# The role of nutraceuticals in the management of glaucoma.

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## Abstract

**Glaucoma is a chronic progressive neurodegenerative process with complex pathophysiology that has been shown to exhibit disease progression despite good control of Intra-Ocular Pressure (IOP). Nutraceuticals with neuroprotective properties may have a role as adjunctive therapy in the management of glaucoma, and should be reviewed by physicians to safely support patients and address their growing interest. Many patients believe the use of nutraceutical products provides therapeutic benefits for their glaucoma, however these may have unintended side effects and drug interactions. We have conducted a literature review exploring the role of supplementation in the management of glaucoma to provide evidence-based guidance regarding their use. It is essential for physicians to ask about the use of nutraceuticals in their patients and to stay informed about literature findings, in order to support their patients and counsel them on unintended side effects.**

**Keywords:** Nutraceuticals, Dietary supplements, Neuroprotection, Glaucoma management, Adjunctive therapy

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## Introduction

Glaucoma is a chronic optic neuropathy characterized by progressive degeneration of Retinal Ganglion Cells (RGC) leading to loss of nerve tissue and consequent visual field impairment. It represents the leading cause of irreversible blindness globally [1]. Patients are often asymptomatic at onset with insidious disease progression, making early detection and management a challenging endeavour. At present, elevated Intra-Ocular Pressure (IOP) remains the only established modifiable risk factor, though many patients continue to show progression, even on IOP-lowering therapies and pressures in the physiological range. Much remains to be discovered about glaucoma's complex pathogenesis and the need for alternative mechanisms for treatment. Ongoing research has demonstrated evidence for extension of the disease beyond the retina and into the central visual pathways of the brain [2]. This has led to the trial of numerous compounds with neuroprotective features, including the rapidly expanding market of dietary supplements [3]. Although the clinical efficacy of nutraceuticals remains controversial, it is important to stay informed about ongoing research to address patient inquiries and growing interest using evidence-based findings.

We conducted a targeted Ovid MEDLINE search of all articles, using the terms: "Nutraceuticals", "Vitamins" or "Dietary supplements" and "Glaucoma". There were no restrictions on language or study type, but we primarily sought relevant reviews, randomized controlled trials and systematic reviews pertinent to the clinical question addressed. Relevant studies were selected, and their references manually searched for additional papers. No limits concerning publication date were applied, however recently published articles were preferred to reflect the most up-to-date evidence for this review.

## Literature Review

### *What are the pathophysiological mechanisms of glaucoma?*

Glaucoma is a complex multifaceted neurodegenerative disease whose pathophysiology remains not well understood. It presents clinically with progressive loss of the Retinal Nerve Fiber Layer (RNFL), particularly RGCs located in the inner retina, leading to axonal degeneration and characteristic optic nerve head cupping [4]. Mechanisms for the loss of RGCs through apoptosis have been heavily investigated with hypotheses not limited to: Deprivation of neurotrophic factors, inflammation, oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, ischemia, and hypoxia [3,4]. It is important to consider these processes as a series of interconnected events leading to the glaucomatous optic neuropathy and vision loss, rather than isolated mechanisms.

### *What are nutraceuticals and why are they important to study?*

According to the Bureau of Nutritional Sciences, of the Food Directorate of Health Canada, a nutraceutical is a purified food product sold in various medicinal forms which claims physiological benefit in the treatment and prevention of disease [5]. Although there is no worldwide consensus on its definition, nutraceuticals are classified as a type of dietary supplement which, unlike pharmaceutical products in Canada, are regulated under the Food and Drugs Act. A multitude of reasons has contributed to their growing popularity over the past decade, including increasing evidence for the underlying connection between nutrition and health, a desire for natural/traditional medicine and complementary therapies, and a consideration of alternative treatments for chronic diseases with poor therapeutic outcomes. Basis for the use of nutraceuticals in the treatment and prevention of glaucoma stems from literature

studies highlighting their antioxidant, anti-inflammatory, and anti-apoptotic features which have demonstrated a role in preventing RGC death in in vitro and in vivo models of retinal degeneration [3]. A Canadian multicenter cross-sectional survey of complementary and alternative medicine use in glaucoma showed that 1 in 9 patients already use herbal and nutritional supplements in conjunction with their conventional glaucoma medications [6]. Interestingly, many of the surveyed patients believed their nutraceutical use provided therapeutic benefit, however majority withheld disclosure of use to their doctor. This not only highlights the importance of having open guided discussions with patients, but it emphasizes the need for comprehensive research into their therapeutic potential as adjuvant therapy for glaucoma and other optic nerve diseases.

## *What are the preclinical and clinical challenges with studying nutraceuticals?*

Since nutraceuticals fall under the scope of the Food and Drugs Act, they lack the tight regulation enforced on their pharmaceutical counterparts, making procurement of accurate reproducible studies difficult. Preclinical challenges also arise due to unsuitability of animal models as mimickers of glaucoma given its complex disease heterogeneity in human populations with multiple comorbidities and polypharmacy [4]. The difference is further magnified by the use of varying mechanisms for inducing RGC injury and resultant rapid onset of optic nerve damage in the laboratory setting. Animal studies further differ from clinical trials conducted on human participants in terms of timing of the intervention.

In animal studies, intervention is typically administered prior to or at the time of optic nerve injury, while in human trials, most participants are eligible for enrollment after the disease has been long established. Animal studies also vary in their measured outcomes which mostly employ histopathologic endpoints to assess treatment efficacy as opposed to functional outcomes that are utilized in human clinical trials and take months to display significant changes. The number of animals utilized in preclinical studies is often determined arbitrarily or increased midway during the study to establish statistical significance, which leads to difficulty translating treatment trends in clinical trials [7]. Ocular bioavailability, CNS penetration and therapeutic window constitute important factors that are often unreported in experimental studies which fail to measure appropriate product serum levels and biomarkers of inflammation or oxidative stress before and after supplementation [8]. Studies of shorter duration are often unable to accurately quantify the effect of nutraceuticals on the chronic, progressive neurodegenerative nature of glaucoma, particularly when focused on functional outcomes and visual field changes which are slow to occur. Furthermore, many studies are also limited by sample size and neglect to control for possible confounding variables.

## *What role do various nutraceuticals play in the management of glaucoma?*

**Carotenoids:** Lutein, zeaxanthin, and meso-zeaxanthin are xanthophyll carotenoids that constitute the macular pigment of the retina [9]. They possess significant antioxidant and anti-inflammatory properties vital for the preservation of retinal health and maintenance of optimal acuity and central vision. Both lutein and zeaxanthin cannot be synthesized in the body and must be obtained exclusively from dietary sources. Although benefits in visual performance with dietary carotenoid supplementation have been demonstrated in healthy adults and those with macular degeneration and other neurodegenerative retinopathies, limited information is known about their potential use for glaucoma [10]. Clinical studies regarding Macular Pigment Optical Density (MPOD) levels in patients with Primary Open-Angle Glaucoma (POAG) have had conflicting findings, and translation to clinical relevance remains controversial [11,12]. Recently, a systematic review on the role of carotenoid supplementation in the management of glaucoma revealed therapeutic benefits and neuroprotection in preclinical experimental models, but inconsistent results based on epidemiological studies and clinical trials [10]. Although there is theoretical rationale for their use in glaucoma, additional prospective control studies are warranted to support their clinical significance and efficacy as adjunctive therapy.

**Coenzyme Q10:** Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant and important cofactor in the mitochondrial respiratory chain that assists in oxidative phosphorylation by serving as an electron carrier for ATP production. It is used in combination with vitamin E to improve ocular penetration and bioavailability [13]. It has demonstrated protection of retinal cells against oxidative stress in vitro and NMDA-induced glutamate excitotoxicity in vivo as well as reduced retinal damage and apoptosis in transient ischemic injury induced by IOP elevation [14-16]. CoQ10 levels in the human retina decrease by 40% with aging, suggesting possible mechanisms for RGC loss and reduced antioxidant activity [17]. Pertinently, dietary oral supplementation in glaucomatous mouse models has demonstrated 29% promotion of RGC survival by preservation of axons, posing therapeutic implications for neuroprotection [18]. In a POAG study of patients on beta-blocker monotherapy, CoQ10 drops combined with vitamin E exhibited beneficial effect on inner retinal function with consequent enhancement of visual cortical responses [19]. Ongoing research is being conducted regarding its promising potential and efficacy for treatment in POAG [20].

**Citicoline:** Citicoline is a naturally-occurring endogenous mononucleotide that functions as a choline donor and intermediate in the biosynthetic pathway of cell membrane phospholipids, with ability to increase neurotransmitter levels within the CNS [21]. As a precursor of the acetylcholine neurotransmitter, it serves a key role in the synthesis of phosphatidylcholine, a critical neuronal membrane phospholipid essential for the integrity and preservation of RGCs. Evidence for its neuroprotective and neurorestorative role in glaucoma has been thoroughly explored in recent reviews outlining several successful clinical trials and

experimental studies [22,23]. Several works have also shown its long-term benefits on improvement of retinal function and neural conduction along visual cortical pathways [24,25].

**Ginkgo biloba:** Ginkgo Biloba Extract (GBE) is a natural product that contains flavonoids and terpenoids, which have been shown to exhibit stabilizing effects on microcirculation and mitochondrial membranes implicated in glaucoma pathogenesis [26]. GBE's function at the level of the mitochondria to stabilize and protect from damage in addition to their free radical scavenging properties. Many types of GBE's can be found on the market, however it is important to note that much of the literature performed utilizes the standardized EGb761 formula of 24% flavonoids and 6%terpene lactones, which removes much for the toxic ginkgolic acids known to cause allergenic and genotoxic effects. GBE has been utilized in neurodegenerative processes such as Alzheimer's disease, for which mechanistic similarities to glaucoma have been drawn [27,28]. It has demonstrated neuroprotective effects in animal models of glaucoma with reduction in RGC loss after IOP elevation and optic nerve crush studies [29]. Clinical studies have reported promising GBE outcomes in terms of increased ocular blood flow in two studies of varying GBE dose supplementation for four weeks, but conflicting results on visual field defect improvements [3]. It is worthwhile to note that a study on the safety profile of GBE revealed an insignificant but possible risk of bleeding when used in conjunction with anticoagulant or antiplatelet agents, particularly in the elderly and those with known bleeding risks [30].

**Forskolin:** Forskolin is a diterpenoid isolated from roots of the Indian Coleus plant, Lamiaceae (*Coleus forskohlii*). It penetrates cell membranes to activate adenylate cyclase, an enzyme found in human nonpigmented ciliary epithelial cells, thereby decreasing aqueous humor inflow and thus lowering IOP [29]. Reviews have commented on its neuroprotective effects through neurotrophin-stimulating activity both in vivo and in vitro, as well as ability to improve axonal survival and regeneration of RGC's [3]. Administration of forskolin with rutina, vitamins B1 and B2, homotaurine, carnosine and folic acid has been associated with improved IOP control and potential synergy with topical pharmacologic therapies in patients with POAG [31-33]. Despite its positive IOP-lowering effects, further research is required given IOP reduction does not directly translate to clinical benefit.

**Vitamins:** Vitamins are essential micronutrients that can be divided into fat-soluble compounds (Vitamins A, D, E and K) which may be stored in fatty tissue for up to months, and water-soluble compounds (Vitamins B and C) that are easily excreted and need to be replaced more often [3]. Their potential neuroprotective role is primarily linked to their antioxidant activity, however for the most part; evidence regarding their efficacy in glaucoma therapy has been controversial [29]. Although vitamin deficiency has been linked to symptoms of optic nerve dysfunction, a definite association between serum vitamin levels and prevalence of glaucoma remains controversial. For instance, the Nurses' Health Study, Health Professionals Follow-up Study and recent meta-analysis found no association between the risk of POAG and vitamins C, E, A, B6, B12 and D consumption [34,35]. In contrast, the longitudinal prospective Rotterdam study reported an association between the risk of POAG and reduced intake of vitamins A and B1 [36]. Furthermore, a recent systematic review and meta-analysis determined a beneficial association between POAG and vitamins A and C, but failed to exhibit similar relation based on serum vitamin levels [37]. Vitamins D and E have similarly been explored in multiple trials which failed to display conclusive coherent outcomes [3].

## Conclusion

Glaucoma is a chronic progressive condition that has been shown to exhibit disease progression despite IOP control within the normal range. This has led to a rising interest in therapeutic alternatives, including nutraceutical products given their neuroprotective properties among others. Despite theoretical rationale for their use in glaucoma, preclinical and clinical studies have proved to be challenging with inconclusive outcomes regarding the role of supplementation in therapy. Nonetheless, it remains critical for physicians to invite patients to open conversations about their nutraceutical use and to stay informed on up-to-date literature findings to provide evidence-based guidance and safety counselling regarding their potential benefits versus serious unintended side effects.

## Disclosure

The author reports no conflicts of interest.

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