Review

Use of nutraceuticals in the management of glaucoma

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Introduction

Glaucoma is a progressive optic retinopathy and one of the major causes of blindness in humans, is characterized by optic nerve degeneration, loss of retinal ganglion cells (RGCs) and cause restructuring of nerve tissues, causing visual loss [1]–[3]. The main factors currently known to cause glaucoma are: elevated intraocular pressure (IOP) [1], optic nerve pressure imbalances [4], decreased vascular flow and irrigation [3], [5], increased glial activity and neuroinflammation [6], oxidative stress [7], glutamate excitotoxicity [8]. As glaucoma shares some of these mechanisms with other diseases that cause neuronal degeneration such as Alzheimer's disease or Parkinson's disease, some authors consider glaucoma a neurodegenerative disease [9].

The most common type of glaucoma is "**open-angle glaucoma**", which occurs mainly due to increased intraocular pressure without any apparent cause. It eventually causes visual defects leading to blindness of the eye. Normotensive glaucoma is a subtype of open-angle glaucoma that occurs when there are visual defects without increased intraocular pressure [10]. In human patients have been reported difficulties in performing daily activities, loss of vision, loss of field of vision, and loss of vision [9].

Since glaucoma shares some of these mechanisms with other diseases that cause neuronal degeneration such as Alzheimer's or Parkinson's, some authors consider glaucoma a neurodegenerative disease [9].

Treatment of the disease is aimed at slowing down (or stopping) the progression of the damage to maintain the patient's vision and quality of life as long as possible. The therapeutic focus in this disease consists of intraocular pressure reduction (beta-blockers, prostaglandins, carbonic anhydrase inhibitors and alpha agonists) has a great effect on the progression of the disease. Even when intraocular pressure is controlled, vision loss and blindness can occur. For this reason, in addition to topical antihypertensive therapy, other complementary therapies are being studied for this disease [9], [10].

Citicoline

It is a molecule that has been extensively studied in neurodegenerative diseases, studies have been published in human medicine on senile dementia, Parkinson's disease and glaucoma with the use of citicoline, suggesting a beneficial effect of citicoline.

The use of oral citicoline has been observed to reduce the progression of glaucoma in clinical studies [11]–[13].

Citicoline (cytidine-50-diphosphocholine) is an essential component in the synthesis of membrane phospholipids, such as phosphatidylcholine [2].

Oral citicoline is absorbed in the intestine and transformed in the intestinal wall and liver into choline and cytidine. These compounds can cross the blood-brain barrier. From here it provides the metabolic precursors of phospholipids and participates in the synthesis of nucleic acids, proteins, phosphatidylcholine, sphingomyelin, cardiolipin and acetylcholine (main neurotransmitter of the cholinergic system that modulates visual processes). It has been determined that

citicoline acts as a rescue resource for cell membranes [14], [15].

Citicoline helps reduce glutamate-mediated excitotoxicity (neuron death caused by elevated glutamate levels) and oxidative stress by increasing neurotrophin levels and supporting mitochondrial function [16].

Oral citicoline increases the release of dopamine and norepinephrine. The efficacy of this action has been proven in diseases such as Alzheimer's, Parkinson's and ischemic and traumatic brain lesions. The neurostimulatory effect, due to the increase of dopamine, justifies the increase in visual range and electrophysiological results obtained in several glaucoma patients [14], [16].

Positive effects of citicoline [2]:

Regulation of Bcl proteins: Animal studies show that citicoline can rescue damaged retinal ganglion cells through increased expression of the anti-apoptotic protein Bcl-2.

Excitotoxicity: Citicoline has a protective effect against retinal damage by counteracting oxidative stress through extracellular reduction of ERK1/2 kinases.

Caspases: Animal studies have shown that citicoline can rescue RGCs through anti-apoptotic mechanisms and can help the regeneration of damaged neurites. It does this by reducing the expression of active forms of caspases 9 and 3.

Mitochondria: In animal models, citicoline can reverse some mitochondrial aging processes, through increasing the availability of essential nucleotides for the synthesis of membrane phospholipids, as well as improving brain metabolism.

Neurotransmitters: Citicoline increases the synthesis of dopamine, acetylcholine, serotonin and noradrenaline. The increase in retinal dopamine is related to an improvement in visual functions.

Membrane integrity: Damage to neuronal axons is part of glaucoma. Citicoline is a precursor of several membrane lipids and helps in the maintenance and regeneration of RGCs.

Retinal circulation: Oral supplementation with citicoline increases cerebral blood flow, possibly due to the effect on calcium release in endothelial cells that regulate nitric oxide (NO) synthesis, improving blood perfusion.

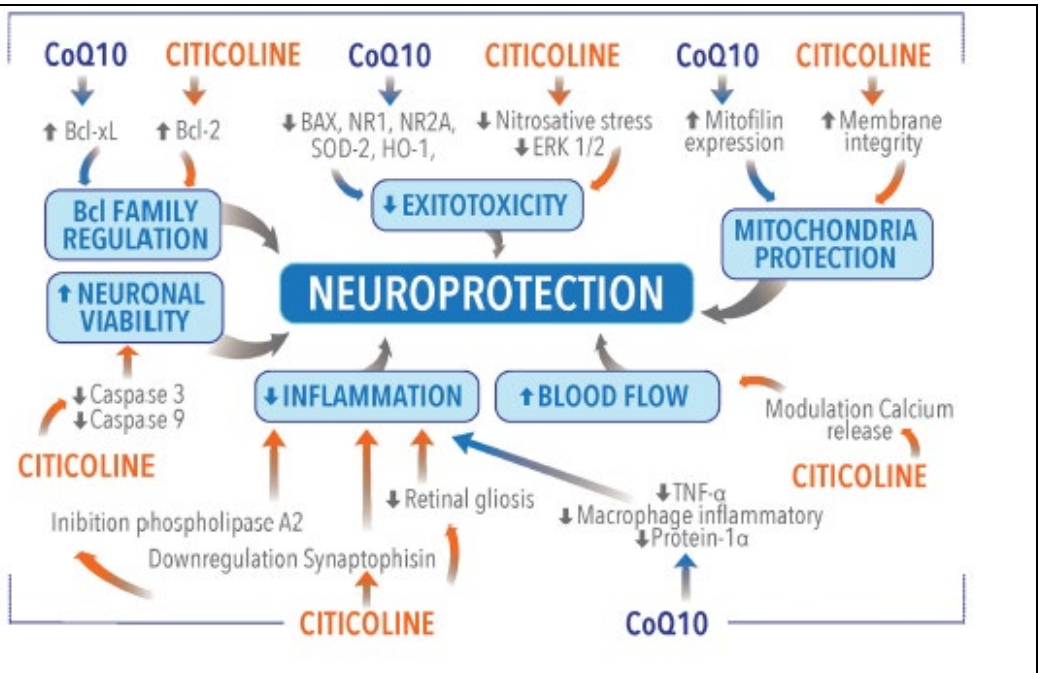

Figure 1. Neuroprotective mechanisms of citicoline and coenzyme Q10 [2]

Ginkgo biloba

Gingko biloba is a medicinal plant from Asia. Extracts of Gingko biloba leaves have been used since ancient times to treat various disorders such as asthma, vertigo, fatigue or circulatory problems. The extracts contain mainly flavonoids (24%) and terpenoids (6%) [3]. Several mechanisms of Ginkgo biloba in the body have been described: reduction of blood viscosity and antagonist of platelet activation (rheological effects), increase retinal blood flow, increase tolerance of neurons to anoxia, beneficial effects on neurotransmitters and prevention of cell membrane damage caused by free radicals [17]–[19].

Ginkgo biloba has antioxidant properties thanks to its flavonoids that yield electrons to free radicals (especially nitric oxide, NO) and also act at the mitochondrial level, preventing oxidative damage [8], [19], [20]. Ginkgo biloba can reduce the activation of neurons under unfavorable stimuli of hypoxia or hypoperfusion, reducing the activity of pro-inflammatory mediators such as TNF Alpha or COX2 [3].

Studies have been conducted demonstrating neuroprotective properties in geriatric mice. Oral administration of ginkgo biloba extracts reduced the levels of reactive oxygen species (ROS) and apoptosis induced by these ROS [3].

Glaucoma patients have several mitochondrial alterations, causing mitochondrial respiration to be 21% lower than healthy individuals [21]. This is important because:

- Mitochondria can produce large amounts of free radicals.
- They have little capacity for DNA repair
- Oxidative stress itself causes a reduction in their membrane potential causing a reduction in ATP production; leaving the cell with low energy levels and vulnerable to damage.
- If mitochondrial damage exceeds a threshold, cytochrome C is released and the process of apoptosis is initiated.

Ginkgo biloba stabilizes the inner membrane of mitochondria and increases their membrane potential, recovering respiratory function and ATP production. [20].

Patients suffering from glaucoma have less retinal blood flow and lower flow velocity than healthy individuals. Numerous studies have been conducted assessing the effect of Ginkgo biloba on retinal microcirculation, showing improvements in supplemented patients compared to placebo groups [18], [22].

Oral supplementation with Ginkgo biloba also increases erythrocyte malleability, reduces fibrinogen levels, reduces blood viscosity and viscoelasticity. Finally, retinal blood flow is significantly increased [23]–[25]. Ginkgo biloba increases microcirculation by increasing endothelial vasodilation, as can be seen in the study by Wu et al. in healthy geriatric humans. Demonstrating an increase in blood flow in coronary and brachial arteries after supplementation with Ginkgo biloba [26].

In the study conducted by Seon Hee Shim et al. in human patients supplemented with Ginkgo biloba or placebo, an improvement in visual function was observed, specifically in the visual range HVF (Humphrey visual field). [8].

Anthocyanins (Vaccinium myrtillus, wild blueberry)

Anthocyanins are pigments found in the vacuoles of plant cells that give color to leaves, flowers and fruits. Their oral consumption has health benefits, with

antioxidant and anti-inflammatory effects, as well as improving visual functions because they have a particular affinity with vascular tissues [8], [28]. The following effects of anthocyanins on the organism have been described: antioxidant action, inhibition of platelet aggregation, prevention of the release and synthesis of proinflammatory compounds (histamine, prostaglandins and leukotrienes), reduction of circulating glucose values, etc [8].

As discussed above: decreased vascular flow and irrigation in the retina and optic papilla are involved in the progression of glaucoma. It has been observed that [28]:

1. Patients with glaucoma frequently present hemorrhages in the optic papilla.
2. Retinal vascular diseases, such as retinal vein occlusion, are frequently associated with glaucoma patients.
3. There is a generalized reduction of ocular flow in patients with glaucoma.
4. Patients have lower plasma endothelin-1 (ET-1) concentrations compared to healthy subjects.
5. There is increased platelet aggregation in patients with glaucoma.

Regarding oxidative stress, it has been observed that individuals with glaucoma have low circulating glutathione levels, showing less resistance to oxidative stress.

In the study by Yoshida K et al. they supplemented one group with anthocyanins showing significantly higher visual flux than the placebo group, with no alteration of IOP or systemic blood pressure [28]. In this study, different regulators of vascular contraction and oxidative stress such as endothelin-1 (ET-1), nitric oxide (NO), oxidation proteins and antioxidant activity were evaluated.

In this study they focused mainly on analyzing the biomarker ET-1, known to be involved in diabetic retinopathy, retinal vein occlusions and open-angle glaucoma [29]. ET-1 is a potent vasoconstrictor that acts in the autoregulation of blood flow. This endothelin is produced by vascular endothelial cells and its receptors ET-A (related to vasoconstriction) and ET-B (related to NO-mediated vasodilation) are mainly expressed in ocular tissues (optic nerve, retina and uvea (Figure 2).

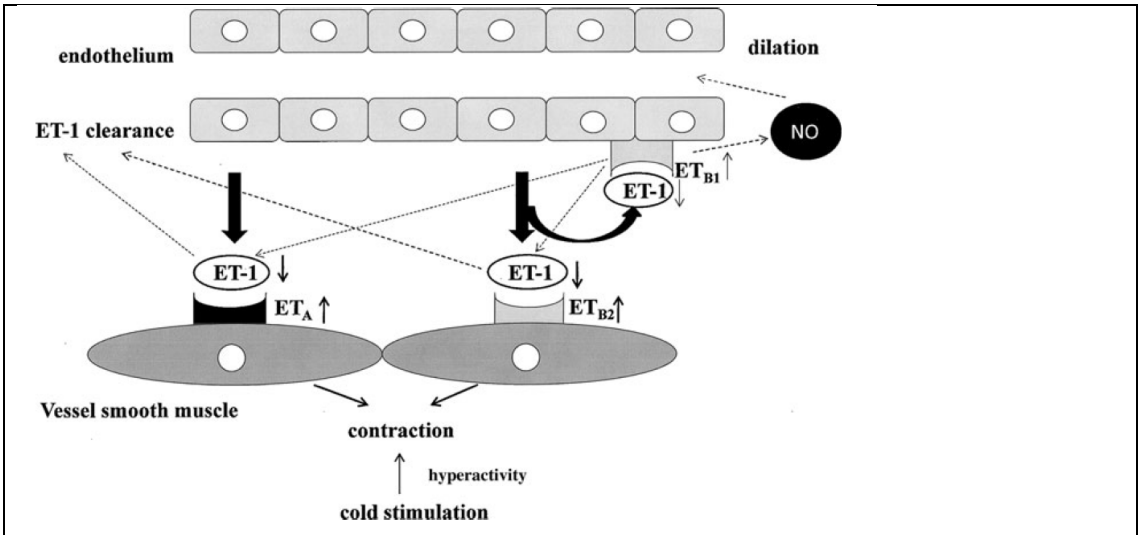

Figure 2. Mechanism of action of endothelin[28]

In patients with glaucoma they observed a lower concentration of ET-1, which has a positive feedback mechanism with its receptors, increasing them when there is a low concentration. It is believed that this mechanism is the cause of the reduction of retinal flow. The imbalance between vasoconstrictor substances such as ET-1 and vasodilator substances such as NO is the cause of vasospasm in glaucoma. Anthocyanin supplementation normalizes circulating ET-1 values and avoids positive feedback in receptors of this endothelin, also acting on the ET-B receptor, causing an increase in vasodilation by NO and increasing ET-1 elimination. In the same study, they also observed increased blood flow in the optic nerve at 12 and 24 months of anthocyanin supplementation [28].

The study by Orie Nakamura et al. showed that oral administration of bilberry extract in mice increased the levels of Grp78 and Grp94 proteins in the retina, which have apoptosis inhibitory effects and prevent neuronal death during ischemia [30].

In another study comparing the placebo group, the group supplemented with Ginkgo biloba and the group supplemented with Vaccinium myrtillus, where the following values were controlled: BCVA (Best corrected visual acuity), HVF (Humphrey Visual Field), intraocular pressure and systemic pressure. In the group supplemented with anthocyanins, an improvement in BCVA and HVF values was observed with respect to the placebo group. These results demonstrate that the effects on microcirculation caused by anthocyanins are beneficial for visual function [8].

Vitamin B3 (Niacinamide or Nicotinamide)

Vitamin B in the form of niacinamide is a precursor of the coenzyme nicotinamide adenine dinucleotide (NAD+), an oxidative molecule essential for mitochondrial functioning and respiration processes that ultimately generate ATP vital for retinal ganglion cell survival. NAD+ levels in retinal mitochondria (and plasma) decrease with age and this lack of NAD+ makes retinal ganglion cells more susceptible to energy deficits, mitochondrial dysfunction and damage caused by elevated intraocular pressure [31]. In addition, reductions in the level of NAD+ have been described in several neurodegenerative diseases, including glaucoma [10].

There is a clear relationship between low plasma NAD+ levels, poor mitochondrial function and the development of glaucomatous changes. The study by Williams et al. studied the efficacy of oral vitamin B3 supplementation and its effect on the prevention and amelioration of glaucoma symptoms in animal models of hypertensive glaucoma (mice). In these mice with glaucoma, they observed a reduction of NAD+ and glutathione levels in retinal ganglion cells with respect to the control group (healthy). Oral vitamin B administration prevented the decline of NAD+ levels over time, without affecting intraocular pressure. The study reported that over a 12-month period of supplementation, 70% of glaucoma-susceptible mice were protected against glaucomatous damage. Vitamin B3 reduced the incidence of optic nerve degeneration, prevented RGC loss, retinal nerve fiber thinning and inhibited the formation of dysfunctional mitochondria [32].

Another study showed that vitamin B3 protects RGC from metabolic damage in animal models. NAD is essential for RGC survival as it collaborates in ATP formation, oxidative stress control, gene expression and DNA repair. They concluded that vitamin B3 is a potent neuroprotectant [33].

Vitamin B9 & Vitamin B12

The effect of vitamins B9 and B12 has been studied especially in the treatment of

exfoliative glaucoma. In exfoliative glaucoma, IOP may be increased due to narrowing of the filtration angle, loss of proteins into the anterior chamber and accumulation of exfoliative material in the trabecular meshwork. Currently there are no strategies for the prevention of this type of glaucoma [34].

A possible risk factor for developing exfoliative glaucoma is homocysteine; an amino acid that is synthesized in the body from methionine. The only source of methionine is ingestion, from animal proteins. Homocysteine metabolism is closely related to vitamins B6, B12 and folic acid, which act as cofactors in its various transformations [35].

When homocysteine is elevated, it can promote the formation of exfoliative material by contributing to vascular damage (occlusion of veins and arteries), oxidative stress and cause alterations of the extracellular matrix. Homocysteine levels in plasma, aqueous humor and tears have been observed to be elevated in patients with exfoliative glaucoma and patients with vascular disease. Reducing homocysteine levels may be a goal in the prevention of exfoliative glaucoma, focusing on increasing the intake of vitamin B6, vitamin B12 and folic acid (B9) [34], [36].

One study found that folic acid intake reduced baseline homocysteine levels by 25%. They also observed the relationship between high homocysteine levels and exfoliative glaucoma [36].

In a prospective study by J. H. Kang et. al. they monitored the intake of vitamins B6, B12 and B9 of human patients over a 20-year period. A trend toward a lower risk of exfoliative glaucoma was observed in those participants with higher intakes of vitamin B9. All the vitamins studied have a homocysteine-lowering effect, but all participants exceeded the minimum recommended intake of B6 and B12, so no relationship with homocysteine was seen in this study [34].

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