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REVIEW ARTICLE

Strategies to Reduce Oxidative Stress in Glaucoma Patients

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Abstract: ***Background*:** Primary open-angle glaucoma (POAG) is a multifactorial pathology involving a variety of pathogenic mechanisms, including oxidative/nitrosative stress. This latter is the consequence of the imbalance between excessive formation and insufficient protection against reactive oxygen/nitrogen species.

***Objective*:** Our main goal is to gather molecular information to better managing pathologic variants that may determine the individual susceptibility to oxidative/nitrosative stress (OS/NS) and POAG.

***Method*:** An extensive search of the scientific literature was conducted using PUBMED, the Web of Science, the Cochrane Library, and other references on the topic of POAG and OS/NS from human and animal model studies published between 2010 and 2017. Finally, 152 works containing relevant information that may help understanding the role of antioxidants, essential fatty acids, natural compounds and other similar strategies for counteracting OS/NS in POAG were considered.

***Results*:** A wide variety of studies have proven that antioxidants, among them vitamins B_3, C and E, Coenzyme Q10 or melatonin, ω-3/ω-6 fatty acids and other natural compounds (such as coffee, green tea, bear bile, gingko biloba, coleus, tropical fruits, etc.,) may help regulating the intraocular pressure as well as protecting the retinal neurons against OS/NS in POAG.

***Conclusion*:** Based on the impact of antioxidants and ω-3/ω-6 fatty acids at the molecular level in the glaucomatous anterior and posterior eye segments, further studies are needed by integrating all issues involved in glaucoma pathogenesis, endogenous and exogenous risk factors and their interactions that will allow us to reach newer effective biotherapies for preventing glaucomatous irreversible blindness.

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1. INTRODUCTION

Glaucoma is the leading cause of visual impairment and irreversible blindness worldwide. Throughout the clinical course, the disease is characterized by a progressive damage and death of the retinal ganglion cells (RGCs) and optic fibers [1]. Neurodegeneration process extends beyond the retina and optic nerve into the visual pathway [2]. Among the pathogenic mechanisms of glaucoma oxidative stress (OS) [3], inflammation [4], excitotoxicity [5], vascular impairment and hypoxia [6], glial dysfunction [7] and altered axonal transport [8] are the most recognized processes.

Glaucoma-related cell death occurs by means of apoptosis, and apoptosis is triggered by oxidative stress *via* (a) mitochondrial damage, (b) inflammation, (c) endothelial dysregulation and dysfunction, and (d) hypoxia. It has been recently reported that proteomics of the aqueous humor is significantly altered in primary open-angle glaucoma (POAG) as a result of oxidation-induced trabecular damage [9]. Those proteins whose aqueous humor levels are increased in this disease are biomarkers of trabecular meshwork damage. Their diffusion from the anterior to the posterior eye segments may be pivotal in the cascade of events triggering apoptosis in the innermost retinal layers.

Current POAG treatment is quite limited. In spite of lowering the intraocular pressure (IOP) the process continues to worsen, and in most cases, it is impossible to delay glaucoma progression. It is imperative to better identify the pathogenic mechanisms [10], to discover IOP-independent risk factors as well as to improve diagnostic techniques (including the multimodal imaging) and to develop more effective therapies.

Hopefully, the issue is moving ahead [11]. New therapeutic strategies are arising, including the rationale use of

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antioxidants and essential fatty acids [12], distinct neurotrophins [13], adenosine receptor antagonists [14], Rho family GTPases inhibitors [15], as well as sophisticated stem cell/gene therapies [16-18].

Taking into consideration that OS has been largely involved in POAG pathogenesis the scientific literature has evaluated the role of antioxidants in glaucoma with controversial results. Some authors described that a diet rich in antioxidant-containing fruits and vegetables was capable to protect the eyes against glaucoma development and progression [19]. Micronutrient supplementation enhances antioxidant defense and healthy eyes and subsequently may help preventing or delaying glaucoma progression, as previously reported [20-22]. Nevertheless, other authors did not find any benefit from the oral supplementation with antioxidants in POAG patients through two-year of follow-up [21]. Till today, applicability of the nutritional and oral supplementation with antioxidants and essential fatty acids upon the glaucoma practice is to a greater extent controversial. A better explanation of the pros and cons of this type of adjunctive interventions in POAG therapy is required for optimal utilization of these means.

In this review, we will take a look to the current concepts in oxidative/nitrosative stress, the role of reactive oxygen species (ROS)/reactive nitrogen species (RNS) and its downstream effectors in the initiation and progression of POAG, and the experimental models and clinical trials with antioxidants, essential fatty acids, natural compounds and other substances than can counteract the generation of ROS/NOS in glaucoma. Our main goal is to provide the readers a comprehensive document that assists in achieving their personal challenges for better understanding glaucoma pathogenesis and therapy.

2. CURRENT CONCEPTS IN GLAUCOMA THERAPEUTICS

Glaucoma is characterized by the slow, progressive degeneration of the RGCs and optic nerve axons. The glaucoma-induced visual loss is irreversible, underscoring the importance of early diagnosis and treatment [24-26]. Among the recognized risk factors for glaucoma, the main is the elevated IOP [27, 28]. Reduction of IOP is today the only proven method to treat glaucoma [29], as reflected in several multicenter clinical trials that have shown the benefit of IOP loweing in preventing glaucoma, as well as slowing disease progression. [26, 28, 30-32]. Treatment options for glaucoma include medications, laser therapy and incisional surgery, with an extraordinary development of microsurgical devices that have arisen through the past decade [33, 34]. For many years hypotensive medical therapy has traditionally been the modality of glaucoma treatment. Up today still remains the gold standard for the onset of glaucoma therapy and even for managing the different stages of disease. Currently,there are two approaches for effective medical IOP reduction: by decreasing the aqueous humor production with the use of β-blockers (inhibition of the beta-mediated stimulation of Na+/K+-ATPase), carbonic anhydrase inhibitors (CAI) and/or sympathomimetic drugs (activation of the α-mediated inhibition of Na+/K+-ATPase), and by increasing the outflow aqueous humor, with the use of cholinergic/parasympathomimetic drugs and prostaglandin analogues (PGAs) (trabecular meshwork: TM), sympathomimetic drugs (uveoscleral outflow) and/or PGAs (uveoscleral outflow) [35-37].

However, some controversy exists as to the degree of IOP reduction that can be achieved with any of these hypotensive drugs (Table **1**). The results of a meta-analysis

Table 1. Overview of the main features of some of the most prescribed topical anti-glaucoma medications available in the market.

Generic Name*	% IOP Reduction from Baseline		Year of Introduction	Instillation Frequency	Preservative Free	Wash-out Time
	Peak	Trough				
Pilocarpine	25	20	1875	3-4 times daily	No	1 week
Timolol	27	26	1978	1-2 times daily	Yes/ No	2-5 weeks
Dorzolamide	20	17	1994	2-3 times daily	Yes	1 week
Brimonidine	25	18	1996	2-3 times daily	No	1-3 weeks
Latanoprost	31	28	1996	Once daily	No/ Yes	4-6 weeks
Brinzolamide	20	17	1998	2-3 times daily	No	1 week
Unoprostone	20	15	2000	2 times daily	No	4-6 weeks
Travoprost	31	29	2001	Once daily	No **	4-6 weeks
Bimatoprost (+)	33	28	2001	Once daily	No/ Yes	4-6 weeks
Tafluprost	27	20	2008	Once daily	Yes	4-6 weeks

Adapted from the Guidelines of the European Glaucoma Society [31] [10] and from van der Valk *et al* [34] [12]. IOP: intraocular pressure. *Drugs are listed based on the year of introduction in the market. ** Without benzalkonium chloride. (+) Bimatoprost 0.03%.

showed that the highest IOP reduction ranged from 33% (bimatoprost) to 17% (brinzolamide) [38]. According to the European Gaucoma Society (EGS) guidelines, PGA, β-blockers, α-2 agonists, and topical CAI are first choice agents [35]. In general, PGAs are the first-line of medical therapy, for being most effective in lowering IOP [39]. Other hypotensive eye drops are used as second-line agents or in cases of intolerance or side-effects to PGAs [40]. Some other new hypotensive agents are actually being investigated (Table **2**) [41-44].

Glaucoma, a long-lasting disease, requires reinforcing the treatment regimen by controlling the compliance with the prescribed medication. When medical treatment does not achieve adequate IOP reduction, laser or incisional surgeries are then indicated. Types of laser surgery used to treat glaucoma include argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) [45-47]. Both techniques induce biological changes in the TM resulting in increased aqueous outflow and IOP lowering. However, in the majority of patients, the reduced IOP effect decreases gradually over time with a failure rate of about 10% per year [47]. Most common surgical procedures to IOP lowering include trabeculectomy and nonpenetrating deep sclerectomy [48]. Alternatives to these procedures have recently been introduced, such as the micro-invasive glaucoma surgery (MIGS) and others that are currently under research [49-51]. It has to be considered that some new surgical devices and maneuvers are succesfully been used at the time of cataract surgery which constitutes itself an effective procedure for glaucoma treatment.

Clearly, elevated IOP plays a major role in glaucomatous RGCs damage, but therapeutic control of IOP in many patients is not sufficient to improve the visual function and to arrest disease progression [52]. Besides, glaucomatous changes have been observed in individuals with normal IOP. This suggests a critical role of other factors and mechanisms in the initiation/progression of glaucomatous changes. Since visual damage in glaucoma is ultimately induced by the visual field loss resulting from optic nerve degeneration, the possibility remains that neuroprotective/neuroregeneration/neuromodulation strategies could be excellent efficacious means to slow or even stop glaucoma progression [53]. Among others, possible future antiglaucoma therapeutic options are: glutamate excitotoxicity inhibitors, nitric oxide synthase inhibitors, blood flow enhancers, calcium/sodium channel blockers, neurotrophins, antioxidants, vasotonic agents, genetic modulators (micro RNAs), gene therapy, as well as regenerative stem cell therapy. Some of them are reflected in the Table **2** [2, 16, 53, 54].

3. OXIDATIVE AND NITROSATIVE STRESS IN GLAUCOMA RESEARCH AND THERAPEUTICS

During the past three decades, major research has demonstrated the mechanisms by which the OS, an imbalance in the redox status of pro-oxidant/antioxidant reactions in cells,

Table 2. Update on the new strategies for glaucoma therapy based on the distinct pathogenic mechanisms.

Mechanisms	Substance	Effect
Renin-Angiotensin System ACE inhibitors	Enalaprilat, Fosinopril, Perindopril, Ramiprilat,	Ocular hypotensive effect
Calcium Channels Ion channel blockers/inhibitors	Betaxolol, Diltiazem, flunarizine, Iganidipine, lomerizine, Nifedipine, Nimodipine, Nilvadipine Verapamil, Nimodipine,	Improving ocular blood perfusion, neuroprotection and IOP lowering.
Cell kinases Cell cyclin-dependent kinase inhibitor	Roscovitine	Cell contraction-relaxation in trabecular meshwork
Cell kinases (Rho family)	AMA0076 AR-13324 K-115 PG324 Y-39983 RKI-983 H-1152	Modulating signal transduction pathways and actin cytoskeleton function and cell motility of trabecular meshwork, canal of Schelmm and ciliary muscle cells
Aqueous humor homeostasis. PGAs EP2 receptor agonist	SAR366234	EP2 receptor agonist. Lowering IOP
Aqueous humor homeostasis PGAs Dual receptor affinity for FP and EP3 receptors,	ONO 9054	Lower and more sustained IOP reduction
Energy supplier Adenosine A2a receptor agonist	OPA-6566	Increase aqueous outflow facility by shrinking TM cell volume
Aqueous humor homeosthasis TM cells contractility Actin modulator	Latrunculin B (INS115644) marine macrolide	Improves TM outflow facility by inhibiting the assembly of actin microfilaments in cell cytoplasm

Abbreviations: ACE: angiotensin converting enzyme; IOP: Intraocular pressure; PGAs: prostaglandin analogs; EP2: prostaglandin E2; EP3: prostaglandin E3; FP: prostaglandin F; TM: trabecular meshwork.

can cause cellular damage by peroxidation of lipids, proteins, carbohydrates, nucleic acids and bases. However, the exact signalling pathways regulated by ROS are not clear. There are both endogenous-exogenous ROS sources. Inside the cells, mitochondria, endoplasmic reticulum, and peroxysomes can generate ROS (Fig. **1**). Also, some enzymes produce ROS from their reaction cycles [55]. External conditions can also generate ROS [56]. In addition to OS, the NS produced by the augmented synthesis of RNS can also induce cell damage and death [57]. The RNS are produced from nitric oxide (NO), by reacting with the superoxide anion, generating peroxynitrite and other highly reactive molecules. The OS/NS has been implicated in ophthalmic processes [58]. Searching for new therapeutic glaucoma strategies a big amount of information emerged from experimental investigations, involving the pathogenic mechanisms, risk factors and potential endogenous-exogenous processes involving the disease. This section looks into the current knowledge on the role of OS/NS stress and the possible pharmacological approaches for glaucoma treatment. As said before, OS is the result of the imbalance between the ROS/RNS formation and the counteracting activity of antioxidant defenses. Regarding glaucoma pathogenesis many questions remain a mystery, but a better knowledge of the cellular and molecular events occurring in the initiation and progression can help improve patient management [59-62]. It has been widely demonstrated that altered redox processes are linked to inflammation [4, 7, 63], apoptosis [63], excitotoxicity [5, 64], vascular disorders and/or glial dysfunction [6, 7, 65, 66]. In this context, it has been recently reported some presumptive biomarkers of all these pathogenic mechanisms and clinical endpoints (including the progression rates) that are fundamental to help managing the affected individuals [67-73] (Table **3**). In spite of this, there is a lack of global standardization in this type of studies (design, sample size, analytical techniques, statistics, reproducibility *etc*.) to improve proper identification of glaucoma biomarkers. In this context, the new disciplines named "OMICs" have arisen in the past years to integrate large amounts of data pertaining to the analysis of specific entire sets of molecules present in a cell, tissue, organ, or the complete organism, with a broad range of biomedical applications (Fig. **2**).

Moreover, the above endogenous processes can be aggravated by the interaction of various exogenous agents, such as ultraviolet radiation, toxic substances, cigarrette smoking and pollutants [74] (see the Fig. **1**). Moreover, animal and *in vitro* models have helped researchers to deep into the knowledge of the mechanisms that affect different cellular types involved in glaucoma and that will be explain in the next sections.

Biomarkers and surrogate end points of OS and its downstream effectors have been extensively studied. Different

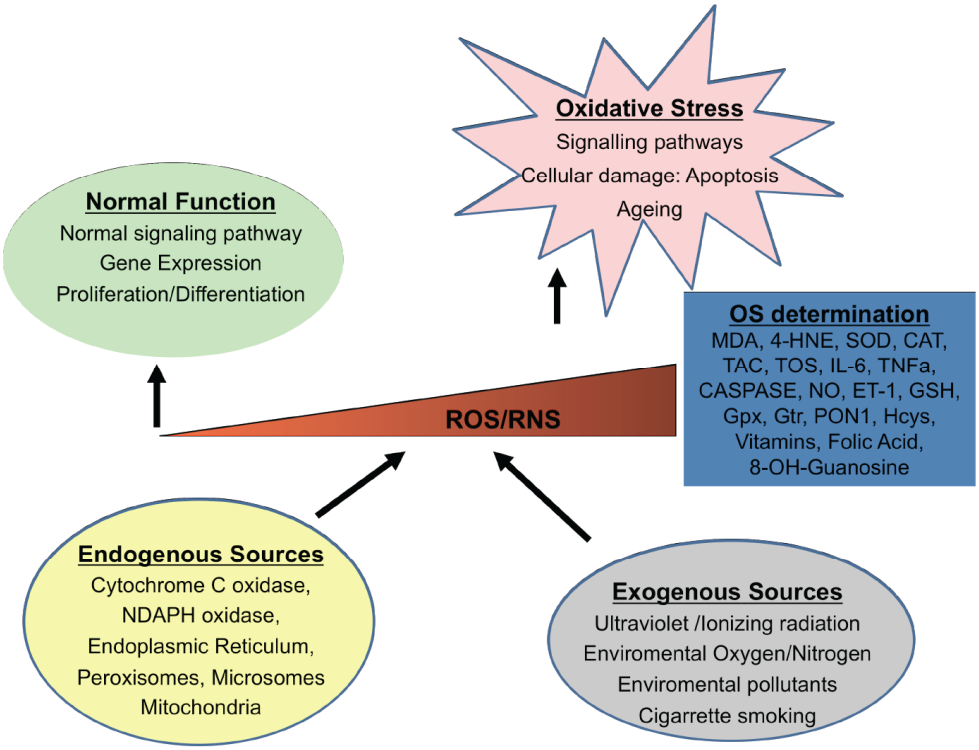

Fig. (1). Endogenous and exogenous sources capable to produce cellular response to reactive oxygen/nitrogen species (ROS/RNS). The level of reactive species is regulated by different antioxidant defense mechanisms. When there are low/normal levels of ROS/RNS the physiological functions are maintained. However when an excess of them exists, an oxidative stress occurs. (MDA: malondialdehyde; 4-HNE: 4 hydroxynonenal; SOD: superoxide dismutase; CAT: catalase; TAC: total antioxidant capacity; IL-6: interleuquin-6; TNFa: tumor necrosis factor alpha; NO: nitric oxide; ET-1: endothelin-1; GSH: glutathione; Gpx: glutathione peroxidase; Gtr: glutathione S-transferase; Hcys: homocysteine).

Table 3. Reactive oxygen and nitrogen species.

Reactive Oxygen Species (ROS)	Reactive Nitrogen Species (RNS)
Singlet oxygen – $^1O_2$	Nitric oxide – $NO^{\cdot}$
Superoxide anion – $O_2^{\cdot-}$	Nitric dioxide – $NO_2^{\cdot}$
Hydroxyl radical – $OH^{\cdot-}$	Peroxynitrite – $ONOO^{\cdot-}$
Hydrogen peroxide – H_2O_2	
Hydroperoxyl radical – $ROOH^{\cdot}$	

molecules have been assayed to evaluate the OS in glaucomatous patients and animal/*in vitro* models using several ophthalmic samples (aqueous humor, vitreous body, human tears). These molecules can be classified into two groups: pro-oxidants, and antioxidants, as exposed below (Table **4**).

3.1. Pro-oxidant Biomarkers

Malondialdehyde (MDA) is the most studied lipid peroxidation by product in human samples and animal models. Many studies have shown significantly higher MDA levels in glaucomatous subjects *vs* controls. Benoist d'Azy *et al*. [75] carried out a meta-analysis reporting higher serum and aqueous humor MDA levels in POAG patiens. Nucci *et al*., [76] and Chang *et al*., [77] found increased MDA levels in serum and/or aqueous humor of POAG patients as compared to the controls. Our group also reported higher MDA concentration in human aqueous humor of glaucomatous individuals, as compared to a comparative group of patients operated from cataracts [3, 58, 61, 69, 78, 79]. Other OS by products have also been identified in glaucomatous eyes, such as 4-hydroxynonenal (4-HNE) or 8-hydroxy-2′-deoxyguanosine (8-OHdG). Regarding these latter metabolites, 4-HNE (or 4-hydroxy-2-nonenal; C9H16O2, is a lipid peroxidation cell by product and it can be found at higher concentration during oxidative stress processes. In fact, 4-HNE plays a key role in cell signal transduction. The 8-OHdG (or 8-oxo-7,8-dihydro-2' -deoxyguanosine) is one of the most abundant forms of free radical-induced oxidative damage to both the nuclear and mitochondrial DNA. It has been widely utilized as a biomarker for oxidative stress. Regarding the role of these metabolites in glaucoma, Malone *et al*. [80] studied the dose and time-dependent effects of 4-HNE on the viability of primary cultures of human ONH astrocytes, concluding that 4-HNE is neurotoxic and that astrocytes itself can counteract these effects, protecting the ONH from glaucomatous injury. Also Chang *et al*., [77] evaluated the serum 4-HNE concentration POAG patients, reporting noticeably higher levels in glaucoma samples than in the healthy ones (with no statistically significant differences). The 8-OHdG is also a marker of oxidative DNA damage and its concentration increases with age in a variety of mammalian tissues [81]. Recent studies have shown significantly higher 8-OHdG levels in POAG individuals *vs* controls [82, 83]. The nitrosative cell damage has also been studied in relation to glaucoma. Luthra *et al*., [84] demonstrated that nitrotyrosine (NT) can be considered a marker for peroxynitrite-mediated oxidative injury in glaucoma. Our research group carried out a case-control study in aqueous humor of POAG patients and a comparative group of cataract subjects, with significantly increased NO concentration in the glaucomatous patients [85]. Openkova *et al*., [86] found similar results, reporting an NO increase and its metabolites in blood serum and lacrimal fluid of POAG patients. These data support NO as a potential biomarker for

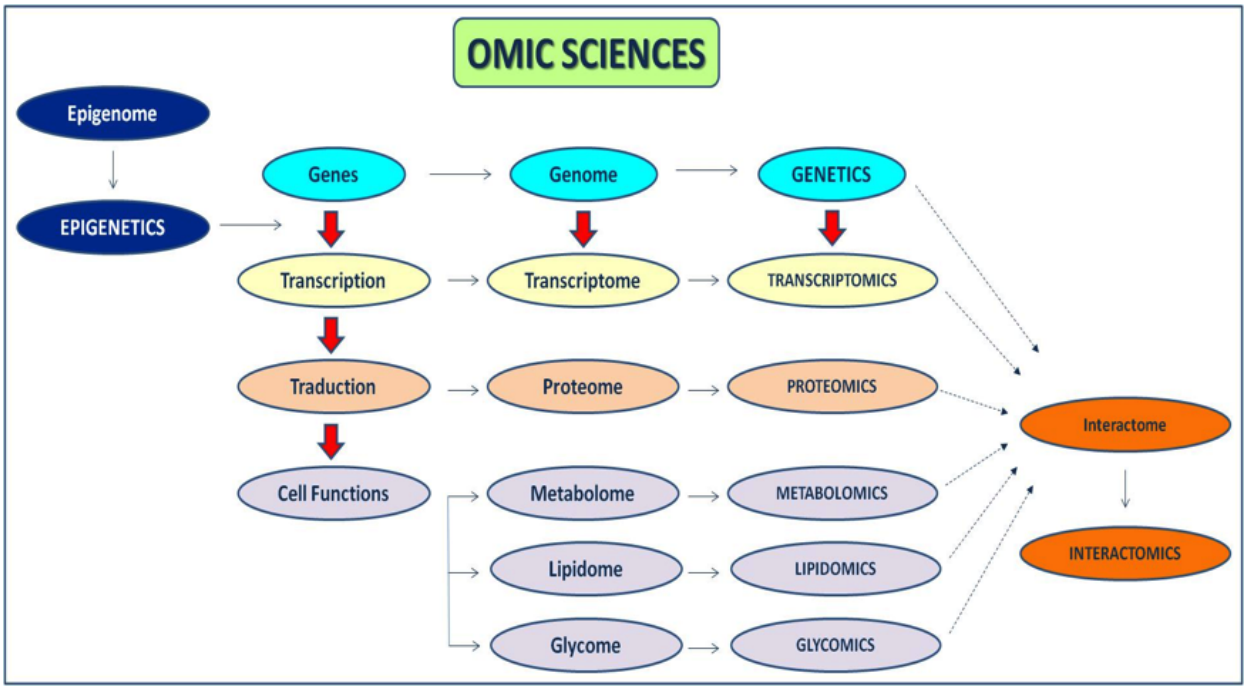

Fig. (2). Flowchart showing the most relevant OMIC sciences.

Table 4. Oxidative stress-related studies in glaucoma.

Study	Sample	Significant Findings	Refs.
OS	Aqueous humor (human)	Higher oxidative status and lower antioxidant activity in POAG	*Zanón-Moreno et al. 2008* [61]
Biomarkers of OS, immune response and apoptosis		ROS, immune inflammatory response mediators, and apoptogenic molecules are engaged in glaucoma disease	*Pinazo-Durán et al. 2013* [69]
Polymorphisms in several genes with biomarkers in POAG	Plasma (human)	Novel association: rs737723 polymorphism (SEC14L2/TAP) from GPX4 and higher POAG risk	*Zanón-Moreno et al. 2013* [91]
Association of TAC with type and severity	Plasma (humor)	TAC levels are lower in glaucoma (more so in POAG and PEG than PACG)	*Mousa et al. 2015* [92]
OS markers evaluation	Aqueous humor (human)	Increased oxidative stress may play a role in the pathogenesis of both POAG and PACG	*Goyal et al. 2014* [87]
Association of clinical indices of PACG with TAC	Plasma (human)	The authors demonstrated an inverse correlation of TAC level with IOP	*Abu-Amero at al. 2014* [93]
Evaluation of GS, NOS, SOD and GST	Aqueous humor (human)	GS, NOS2, SOD and GST may be useful oxidative markers in glaucoma	*Bagnis et al. 2012* [89]
OS and antioxidants	Systematic Review and Meta-Analysis	The increase of some antioxidant markers could be a protective response of the eye against oxidative stress.	*Benoist dÁzy et al. 2016* [75]
OS markers	Blood and aqueous humor (human)	Oxidative stress and decreased antioxidant defenses are involved in POAG.	*Nucci et al. 2013* [76]
OS	Serum (human)	Involvement of oxidative stress in PACG. Identify ischemia-modified albumin as a new biomarker to asses oxidative stress in PACG	*Chang et al. 2011* [77]
OS markers (MDA, 8-OHdG and PON1)	Blood samples (human)	Higher MDA and 8-OHdG levels may be correlated with decreased PON1 activity in POAG	*Mumcu et al. 2016* [82]
Apoptosis markers (PARP1 and OGG1)	RNA from Blood (human)	Results suggest that oxidative stress-induced DNA damage is associated with POAG. This increase could be by the decreased expression of DNA repair enzymes	*Mohanty et al. 2017* [83]
NS	Aqueous humor (human)	Involvement of NO in POAG	*Zanón-Moreno et al. 2008* [85]
Biochemical indicators of lipid peroxidation	Serum and tear (human)	In POAG there are: free radical oxidation, suppression of antioxidant system defense and endothelial dysfunction	*Openkova et al. 2013* [86]
OS	Red Blood Cells (human)	An oxidative disorder was observed in POAG: CAT and GPX upregulation and higher MDA levels	*Rokicki et al. 2016* [90]

Abbreviations: OS: Oxidative stress; NS: Nitrosative stress; POAG: primary open-angle glaucoma; ROS: reactive oxygen species; GPX: glutathione peroxidase; TAC: total antioxydant capacity; PEG: pseudoexfoliation glaucoma; PACG: primary angle closure glaucoma; IOP: intraocular pressure; GS: glutamine synthase; NOS: nitric oxide synthase; SOD: superoxide dismutase; GST: glutathione transferase; MDA: malondialdehyde; 8-OHdG: 8-hydroxy-2' –deoxyguanosine; PON: paraoxonase PARP1: Poly(ADP-ribose) polymerase; OGG1: 8-Oxoguanine DNA glycosylase NO: nitric oxide.

identifying those individuals at risk of glaucoma progression and visual loss.

3.2. Antioxidant Biomarkers

Among the antioxidant molecules the endogenous-exogenous sources of these compounds must be considered. Endogenous antioxidants are mainly enzymes with antioxidant activity, such as superoxide dismutase (SOD), catalase (CAT), and both glutathione peroxidase (GPx) and S- transferase (GS-T). Also, a wide spectrum of non-enzymatic molecules (glutathione: GSH, coenzyme Q-10; CoQ-10 and co-factors) are enclosed within this type of antioxidants. Exogenous antioxidants are mainly the vitamins E and C, β-carotene and flavonoids, as well as minerals involved in the corresponding redox reactions (selenium, copper, zinc, manganese and iron). Goyal *et al*. [87] found increased SOD and GPx activity and decreased vitamin C and E in POAG patients. In this context, melatonin (a pineal hormone) has a potent antioxidant function acting as effective free radical scavenger. It has been shown that metalotin is capable to protect the ocular tissues from oxidative stress, and ultimately metatolin analogs have been proposed as promising candidates for glaucoma theraphy [88].

Bagnis *et al*. [89] observed a reduction in the expression of SOD and GS-T in the aqueous humor of POAG patients *vs* controls. Rokicki *et al*., [90] showed significant increased GPx and CAT activities in red blood cells of POAG patients *vs* controls. Our group analysed the concentration of vita-

mins C and E and GPx in serum of POAG patients. Significantly lower levels of these antioxidants were seen in the glaucomatous eyes *vs* the controls [91]. Independently of the source and type of antioxidant, one of the most generalized biomarkers is the total antioxidant capacity (TAC), reflecting the complete antioxidant status in biological samples. In this regard, our group incorporated the TAC determination throughout distinct glaucoma studies, concluding that TAC was significantly reduced in glaucomatous patients [3, 58, 51, 69, 76, 78]. Also Mousa *et al*. [92] and Abu-Amero *et al*., [93] found similar results by comparing the TAC activity in different glaucoma types, as well as in relation to glaucoma severity. Regarding the NS Yokota *et al*., [94] reported that molecular hydrogen importantly reduces the cellular peroxynitrite concentration, suggesting that it may be a useful and effective molecule to develop new therapeutic drugs for glaucoma. Moreover, it has been sugeested that lower systemic antioxidant capacity measured by ferric-reducing activity is associated with more severe visual field damage in POAG, partly explaining its roles in IOP elevation [95].

For summarizing, the antioxidants counteract the ROS/RNS generation, constituting the first natural barrier to fight against oxidative attack in glaucoma disease. Specific animal models and clinical trials in this topic will be discussed in the following sections.

4. EXPERIMENTAL GLAUCOMA MODELS OF ANTIOXIDANTS, ESSENTIAL FATTY ACIDS AND OTHER NATURAL PRODUCTS

Animal models are extremely useful to avoid interaction of confounding factors that are impossible to control in humans. With these models of elevated IOP, unique and powerful tools to further explore the pathogenic mechanisms of glaucomatous RGC and optic fiber damage and death have been getting into the scientific landscape through the latter decades. Experimental glaucoma can be induced by a variety of techniques with the main goal of elevating the IOP, leading to RGCs and axonal damage (Fig. **3**). The most utilized experimental glaucoma models have been set up in rats and rabbits by means of the cauterization of the limbal veins [96, 97], the hyaluronic acid intracameral seriate injections (see the Fig. **3**) [98, 99] the microbead/viscoelastic intracameral injection [100], and the magnetic latex microspheres (Polybead) [101]. Other researchers have used transgenic mice, such as the mouse glaucoma model DBA/2J (D2), which spontaneously develops elevated IOP [102]. Other species have also been used for excellent glaucoma models [103]. It has been demonstrated that OS leads to lipid peroxidation [104, 105] as well as to conformational changes of proteins [106] and nucleic acids damage with the activation of apoptotic signals causing RGCs death [107]. In this scenario, several authors that have supported the role of OS in glaucoma pathogenesis, have also investigated the protective effects of antioxidants, omega 3 fatty acids and a wide variety of natural compounds in experimental models of glaucoma, with the aim of offering alternative/adjunctive means for preventing the irreversible loss of RGCs and optic fibers in glaucoma. The main contributions are set out below.

4.1. Antioxidants

From a theoretical viewpoint ROS/NOS inhibition, together with the strengthening of antioxidant defences can help improve cell health and survival. In a rat glaucoma

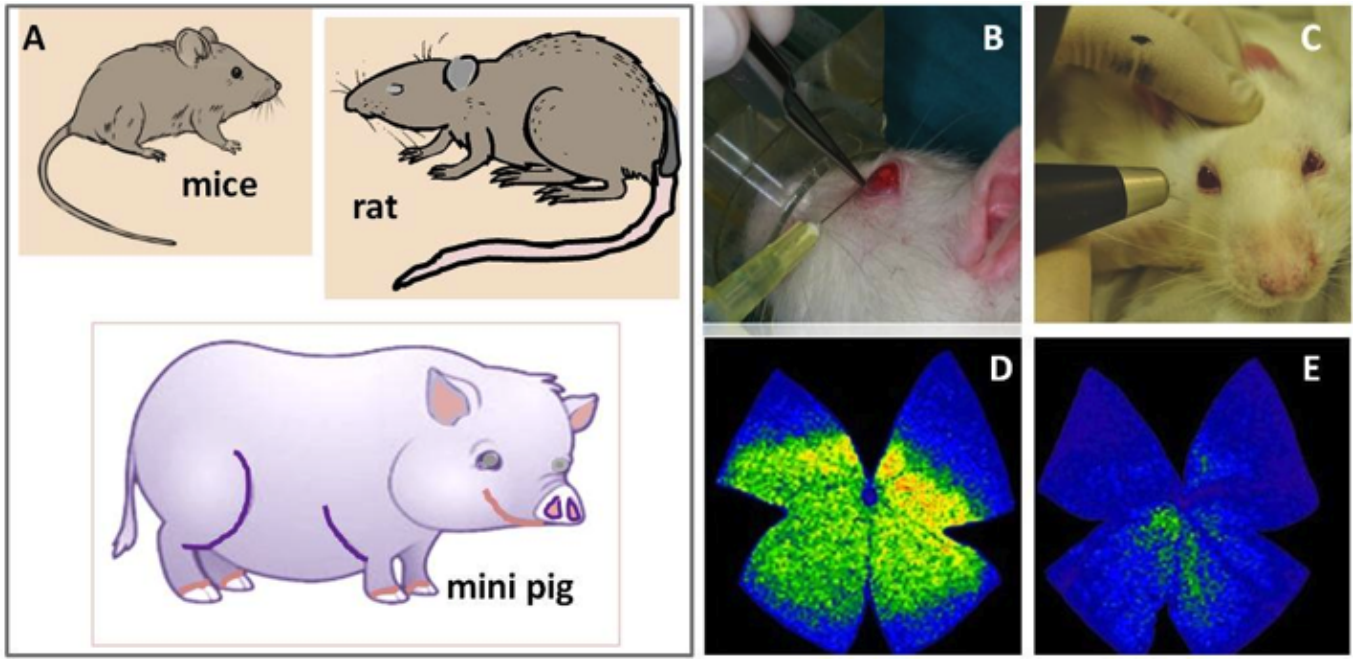

Fig. (3). Experimental glaucoma models. **A**) The most usual animal models utilized in glaucoma research have been set up in mice, rat and mini pig. **B**) Experimental rat model of chronic glaucoma by seriate intracameral injections of sodium hyaluronate in the left eye *vs* balanced salt solution injection in the sham operated right eye [92]. **C**) rat ocular tonometry. **D**) Whole mount retinal staining of the RGCs in the non glaucomatous rat eye, and **E**) showing the significant decrease in RGCs density in the induced glaucoma eye (left).

model, vitamin E-deficiency induced greater lipid peroxidation and subsequently increased RGCs death as compared to normal feed rats [108] Moreover, other researchers have developed a contact lens with extra-vitamin E loading, demonstrating the effectivity of this technique for providing antihypertensive combination therapy (timolol + dorzolamide) by contact lenses, [109]. Mice genetically predisposed to glaucoma receiving vitamin B3 in the drinking water showed signs compatible with disease prevention. In this mice glaucoma model, vitamin B3 averted early signs of glaucoma in young mice, as well as halted further glaucoma development in aged mice [110]. Xu *et al*., [111] demonstrated that vit C can help managing glaucoma progression. Ammar *et al*., [112] using primary porcine TM cells, examined the effect of the pretreatment with resveratrol, urate, ascorbate, reduced glutathione (rGSH), or ρ-coumarate after H_2O_2 exposition, concluding that these antioxidants protected TM cells from H_2O_2-induced damage. Coenzyme Q10 (CoQ10), a cofactor of the electron transport chain, is known to protect neurons against oxidative injury. Major function of CoQ10 is to stabilize the mitochondrial membrane potential, supporting ATP as well as to inhibit ROS formation. Nucci *et al*., [113], Russo *et al*., [114] and Nakajima *et al*., [115] among others, reported that CoQ10 was capable to prevent RGCs damage from elevated IOP. Moreover, in a mouse glaucoma model supplemented with CoQ10, Lee *et al*., [116] reported a significant glutamate excitotoxicity inhibition. Analyzing peroxide stress assays in human TM cells, Famili *et al*., [117] observed that samples receiving pre- and co-treatment of ethyl piruvate (a pyruvic acid ethyl ester that is utilized as a food flavoring compound with anti-inflammatory properties) showed significantly higher TM cell survival respect the non treated samples. The effects of tempol, a multifunctional antioxidant were analyzed in a rat glaucoma model. Data showed that interleukins (IL) -1, -2, interferon-γ, tumor necrosis factor-α, and NF-κB significantly descreased in the glaucoma tempol-treated eyes [99]. By means of the transgenic mouse model of glaucoma, DBA/2J (D2), and "*in vitro*" RGC cultures, Kim *et al*., [102] reported that OS enhanced mitochondrial damage and loss by increasing dynamin-related protein 1 (Drp1) in the retina of DBA/2J mice. The authors concluded that inhibiting Drp1 substantial res-

Table 5. Animal models on the effects of antioxidants, essential fatty acids and natural compounds in glaucoma.

Study (Assayed Substance)	Animal Model	References
Antioxidants: Vit E	Rat	*Ku et al. 2010* [108]
Antioxidants: Vit E	Mouse	*Hsu et al. 2015* [109]
Antioxidants: Vit C	Pig	*Xu et al., 2014* [111]
Antioxidants: Resveratrol, Urate, Ascorbate, GSH, P-Coumarate	Pig	*Amman et al,. 2012* [112]
Antioxidants: Co Q-10	Rat	*Nucci et al., 2007* [113] *Russo et al., 2008* [114] *Nakajima et al., 2008* [115]
Antioxidants: Co Q-10	Mouse	*Lee et al. 2014* [116]
Antioxidants: Tempol	Rat	*Yang et al., 2016* [100]
Essential Fatty Acids: ω-3	Rat	*Nguyen et al., 2007* [121]
Essential Fatty Acids: ω-3, Vit A	Rat	*Schnebelen et al., 2009* [124]
Essential Fatty Acids: ω-3/ω-6	Rat	*Huang et al., 2011* [125]
Natural compounds: epigallocatechin (green tea)	Rat	*Osborne 2008* [128]
Natural compounds: gallocatechin and epigallocatechin (dark green tea)	Rat	*Chu et al., 2010* [129]
Natural compounds: forskolin, homotaurine, L-carnosine	Rat	*Russo et al., 2015* [130]
Natural compounds: intravitreal (AAPH)	Mouse	*Yokohama et al., 2014* [131]
Natural compounds: Brimonidine	Rat	*Lee et al., 2012* [132]
Natural compounds: TUDCA	Rat	*Boatright et al., 2006* [113]
Natural compounds: Saffranal (saffron) and bear bile	Rat	*Fernández-Sánchez et al., 2011* [134], *2005* [135]
Natural compounds: Ginkho Biloba	Rat	*Eckert et al., 2005* [136] *Cybulska-Heinrich et al, 2012* [137]
Antioxidant: Melatonin and 5-MCA-NAT	Mouse	*Martínez-Águila et al., 2016* [118]
Antioxidant: Tempol	Mouse	*Yang et al., 2016* [119]

Abbreviations: Vit: vitamin; GSH: glutathione; Co Q-10: Coenzyme Q-10; ω-3 / ω-6: omega-3/omega-6 fatty acids; AAPH: 2,2'-azobis (2-amidinopropane) dihydrochloride; TUDCA: Taurousodeoxycholic acid; 5-MCA-NAT: 5-Methoxycarbonylamino-N-Acetyltryptamine.

cue of the RGCs and optic axons by preserving mitochondrial function and integrity was seen. All these experiments have been summarized in the Table **5**. Moreover, it has recently reported the hypotensive effects of melatonin as well as of 5-MCA-NAT, a putative melatonin MT3 receptor agonist, which effectively reduced IOP in a glaucoma model [118]. Also Yang *et al*, [119] using Tempol in a SOD1(-/-) mice model, showed that proinflammatory cytokines such as the IL-1, IL-2, IFN-γ, and TNF-α, exhibited more than 2-fold decreased titers in the Tempol-treated ocular hypertensive eyes. Evenmore, antioxidant treatment also resulted in a prominent decrease in NF-κB activation in the ocular hypertensive retina and optic nerve.

4.2. Essential Fatty Acids

Essential fatty acids, omega (ω)-6 and ω-3 are important in biomedical research because their anti-inflammatory, anti-angiogenic, antithrombotic, hypolipidemic, and vasodilatory functions [120] It has also been suggested that excessive availability of ω-6 fatty acids or a dysbalance ω-3/ω-6 ratio may induce inflammatory, metabolic, cardiovascular, cerebrovascular, or autoimmune diseases, as well as cancer, neurodegenerative disorders or ageing. Studies involving essential fatty acids in experimental glaucoma model are less abundant. Nguyen *et al*., [121] demonstrated that dietary ω-3 reduces IOP with age in response to an increased outflow facility, resulting from an increase in docosanoids availability in rats. In relation to the beneficial effects of ω-3/ω-6 fatty acids on peroxide-mediated OS responses, Tourtas *et al*., [122] studied changes of mitochondrial activity, proliferation, heat shock proteins, extracellular matrix components, and inflammatory markers in hTM cells, concluding that ω-3 appears to be beneficial respect to prophylactic intake for glaucoma prevention. Inman *et al*., [123] demonstrated that the dietary administration of the antioxidant α-lipoic acid (ALA) to DBA/2J mice resulted in a significant decreased in RGCs death and dysfunction that was measured in specific genes and proteins related to OS. In the same research line, Schebelen *et al*., [124] reported that in a rat glaucoma model the dietary intervention with both ω-6 and ω-3 is better than only single supplements for protecting against the retinal damage induced by IOP elevation. In addition, Huang *et al*., [125] published that oral supplementation with cod liver oil containing high doses of DHA to rats exerts a protective effect against glaucomatous damage. In this context, to better understand the tolerability of DHA eye injections, Dolz-Marco *et al*., [126] indicated that intravitreal DHA is safe in the albino rabbit model up to the maximum tolerated dose of 25 µg/50 µl. These data can be extrapolated to treatment, alone or in combination, of different retinal diseases including glaucoma.

4.3. Natural Substances

Natural substances including polyphenolic flavonoids present in coffee, green tea, dark chocolate or wine, anthocyanosides present in bilberries or blueberries, as well as in raspberries, blackberries, peppers, greens, grapes or tropical fruits, and other similar compounds may possess antioxidant activity, as suggested before [127]. Osborne *et al*., [128] in rat studies with oral administration of epigallocatechin demonstrated a reduced light-induced retinal neuronal death, suggesting that this substance can be useful for preventing retinal neurons damage and death. In fact, Chu *et al*., [129] in experiments with rats that drank green tea, reported that the retina absorbed the highest levels of gallocatechin, and the aqueous humor better absorbed epigallocatechin. These data confirmed that green tea consumption could protect our eyes against oxidative attack. Forskolin (Coleus) is an extract from the roots of this plant that traditionally has been utilized in ayurvedic practices. Russo *et al*., [130] intravitreally administered forskolin, homotaurine, and L-carnosine to adult male Wistar rats in which the IOP was acutely increased. These authors reported a significant neuroprotective RGCs effect associated with reduced calpain activity upregulation of phosphoinositide 3-kinase (PI3K)/Akt pathway, and inhibition of glycogen synthase kinase-3β (GSK-3β). In the same atmosphere, Yokoyama *et al*., [131] analyzed the role of calpain in C57BL/6 mice model of OS-induced RGC damage by means of intravitreal administration of 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH). Data showed that AAPH administration was an effective model for inducing OS in the RGCs. The authors also demonstrated that the inhibition of the calpain pathway significantly protected the RGCs after AAPH administration. By using brimonidine, an alpha 2-adrenergic agonist receptor, Lee *et al*., [132] demonstrated that administration of this product to rats contributes to RGCs neuroprotection. A series of natural products have been investigated in animal models of retinal degeneration. Boatright *et al*., [133] and Fernández-Sánchez *et al*., [134] evaluated the effects of a systemic injection of tauroursodeoxycholic acid (TUDCA), primary constituent of bear bile, in mouse models of retinal degeneration. Data showed that TUDCA is a substance able to protect the retinal cells from degeneration. Fernández-Sánchez *et al*., [135] reported amelioration of the induced retinal degenerative damage in P23H rats by the bear bile and by saffranal, a constituent of saffron, a plant native to the eastern Mediterranean regions (widely used to color foods and as a cooking spice) [135]. The antioxidant effects of Ginkgo biloba could be due to its poly-phenolic flavonoids contents, which might protect the tissues against OS injury. It has been reported that the organic acids of Ginkgo biloba extract may be the responsible for its antioxidant, anti-inflammatory, antiproliferative and antiallergic properties, among others. Several authors have cloncluded that Ginkgo Biloba may theoretically prevent oxidative stress in the mitochondria and thereby protect the glaucomatous RGCs [136, 137].

5. CLINICAL GLAUCOMA TRIALS OF ANTIOXIDANTS, ESSENTIAL FATTY ACIDS AND OTHER NATURAL PRODUCTS

Some oral antioxidants, such as extract of Ginkgo biloba (EGB), anthocyanins, vitamins, saffron and essential fatty acids, have been studied in different clinical trials in POAG, and normotensive glaucoma (NTG). The clinical effects of these supplementations have been estimated in terms of IOP decrease or progression of distinct parameters in automated perimetry, optical coherence tomography (OCT) or electroretinogram (ERG) and ocular blood flow (Table **6**). The ECB (containing flavonoids), has been tested mainly on NTG but also recently on POAG. Quaranta *et al* [138]

Table 6. Results of clinical trials with antioxidants, essential fatty acids and natural compounds in glaucoma patients.

Oral Antioxidant Studied	Sample Size	Outcomes in Treated Patients	Follow-up (Type of Study)	Reference
ω-3 PUFAs	40 ocular hypertensive patients (2 groups: treated vs placebo)	Improvent of global perimetric indices (blue/yellow automated perimetry)	3 months (prospective)	*Cellini et al., 1999* [148]
Epigallocatechin-gallate	18 ocular hypertensive patients and 18 POAG patients	Improvements in ERG. Automated perimetry did not show changes.	3 months (prospective)	*Falsini et al., 2009* [147]
Two AREDS-based antioxidant formulas (antioxidants + minerals) with/without ω-3 PUFAs	117 POAG patients (2 groups according to supplementation with/without ω-3 PUFAs, and a control group	No significant differences between perimetric global índices, peripapillary RNFL or macular GCC at the beginning and at the end of follow-up.	2 years (prospective)	*Garcia-Medina et al., 2015* [21]
Extract of Ginkgo biloba	35 NTG patients (2 groups: treated vs placebo)	No effect on automated perimetry or contrast sensitivity	4-8 weeks-of washout- 4 weeks (prospective, crossover study)	*Guo et al. 2014* [142]
Extract of saffron	34 POAG patients (2 groups: treated vs placebo)	IOP decrease	4 weeks (prospective)	*Jabbarpoor Bonyadi et al., 2014* [146]
Extract of Ginkgo biloba	42 NTG patients	Improvement of perimetric global indices with no changes in IOP	12 years (4 years observation + 8 years treatment) (retrospective)	*Lee et al., 2013* [140]
Combination of forskolin, homotaurine, carnosine, folic acid, vitamins (B1, B1, B6) and magnesium	22 POAG patients (2 groups: treated vs not treated)	Lower IOP and better ERG parameters and foveal sensitivity	1 year (prospective)	*Mutolo et al., 2016* [20]
Extract of blackcurrant anthocyanins	38 POAG patients (2 groups: treated vs placebo)	Improvement of MD and increase of ocular blood flow	2 years (prospective)	*Ohguro et al., 2012* [144]
Extract of blackcurrant anthocyanins	21 POAG patients (2 groups: treated vs placebo)	Lower IOP	2 years (prospective)	*Ohguro et al., 2013* [145]
Extract of blackcurrant anthocyanins	12 healthy subjects (2 groups: treated vs placebo)	Lower IOP	4 weeks-2 weeks of washout-4 weeks (prospective, crossover study)	*Ohguro et al.,2013* [145]
Extract of Ginkgo biloba	30 NTG patients (2 groups: treated vs placebo)	Increase of peripapillary retinal blood flow	4 weeks (prospective)	*Park et al., 2011* [141]
Extract of Ginkgo biloba	27 NTG patients (2 groups: treated vs not treated)	Improvement of perimetric indices without IOP changes	4 weeks (prospective)	*Quaranta et al,. 2003* [138]
Extract of Ginkgo biloba	40 POAG patients (2 groups: treated vs placebo)	Improvement of perimetric global indices, slower decrease of superior and inferior peripapillary RNFL. No changes in IOP	6 months (prospective)	*Sari et al., 2016* [143]
Extract of Ginkgo biloba or bilberry anthocyanins	332 NTG patients (3 groups according to supplementation)	Improvement of MD in both supplemented groups. Better visual acuity with anthocyanins	Almost 2 years (retrospective)	*Shim et al,. 2012* [139]

Abbreviations: AREDS, age-related eye disease study; ERG, electroretinogram; IOP, intraocular pressure; GGC, ganglion cell complex; MD, mean deviation (automated perimetry); NTG, normotensive glaucoma; POAG, primary open-angle glaucoma; ω-3: omega-3 fatty acids; PUFAs: polyunsaturated fatty acids; RNFL, retinal nerve fiber layer.

showed that oral EGB supplementation improved preexisting perimetric indices (mean deviation -MD- and pattern standard deviation -PSD-) without IOP changes in NTG patients. Later on, it was demonstrated that intake of EGB (80 mg, 2 times daily) or bilberry anthocyanins (60 mg, twice a day) during almost 2 years was associated with MD improvement in NTG patients. In addition, patients supplemented with bilberry anthocyanins exhibited a better visual acuity [139]. Another trial concluded that NTG patients with preexisting perimetric progression during a 4-year period showed attenuation of this progression in relation to EGB intake (80 mg, 2 times daily) during additional 8 years of follow-up

[140]. Moreover, 80 mg of EGB (twice daily) during 4 weeks has proved to improve peripapillary retinal blood flow in NTG patients [141]. In contrast with these results, a more recent work did not find any improvement of MD in NTG patients after supplementation with EGB (40 mg 3 times daily) in the short term (two periods of 4 weeks) [142]. The EGB has also been administrated during 6 months (40 mg 2 times daily) to POAG patients, and the results showed a significant correltion with the improvement of perimetric global indices and a slower decrease of peripapillary retinal nerve fiber layer (RNFL) thickness (superior and inferior quadrants) [143]. Additionally, other supplementations have also demonstrated positive effects in glaucoma patients. Extract of black currant anthocyanins (EBCA) during two years (50 mg per day) was related to smaller deterioration of MD and augmentation of ocular blood flow [144]. Same authors also reported that EBCA lowered the IOP both in healthy and POAG subjects [145]. Similarly, oral intake of extract of saffron (30 mg per day) for 4 weeks has been found to diminish IOP in POAG patients [146]. In addition, the 3-month intake of epigallocatechin-gallate, have showed to improve ERG parameters but not perimetric indices in hypertensive and POAG patients [147]. Otherwise, two randomized, controlled trials have been performed using different combinations of antioxidants and minerals in POAG patients. Our investigational team did not find differences between global perimetric indices, peripapillary RFNL thickness and macular ganglion cell complex thickness among the groups taking antioxidant supplements with or without ω-3 fatty acids at the beginning and at the end of 2 years of follow-up [21]. However, in a previous study Cellini *et al*., found that oral supplementation with high doses of ω-3 fatty acids for three months in hypertensive patients were related to amelioration of blue/yellow, perimetric global indices [148]. Mutolo *et al*. [20] recently concluded that the intake of a combination of forskolin, homotaurine, carnosine, folic acid, vitamins (B1, B2, B6) and magnesium during 12 months (with results quarterly checked) was associated to IOP decrease and improvement of ERG (at 6, 9 and 12 months) and foveal sensitivity obtained by frequency doubling perimetry (at 12 months).

Besides, as far as we know, some other clinical trials relating antioxidant supplementation and ω-3/ω-6 fatty acids have been completed. However, their results have not been already published [149-152].

CONCLUSION

A wide variety of studies in human and experimental animals have proven that antioxidants, ω-3/ω-6 fatty acids and some other natural compounds help regulating IOP as well as protecting the RGCs against OS/NS in glaucoma. The question arises as it is posible to incorporate these substances for glaucoma therapy. Based on the impact of antioxidants and ω-3/ω-6 fatty acids at the molecular level in the glaucomatous anterior and posterior eye segments, ongoing research have to ultimately decipher whether or not sustainable differences can exists in taking or not these supplements for glaucoma progression in order to prevent optic atrophy and irreversible blindness.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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