorogenesis effects, antioxidative activity, and its inhibitory effects on histone acetyltransferases. Concerning its antioxidative activity, several studies have proven that curcumin inhibits oxidative and nitrative DNA damage by inhibiting the stress-induced elevated levels of 8-hydroxydeoxyguanosine (a biomarker of DNA oxidation) and 8-nitroguanine [188, 189]. Curcumin also inhibits oxidative damage by regulating oxygen consumption, ATP content, calcium retention, mitochondrial membrane potential, the activities of mitochondrial respiratory complexes I, II, III, and V, and mitochondrial respiratory capacity [190, 191]. Recently, in a chronic IOP rat model, pretreatment of curcumin protected against RGC loss

and was correlated with significantly increased cell viability of BV-2 microglia [192]. In another research, staurosporine-induced ganglion cell death was attenuated by low dosages of curcumin both *in vitro* and *in vivo* [193]. Moreover, in an acute IOP model in rat, curcumin pretreatment was able to reverse the decrease of mitofusin 2 (mfn2), a mitochondrial fusion protein, and increase nuclear factor erythroid 2-related factor 2 (Nrf2) in the retinal I/R-induced open-angle glaucoma model *in vivo*, indicating that the compound could maintain the normal mitochondrial function and alleviate the retinal I/R injury by regulating the antioxidant system [194]. Interestingly, curcumin significantly attenuated NMDA-induced apoptosis in retinal neuronal/glial cultures *in vitro* by inhibiting the NR1 subunit of the NMDA receptor phosphorylation and NMDAR-mediated Ca<sup>2+</sup> increase [195]. More recently, the same Authors confirmed the neuroprotective activity of curcumin against NMDA toxicity, possibly related to an increased level of NR2A [196]. Interestingly, using TM cells as *in vitro* model system, Lin and Wu reported that curcumin treatment protected TM cells against oxidative stress-induced cell death [197]. In addition, curcumin pretreatment significantly inhibited proinflammatory factors, including IL-6, ELAM-1, IL-1 $\alpha$ , and IL-8, whereas it decreased activities of senescence marker SA- $\beta$ -gal, and lowered levels of carbonylated proteins and apoptotic cell numbers [197].

## 11. ERIGERON BREVISCAPUS

*Erigeron breviscapus* (vant.) Hand. Mazz. (EBHM) is a widely used Chinese medicinal plant for heart disease [198]. Its major active compounds are scutellarin, 1,5-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid and erigoster B [199]. EBHM has been suggested as neuroprotectant in glaucoma. Particularly, some studies have shown that *Erigeron breviscapus* could improve the activity of cytochrome oxidase in RGCs [200] and optic nerve axoplasmic transport in rat models of acute elevated IOP [201]. Interestingly, in the experimental optic nerve crush model in rats, EBHM treatment increased the survival rate of the RGC and was able to rescue and/or restore the injured RGCs [202]. Moreover, administration of EBHM solution partially protected RGC loss in NMDA-induced retinal neuronal injury in rats [203]. EBHM extract also showed a partial protective effect on the visual field of glaucoma patients with controlled IOP [204]. In addition, *Erigeron breviscapus* extract treatment improved the impaired visual function (detected by multifocal electroretinogram) of persistently elevated IOP in rats [205]. Although it is not known to which components of EBHM are attributed the specific effects, it has been suggested that the combined activity and a certain interdependency of several active constituents of EBHM extract are responsible for its beneficial effects [206, 207]. For example, Bastianetto and colleagues reported that the flavonoid fraction strongly inhibited both the toxicity and the free radical accumulation induced by sodium nitroprusside and/or 3-morpholinopyridone [208]. Several studies also showed neuroprotective effect of scutellarin and other ingredients extracted from *Erigeron breviscapus* against neuronal damage following cerebral ischemia/reperfusion [209-213]. Interestingly, Wang and Colleagues observed that scutellarin inhibited lipopolysaccharide (LPS)-induced production of

proinflammatory mediators and suppressed LPS-stimulated inducible nitric oxide synthase (iNOS), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and IL-1 $\beta$  mRNA expression in rat primary microglia or BV-2 mouse microglial cell line [212]. More recently, Yin and Colleagues, reported that DSX, an active component extracted from *Erigeron breviscapus*, suppress outward potassium channel currents in rat RGCs, suggesting it may be one of the possible mechanisms underlying *Erigeron breviscapus* prevents vision loss and RGC damage caused by glaucoma [214].

## 12. LYCIUM BARBARUM

*Lycium barbarum L.* belongs to the Solanaceae family (also named *Fructus Lycii* or called Wolfberry or Goji berries). It has been used for centuries as a traditional medicinal and food supplement in East Asia, however, since the beginning of the 21<sup>st</sup> century, wolfberries have become increasingly popular in Europe and North America [215, 216]. The active components in wolfberry include *L. barbarum* polysaccharides (LBP), zeaxanthine, betaine, cerebroside and trace amounts of zinc, iron, and copper [217]. LBP are the primary active components and have been reported to possess a wide array of pharmacological activities [216, 218]. It has been reported that LBP exerts beneficial effects in animal models of ocular diseases. For example, several studies have shown neuroprotective effects of LBP on RGCs in acute model of glaucoma [219, 220]. Particularly, Mi and Colleagues reported that *Lycium barbarum* polysaccharides protect RGCs and retinal vasculature in a mouse model of acute ocular hypertension and provide neuroprotection by down-regulating receptors for advanced glycation end products (RAGE), endothelin-1 (ET-1), amyloid-beta peptide and advanced glycation end products (AGE) in the retina, as well as their related signaling pathways [219]. He and Colleagues demonstrated that LBPs elicit retino- and neuro-protective effects *via* the activation of nuclear factor erythroid 2-related factor (Nrf2) and upregulation of expression of heme oxygenase-1 (HO1) [220]. *Lycium barbarum* have shown neuroprotective effect also in chronic ocular hypertension model of glaucoma [221-223] and MCAO-induced ischemic retina [218]. Particularly, Chan and Colleagues suggested that the neuroprotective effect of LBPs in chronic ocular hypertension (COH) rats is partly due to modulating the activation of microglia [221], whereas Chiu and Colleagues suggested that the prosurvival effect of LBPs on rat RGCs in COH may be mediated by an increase in the upregulation of  $\beta$ B2 crystalline, a neuroprotective agent [223]. In addition, Li and Colleagues reported that LBP reduces secondary degeneration of RGCs after partial optic nerve transection suggesting that this effect may be linked to the inhibition of oxidative stress and the JNK/c-jun pathway in the retina [224].

## CONCLUSION

Glaucoma it is not always under the control of currently available drugs, thus a need exists for novel therapies able to save retinal ganglion cells from injury or to repair damaged neurons. Nutraceuticals may offer some therapeutic potential in glaucoma management, however the lack of well designed clinical trials examining their benefits for glaucoma limits their current therapeutic use. The finding of appropriate use

of nutraceuticals that may be able to modify the risk of glaucoma may provide insight into glaucoma pathogenesis and decrease the need for, and therefore the side effects from, conventional therapies.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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