Ageing Research Reviews 75 (2022) 101572

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Restoring the oxidative balance in age-related diseases – An approach in glaucoma

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ARTICLE INFO

Keywords:
Age-related disease
Glaucoma
Oxidative stress
Mitochondrial dysfunction
Antioxidant therapy
Nanotechnology

ABSTRACT

As human life expectancy increases, age-related health issues including neurodegenerative diseases continue to rise. Regardless of genetic or environmental factors, many neurodegenerative conditions share common pathological mechanisms, such as oxidative stress, a hallmark of many age-related health burdens. In this review, we describe oxidative damage and mitochondrial dysfunction in glaucoma, an age-related neurodegenerative eye disease affecting 80 million people worldwide. We consider therapeutic approaches used to counteract oxidative stress in glaucoma, including untapped treatment options such as novel plant-derived antioxidant compounds that can reduce oxidative stress and prevent neuronal loss. We summarize the current pre-clinical models and clinical work exploring the therapeutic potential of a range of candidate plant-derived antioxidant compounds. Finally, we explore advances in drug delivery systems, particular those employing nanotechnology-based carriers which hold significant promise as a carrier for antioxidants to treat age-related disease, thus reviewing the key current state of all of the aspects required towards translation.

1. Oxidative balance in ageing and glaucoma

With the current global demographic increase in life expectancy, the social and economic burden of age-related diseases including those causing vision loss are projected to increase significantly (Flaxman et al., 2017). Oxidative stress has been postulated to play an important role in the rate of ageing as oxidative damage contributes to the essential components in pathological pathways, which are thought to drive multiple age-related diseases. Mitochondrial dysfunction driving oxidative stress have been implicated in a number of age-related neurodegenerative diseases, including glaucoma (Chrysostomou et al., 2013; Lawler et al., 2019; Osborne, 2010; Tezel, 2006) and may represent a point of convergence that can be targeted regardless of the causative factors in individual patients.

Glaucoma, a leading age-related cause of irreversible blindness is predicted to affect more than 110 million people by 2040 (Tham et al., 2014; Tosun et al., 2014). Although a host of population-based studies have established key risk factors for glaucoma (age, ethnicity, intraocular pressure, family history and genetics, thinner central corneal thickness) (Jonas et al., 2017; Kreft et al., 2019), how such risk factors impact retinal ganglion cells (RGC) and axonal health is still unclear. Thus, the mechanisms of RGC injury and death are still being elucidated; although a range of age-related biomechanical (Stowell et al., 2017), vascular/bioenergetic (Flammer et al., 2002) and immune factors have been implicated alongside age-related decline in mitochondria function and increased oxidative stress (Osborne, 2010). Emerging evidence from recent genome wide association and other genetic studies support the common pathological role of mitochondrial dysfunction, showing a link between mutations in mitochondrial DNA (mtDNA) and in nuclear DNA genes that encode mitochondrial proteins (e.g., OPA1, MFN1, MFN2, CYP1B1, PARL, SOD2, SRBD1, GST, NOS3, TNF-α and TP53) and glaucoma pathogenesis.

Despite great progress in the field, there are as yet no viable treatments for glaucoma targeting oxidative stress. Thus, an urgent and growing need for novel therapeutic approaches remains, as many individuals continue to lose vision despite some success with current surgical treatments (lowering intraocular pressure).

Here, we summarise the current evidence and understanding for the role of oxidative stress induced glaucomatous injury, and provide a review focused on advancing antioxidant strategies. In order to achieve tangible human benefit, we present the current state of approaches along the translational journey. These include highlighting the utility of

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https://doi.org/10.1016/j.arr.2022.101572
Received 17 June 2021; Received in revised form 10 December 2021; Accepted 18 January 2022
Available online 20 January 2022
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different preclinical animal models of glaucoma, for assessing novel treatment approaches and current and developing delivery technology required for translation. The principles and approaches reviewed here will have particular relevance to distinct age-related systemic and organ specific diseases that are also driven by increased oxidative stress, particularly in the ageing human world population.

1.1. Physiological reactive oxygen species production

Reactive oxygen species (ROS), produced by several organelles, are generated as a by-product of physiological functions. Mitochondrial oxidative phosphorylation (OXPHOS) uses electrons to pump protons from the mitochondrial matrix to the inter- membrane space, thus creating potential energy for Adenosine triphosphate (ATP) generation (Kamel et al., 2017). Inefficiencies in this process leads to electron leakage, which reacts with O_2 to form oxygen free radicals (Ferrington et al., 2020; Nita and Grzybowski, 2016; Zhao et al., 2016). Leakage of electrons can occur via flavin-dependent enzymes or OXPHOS complex I (Nita and Grzybowski, 2016). Peroxisomes are very dynamic and metabolically active organelles, and can generate ROS, hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet -}$) and hydroxyl radicals ($HO^{\bullet}$) (Sandalio et al., 2013). These organelles contain enzymes including flavoenzymes, xanthine oxidase and oxidoreductases that support production of key metabolites including fatty acids, amino acid, glyoxylate/dicarboxylates and spermidine, a stimulator of autophagy (Henríquez-Olguin et al., 2019; Zhao et al., 2016). The endoplasmic reticulum (ER) has a unique oxidizing environment important for protein production. Under ER-associated stress conditions, increased ROS generation can occur via electron leakage from cytochrome P450 mono-oxygenases (Zeeshan et al., 2016; Zhao et al., 2016). P450 is responsible for synthesis and degradation of endogenous substances and detoxification of xenobiotics and lipophilic compounds by hydroxylation. Finally, within the cell cytosol, ROS are also produced by several pathways. ROS are a by-product of arachidonic acid metabolism, generated for example by NADPH oxidase (NOX) and xanthine oxidase (Henríquez-Olguin et al., 2019). Ferrous iron reacts with H_2O_2 and, via the Fenton reaction to generate hydroxyl radicals ($HO^{\bullet}$), and hydroxide (HO^{-}) (Zhao et al., 2016). Furthermore, superoxides can be a by-product of arachidonic acid metabolism by cyclooxygenase and lipoxygenase enzymes. ROS production throughout cells reflect their normal role in cell signaling, however excessive ROS buildup results in oxidative stress which can result in cellular damage (Nita and Grzybowski, 2016). Growing evidence suggests a crucial connection between ROS formation and age-related disorders, including cardiovascular and neurodegenerative diseases as well as cancer (Madreiter-Sokolowski et al., 2020).

1.2. Mitochondrial function in the eye

Mitochondria are responsible for many metabolic processes that are critical for cellular health, including OXPHOS and mitochondrial fatty acid β-oxidation (FAO) (Gomes et al., 2020; Kamel et al., 2017; Lascaratos et al., 2012; Luo et al., 2020; Osborne et al., 2016). Mitochondria

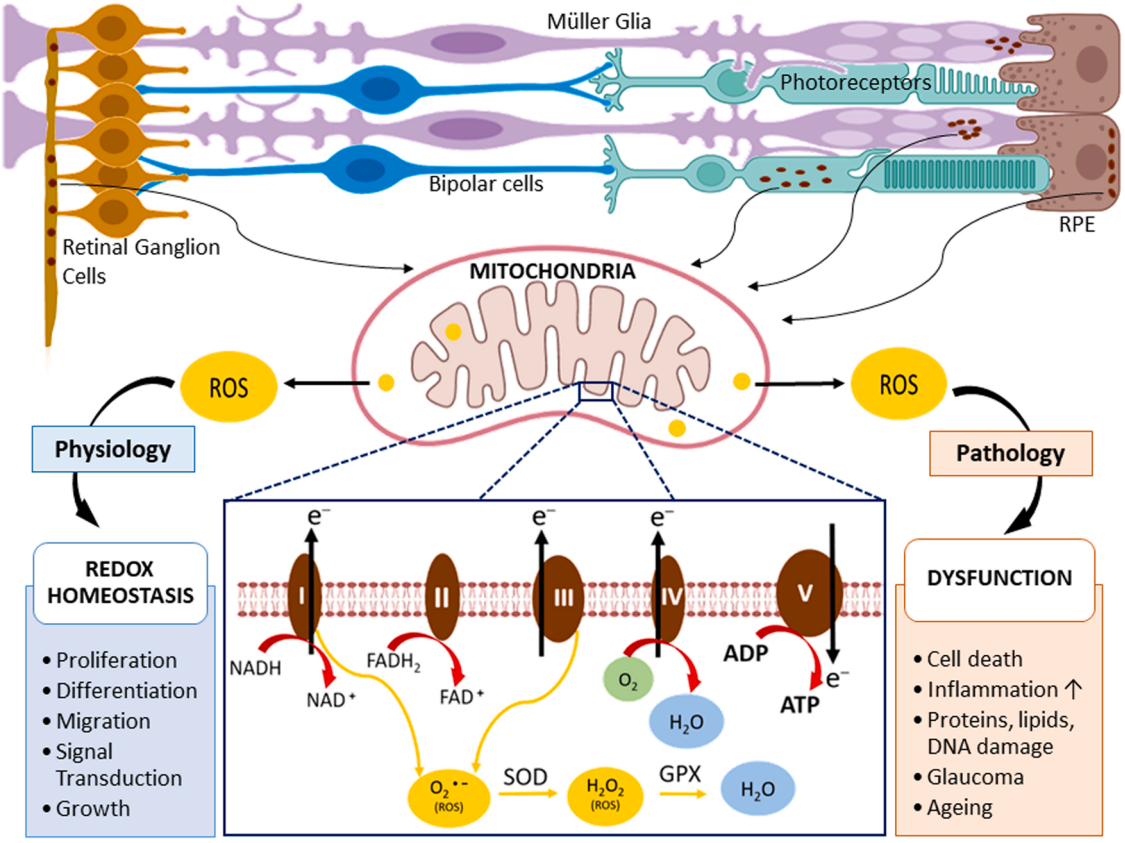

Fig. 1. Mitochondria in the eye. Retinal ganglion cells, Müller glia, photoreceptors, and retinal pigment epithelium (RPE) cells contain high numbers of mitochondria (brown dots). These cells exist in a highly oxidative environment being exposed to light and high local oxygen levels. Mitochondria are the major source of endogenous ROS (yellow circles), which can be a by-product of oxidative phosphorylation (blue square) for ATP production. During mitochondrial respiration, ROS ($O_2^{\bullet -}$, H_2O_2) can be also produced when high-energy electrons escape before they reach the final acceptor O_2 (green). The maintenance of redox homeostasis is important for cellular health as ROS play a key role in cell physiology (blue box on the left) determines the proper course of a number of vital cell processes. Age-related redox imbalance and excessive accumulation can further damage cell and their organelles, leading cell death and increased risk of disease (orange box on the right). Some figure aspects were created with BioRender.com.
Adapted from Lefevere et al. (2017).

also play a pivotal role regulating cell survival and death signaling pathways (Fig. 1), intracellular pH maintenance, calcium signaling, neuronal excitability, balancing ROS production and detoxification, and control of synaptic transmission (Eells, 2019; Lascaratos et al., 2012; Osborne et al., 2016; Pinazo-Durán et al., 2015). Not surprisingly, age-related decline in mitochondrial function and dynamics have been associated with age-related diseases such as glaucoma. Mitochondria are abundant in metabolically active tissues, including the central nervous system (CNS), retina and optic nerve (Kamel et al., 2017; Lefevere et al., 2017; Toft-Kehler et al., 2017). Tissues with high metabolic demands are particularly susceptible to periods when bioenergetic supply falls below minimum thresholds (Luo et al., 2020). Unlike some cells that can maintain sufficient ATP production through mitochondria-independent processes like glycolysis (Osborne et al., 2014), neurons have an absolute requirement for mitochondrial function for maintenance of transmembrane ion gradients and survival (Eells, 2019; Osborne et al., 2014; Tao et al., 2019). Within the eye high mitochondrial density can be found within the retinal pigment epithelium, photoreceptors, Müller glia and also in the unmyelinated axons of RGCs (Lefevere et al., 2017; Toft-Kehler et al., 2017) (Fig. 1). Lacking alternate energy stores, even brief periods of impaired substrate supply from mitochondrial respiration leads to cellular dysfunction and subsequent cell death (Osborne et al., 2014; Tao et al., 2019) (Fig. 1). Thus, not surprisingly, age-related decline in mitochondrial function and dynamics have been associated with age-related diseases including in metabolically demanding retinal cells in the eye. However, while observational studies find detrimental effects of high oxidative stress levels on glaucoma disease status, randomized clinical trials examining the beneficial effect of antioxidant supplementation has generally shown null effects (Luo et al., 2020). These conflicting results could be due differences in participant selection and a lack of reliability and specificity of traditionally used biomarkers for measuring oxidative stress and highlight the need for combining current data and developing standardized comparable models.

1.3. Balancing reactive oxygen species and antioxidants

Abnormally elevated ROS production can arise from age-related mitochondrial dysfunction via a number of pathways, including enzymatic degradation of neurotransmitters, neuroinflammatory mediators, redox reactions (Halliwell, 2006), abnormal protein folding, phagocytosis, and defective ubiquitination and proteasome degradation systems (Andersen, 2004; Zhao et al., 2016) as well as external sources (Pinazo-Durán et al., 2015). In order to maintain the appropriate ROS balance, organisms employ (Martins et al., 2016) a range of enzymatic (e.g. Catalase, Glutathione peroxidase, Superoxide dismutase, metallothionines, glutathione transferase) and nonenzymatic (e.g. glutathione, vitamin C, vitamin E, beta-carotene) antioxidants (Birben et al., 2012; Kapravelou et al., 2015; Martins et al., 2016; Nita and Grzybowski, 2016; Osborne et al., 2016; Valko et al., 2007). When ROS balance cannot be maintained, oxidative stress leads to cell damage and eventually death by oxidation of cellular proteins, lipids as well as nuclear/mitochondrial DNA (Butterfield et al., 2002; Cross and Templeton, 2004; Lascaratos et al., 2012; Osborne et al., 2014; Sohal et al., 2000) (Fig. 1). In addition to being a trigger, a spiral of ROS accumulation is also a consequence of neurodegeneration (Almasieh et al., 2012).

Oxidative damage and ROS production can be exacerbated by interactions with exogenous agents, such as ultraviolet radiation, toxic substances, cigarette smoking, pollutants, X-rays, chemotherapies and inflammation (Pinazo-Duran et al., 2017; Zhao et al., 2016). For example, UV-irradiation can damage mitochondrial DNA (mtDNA) resulting in increased ROS production. Infrared light absorbed by the mitochondrial electron transport chain, can also increase electron leakage into the mitochondrial matrix. Importantly, mtDNA is particularly vulnerable to oxidative stress due to a number of key factors; proximity to OXPHOS enzymes, limited mtDNA repair mechanisms and lack of protective histones (Ferrington et al., 2020; Kamel et al., 2017; Lascaratos et al., 2012; Nita and Grzybowski, 2016). Less effective repair system for mtDNA may result in age-related accumulation of errors with subsequent fission events, thus increasing electron leakage and oxidative stress. In addition, a wide variety of nuclear transcription factors with are present in mitochondria, including p53, nuclear factor kappa B, and the signal transducer and activator of transcription (STAT), all of which play significant roles in regulating mitochondrial function and ROS levels (Pinazo-Durán et al., 2015). Mitochondrial oxidative stress can also accelerate the release of cytochrome C to the cytosol, thereby activating apoptosis. Thus, age-related reduction in mtDNA repair is thought to be a contributor to a number of neurodegenerative diseases, including those affecting the outer retina and glaucoma (Lefevere et al., 2017; Nita and Grzybowski, 2016).

2. Mechanisms of oxidative damage in ageing and glaucoma

2.1. Evidence for oxidative stress and mitochondrial dysfunction

Within ocular fluids and tissues, enzymatic superoxide dismutase are present to convert reactive $O_2^{\bullet -}$ to oxygen (O_2) and H_2O_2, which in turn is removed by catalase or by glutathione peroxidase (Aslan et al., 2013; Lawler et al., 2019). Although there appears to be an upregulation of the antioxidant enzymes, superoxide dismutase and glutathione peroxidase with age, the levels of nonenzymatic antioxidants, vitamin C and vitamin E are significantly reduced (Bourdel-Marchasson et al., 2001). Other studies have found decreased superoxide dismutase activity in the trabecular meshwork of patients with glaucoma (Behndig et al., 1998; De La Paz and Epstein, 1996). Moreover, overall antioxidant status has been found to be lower in aqueous humor (Nucci et al., 2013; Sorkhabi et al., 2011), blood (Nucci et al., 2013; Pinazo-Durán et al., 2013) and plasma samples obtained from subjects with glaucoma (Abu-Amero et al., 2016a; Mousa et al., 2015).

Consistent with reduced antioxidant activity, specific biomarkers of oxidative stress are increased. From aqueous humor samples, increased levels of protein carbonyls, advanced glycation end products (Hondur et al., 2017), malondialdehyde (Nucci et al., 2013), and the oxidative DNA damage marker 8-hydroxy-2-deoxyguanosine (8-OHdG) have been observed (Sorkhabi et al., 2011). Blood samples from those with open angle glaucoma over the age of 55 show an increase in oxidative stress markers (Hondur et al., 2017; Nucci et al., 2013; Yaz et al., 2019), and specifically in pseudoexfoliation glaucoma there appears to be a reduction in superoxide dismutase and catalase (Yaz et al., 2019). Assessment of plasma samples also show some differences, with increased myeloperoxidase (Yıldırım et al., 2005), but unchanged catalase and malondialdehyde levels in those with open angle glaucoma (Yıldırım et al., 2005). There have also been reports that increases in 8-OHdG is associated with higher risk of visual field progression in normal tension glaucoma (Yuki and Tsubota, 2013). Previously, Van Bergen et al. (2015) found that OXPHOS Complex-I linked respiration was reduced in lymphoblasts derived from human individuals with POAG, consistent with impaired mitochondrial function. These finding have led to a body of research targeting blood levels of oxidised proteins or oxidative stress end products as a biomarker for glaucoma diagnosis (Hondur et al., 2017).

There is also growing evidence that gene mutations associated with mitochondrial dysfunction and thus oxidative stress are major contributors to the pathogenesis of many age-related diseases including glaucoma. When mitochondrial energy generation drops below critical thresholds (Gomes et al., 2020), mitophagy and mtDNA replication can be perturbed leading to accumulation of somatic mtDNA mutations. This would result in progressive decline of mitochondrial function and increased risk of ROS generation with age (Luo et al., 2020).

In addition to key genetic risk factors initially identified through classical family inheritance studies such as myocilin, optineurin, TANK-binding kinase 1 (TBK1) (Springelkamp et al., 2017; Trivli et al., 2020),

recent genome wide association studies have uncovered > 70 new single nucleotide polymorphisms (SNPs) linked to increased glaucoma risk (Liu and Allingham, 2017; Wiggs and Pasquale, 2017). Several of these gene candidates are involved in the regulation of mitochondrial health, which is critical for preventing oxidative stress (Bailey et al., 2016; Springelkamp et al., 2017; Trivli et al., 2020; Wiggs and Pasquale, 2017). Optineurin and TBK1 are associated with normal tension glaucoma and play critical roles in autophagy of used or damaged mitochondria (Minegishi et al., 2016). Slow mitochondria turnover increases the chance of electron leakage and ROS production. Thioredoxin reductase 2 (TXNRD2) has been associated with primary open angle glaucoma and is important for reducing the levels of ROS generated by OXPHOS and other mitochondrial functions (Bailey et al., 2016).

2.2. Mechanism of retinal ganglion cell injury in glaucoma

Although it is accepted that RGC death in glaucoma occurs via apoptosis (Maes et al., 2017; Nickells, 2007), a range of mechanisms may drive changes to synapses, dendrites, axons and cell soma prior to cell death. Extensive histological and molecular genetics studies have shown that the site of initial RGC injury due to ocular hypertension is to the axons at the lamina cribrosa (Howell et al., 2013; Quigley et al., 1983, 1981). IOP elevation has been well documented to impede anterograde and retrograde axonal transport (Fahy et al., 2015) including the movement of mitochondria (Takihara et al., 2015) at the optic nerve head in human glaucoma, and experimental models in non-human primates (Anderson and Hendrickson, 1974; Knox, 2007; Quigley and Addicks, 1980), and rodents (Kim et al., 2004; Pease et al., 2000; Quigley et al., 2000; Salinas-Navarro et al., 2010, 2009). Apoptosis can be reduced if the axonal transport blockage at the optic nerve head is reversed (Yokota et al., 2015). Whilst the initial injury to RGCs is at the axonal level, Simon et al. (2016) have shown that there are interactions between RGC compartments, whereby anterograde signaling from the cell body actively regulates axonal degeneration (Crish et al., 2010).

The RGC soma undergoes apoptosis when it is injured (Maes et al., 2017; Nickells, 2007), via activation and translocation of BAX to the mitochondrion leading to cytochrome c release, caspase activation and cell death (Chang et al., 2002). Libby et al. (2005) showed that blocking the pro-apoptotic *Bax* gene (BCL2 family) in a mouse model of glaucoma prevented RGC soma degeneration. Injury to axons at the level of the optic nerve may trigger an active process of Wallerian degeneration. Indeed, the Wallerian degeneration slow allele, Wld^{S}, is a Ube4b/NMNAT1 chimeric gene that has been shown to be protective of RGC axons (Mack et al., 2001) following optic nerve crush (Howell et al., 2007) and in DBA/2 J mice (Harder et al., 2017a, 2017b).

It is increasingly understood that injury or adaptive changes occur to RGCs prior to cell death, including reduction in the number and strength of synaptic connections and dendritic field size and axonal degeneration. In a non-human primate model of glaucoma, Weber et al. (1998) found reduced size and complexity of dendritic arbors, prior to axonal and somal changes. Dendritic alteration were associated with reduced responsiveness in RGCs to visual stimuli (Weber and Harman, 2005). In the DBA/2 J mouse, synapse loss and dendrite remodelling occur early and almost at the same time (Berry et al., 2015). Similarly, early dendritic retraction and remodelling has also been shown in rat (Morgan et al., 2016) and cat (Shou et al., 2003) glaucoma models. Fu et al. (2009) showed reduced RGC expression of c-fos, a neuronal connectivity marker, 5 days after laser-induced ocular hypertension, providing further support of synaptic disconnection prior to cell death. RNA-Sequencing has also detected early transcriptional changes in axonal and synaptic pathways in DBA/2 J mice, prior to ON degeneration (Williams et al., 2017c). The involvement of oxidative stress in driving synaptic and dendritic changes to RGCs are still being elucidated, with caspase-dependent, complement-driven pruning of synapses (Ren and Danias, 2010; Rosen and Stevens, 2010), and bioenergetic deficiency (such as reduced levels of NAD^{+}) all being potential pathways of investigation (Inman and Harun-Or-Rashid, 2017; Schoenmann et al., 2010).

2.3. Effects of oxidative stress on retinal ganglion cells

Retinal explants have been used to model an in vivo-like interaction between retinal cells (Bull et al., 2011). Kimball et al. (2017) demonstrated in a mouse eye and optic nerve explant, that chronic IOP elevation of 14 h or longer led to progressive RGC axonal degeneration. After 3 days of IOP elevation, there was an increase in mitochondrial density behind the optic nerve head presumably from anterograde and retrograde axonal transport disruption. Older mice (14 months) demonstrated a greater reduction in mitochondrial movement compared to young mice (4 months) following chronic IOP elevation (Kimball et al., 2018). Hurst et al. (2017) showed in a porcine *ex vivo* retinal culture model that H_2O_2 (to induce oxidative stress) caused RGC apoptosis and increase in TNF-a expression on Day 8 (Hurst et al., 2017). Yu et al. (2019) found reduced SIRT6 expression in RGCs following H_2O_2. Conversely, overexpression of SIRT6 improved RGC survival and reduced ROS production in RGCs by promoting the Nrf2/Antioxidant Response Element signaling pathway, an important mediator of oxidative stress (Petri et al., 2012). Indeed, it has been recently shown that Nrf2 expression is down-regulated in human glaucomatous trabecular meshwork cells compared to controls (Cheng et al., 2017) and a rat glaucoma model (Hvozda Arana et al., 2020). The activation of the Nrf2/HO-1 pathway also protected RGCs in a rat model of ocular hypertension(Wang and Yuan, 2019), highlighting a new potential therapeutic target for the disease.

Glaucomatous oxidative stress has also been examined extensively in a range of in vivo glaucoma models (Pang and Clark, 2020) as summarized in Tables 1 and 2. Acute moderate IOP elevation as sub-ischaemic “stress test” causes RGC dysfunction, increased expression of the oxidative stress marker HO-1, and reduced BDNF levels in the retina after injury that is more pronounced in older mouse eyes (Bui et al., 2005; Chrysostomou et al., 2016; Crowston et al., 2015; Kong et al., 2012). Similarly, mitochondrial dysfunction, reduced antioxidant capacity and reduced protein expression for glutathione metabolism has been observed in chronic IOP elevation induced by intracameral microbead injection in mouse eye (Mirzaei et al., 2020; Yang et al., 2016). Injection of hyaluronic acid to elevate IOP by impeding trabecular outflow results in decreased total retinal superoxide dismutase and catalase activity and decreased glutathione levels (Moreno et al., 2004). Moreno et al. (2004) demonstrated reduced levels of SOD using the hyaluronic acid model in rat. Indeed, SOD1 knockout mice show increased RGC vulnerability compared to wild-type (Yuki et al., 2011), with dysfunctional mitochondria and progressive retinal dysfunction (Hashizume et al., 2008).

It is of note that similar signs of oxidative stress are also found with severe injury induced by optic nerve crush (O’Hare Doig et al., 2014) or transection. In the ischaemia/reperfusion model, whereby IOP is increased to ischaemic (100–110 mmHg) levels for ~1 h, there is evidence of microglial activation, increased caspase-3 activity and abnormal accumulation of ROS (Ju et al., 2018; Lafuente et al., 2002). Thus, accumulation of ROS can be a consequence of severe cell injury and death that leads to further damage.

Transgenic mouse models of glaucoma also show signs of oxidative stress. Of the genetic models, DBA/2 J mice have been most widely studied for oxidative stress. The DBA/2 J mouse phenotype arises due to mutations in the $Gpnmb^{R150X}$ $Tyrp1^{isa}$ alleles, and as such, develop a pigment dispersion-like glaucoma, with high IOP, RGC dysfunction and cell loss as the mice age (Moon et al., 2005; Saleh et al., 2007). With age, there is reduced axonal transport, increased autophagic activity, mitochondrial fission and dysfunction (Kleesattel et al., 2015a, 2015b). Baltan et al. (2010) found that DBA/2J mice had reduced optic nerve ATP levels, reduced mitochondrial oxidative capacity, and increased

Table 1
Oxidative stress in rodent glaucoma models.

Rodent model	Method/Gene	Findings
Pressure-dependent models		
Ischaemia-reperfusion injury	Increase IOP to ischaemic levels (>70 mmHg) for ~1 h	Gradual RGC loss over weeks following transient ischaemia; astroglial and microglial activation, increased caspase-3 activity, abnormal accumulation of ROS. (Ju et al., 2018; Lafuente et al., 2002)
Acute IOP elevation	Intracameral saline infusion (sub-ischaemic 50 mmHg for 30 min)	Age-dependent RGC dysfunction, astrocytic gliosis, upregulation of GFAP and increased retinal expression of oxidative stress marker HO-1, reduced BDNF. (Bui et al., 2005; Chrysostomou et al., 2016; Crowston et al., 2015; Kong et al., 2012)
Chronic IOP elevation	Intracameral injection Microbeads	Reduced antioxidants and glutathione metabolism, mitochondrial dysfunction, increased apoptosis, oxidative stress. Increased pro-inflammatory cytokines, RGC axon cell loss. (Mirzaei et al., 2020; Yang et al., 2016)
	Intracameral injection Hyaluronic acid	Decrease total retinal superoxide dismutase and catalase activity. Increased glutathione peroxidase (GPX) activity, decreased glutathione (GSH) levels. (Moreno et al., 2004)
	Hypertonic saline injection	Oxidative modification of retinal proteins in ocular hypertensive eyes. (Tezel et al., 2005)
	Laser photocoagulation	Selective hypoxia and axonal transport disruption, upregulation of ceruloplasmin and active subunit of the superoxide-generating enzyme NADPH oxidase, increased superoxide radicals. (Chidlow et al., 2017)
	Episcleral vein cauterization	Increased superoxide dismutases and catalase activity. Increased chemiluminescence, nitrite concentration (NC), and lipid peroxidation markers (TBARS); reduced total antioxidant capacity. (Ferreira et al., 2010; Ko et al., 2005)
Pressure-independent models		
Optic nerve transection or crush	Partial or complete crush/ cut of the optic nerve	Modest increases in antioxidant enzymes, increases in ROS and oxidative damage to DNA, lipid, and protein, increasing abnormal mitochondria. Early changes to oxidative stress-associated enzyme MnSOD after injury, changes to calcium ion distribution pattern. (O'Hare Doig et al., 2014; Wells et al., 2012)
Intravitreal injections	TNF-α injection	Oligodendrocyte death, delayed RGC loss. (Nakazawa et al., 2006)
	2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH)	Induces oxidative stress, activated calpain pathway and caused significant RGC loss 7 days after treatment. Inhibition of calpain pathway protected RGCs from AAPH. (Yokoyama et al., 2014)
Genetic models		
DBA/2 J mice		Gradually develops increased IOP with age, iris transillumination, RGC loss. Reduced anterograde axonal transport, increased autophagic activity, and a dissociation of the relationship between axon and mitochondrial volumes. Reduced optic nerve ATP levels. Reduced mitochondrial cristae volume in RGC somal and dendritic mitochondria; reduced mitochondrial oxidative capacity. (Baltan et al., 2010; Coughlin et al., 2015; Ju et al., 2008; Kleesattel et al., 2015a, 2015b; Williams et al., 2017c)
	Alleles contributing to phenotype: *Gpnmb*^{R150X}*Tyrp1*^{isa}	
Glutamate transport protein KO mice	GLAST$^{-/-}$EEAC1$^{-/-}$	GLAST or EAAC1 KO mice show progressive RGC loss and optic nerve degeneration without increased IOP. GLAST-deficient mice: reduced GSH levels in glia. EAAC1-deficient mice: RGCs more vulnerable to oxidative stress. (Harada et al., 2020, 2007)
SOD1 KO mice	SOD1$^{-/-}$	Reduced RGCs, nerve fibre layer thinning. (Yuki et al., 2011)

Table 2
Oxidative stress in non-human primate glaucoma models.

Non-human primate model	Method/Gene	Findings
Acute IOP elevation	*Macaca fascicularis:* Anterior chamber cannulation	Obstruction of orthograde and retrograde axonal transport at the optic nerve head at 25–50 mmHg. (Minckler et al., 1977; Quigley and Anderson, 1976)
Chronic IOP elevation	Intracameral injection Microbeads	IOP elevation over 28 weeks reduced anterograde transport, RGC axons loss 22%, upregulation of complement 1q, IL-6 and BDNF. (Lambert et al., 2019)
Aged marmoset	Spontaneous glaucoma	11% developed glaucoma-like characteristics. Increased oxidative stress, reduced cerebrospinal fluid (CSF) pressure, BDNF and TrkB expression in retina, optic nerve head and CSF. (Noro et al., 2019)
Tissue culture	*Macaca mulatta:* Incubated retina in hypoxic conditions (95% N_2 and 5% CO_2)	Calpain autolysis, proteolysis of major proteins, vimentin, β-tubulin, α-enolase, and Hsp70. (Nakajima et al., 2006)

RGC vulnerability to oxygen-glucose metabolic challenge induced by IOP-elevation. Notably, bioenergetic deficiency occurred prior to signs of axonal pathology. In line with this, Williams et al. (2017c) reported significant mitochondrial dysfunction and reduction in NAD^+ levels in the retina of DBA/2J mice that worsened with disease progression. Using scanning electron microscopy, Kleesattel et al. (2015a), (2015b) found that anterograde axonal transport was reduced in DBA/2J mice, along with a dissociation of the tight relationship between axon and mitochondrial volumes. Williams et al. (2017b) have shown that bioenergetic substances to support mitochondrial function, such as nicotinamide, or via gene therapy targeting *NAMPT* prevents RGC loss. Similarly, some antioxidant studies have been performed in DBA/2J mice as described in the Section 3.1.

In a glutamate transport protein knockout model, mice that are

deficient of the glutamate transporters, GLAST or EEAC1, showed progressive RGC loss and reduced glutathione levels in glia (Harada et al., 2020, 2007). Thus, existing animal models of glaucoma support the oxidative and mitochondrial changes implicated from the human samples, highlighting the interactions with RGCs and demonstrate the relevance and use of preclinical models.

2.4. Role of neurotrophins in mitigating oxidative stress induced retinal ganglion cell injury in glaucoma

Neurotrophins, either retina-derived or retrogradely transported, play an important role in RGC health and survival. Of the neurotrophins, brain-derived neurotrophic factor (BDNF), NT3/4/5 and NGF are found in the optic nerve and have been shown to change with chronic IOP elevation (Guo et al., 2011; Quigley et al., 2000; Rudzinski et al., 2004). The receptors for neurotrophins, TrkC, TrkA and $p75^{NTR}$ are also altered (Cui et al., 2002; Guo et al., 2011; Lebrun-Julien et al., 2009).

Severe BNDF reduction leads to cell death, however smaller changes in BDNF can regulate synaptic plasticity and memory (Arancio and Chao, 2007; Lu et al., 2008). Binley et al. (2016) demonstrated in a retinal explant model that increasing local BDNF levels can prevent dendritic retraction, before loss of the cell body. Studies of neurodegenerative conditions in the brain point to a feedback loop, whereby neurotrophic factors upregulate antioxidant enzymes and proteins (Gardiner et al., 2009). Reduced neurotrophic support will thereby increase oxidative stress. It is of interest that dietary restriction protection against age-related susceptibility to IOP elevation in mice was associated with improved mitochondrial OXPHOS activity and reduced oxidative damage (Kong et al., 2012). Williams et al. (2017a) demonstrated that *Wld*^{s} expression prevented axonal degeneration and preserved RGC function by increasing retinal bioenergetics through NAD^{+} levels. Critically, Chrysostomou et al. (2016) reported that protection of RGCs against IOP elevation in older mouse eyes with exercise was associated with improved retinal BDNF levels. Additionally, recent evidence shows a role of mesencephalic astrocyte-derived neurotrophic factor (MANF) in regulating metabolic homeostasis (Sousa-Victor et al., 2019) in ageing. Ko et al. (2021) recently discovered a potential role of MANF in protecting RGCs from oxidative stress. Therefore, restoring the feedback between neurotrophins and the antioxidant system, through improving bioenergetics may be an important target in glaucoma.

2.5. Downstream pathways of oxidative stress

Within the neural retina, reactive oxygen species can impact a range of cellular pathways to modify RGC health, including nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), neurotrophic factor production and neuroinflammation. There is strong evidence that ROS can activate the immune response (Harder et al., 2017a, 2017b; Williams et al., 2017) by causing antigen-specific immune responses in retinal glial cells (Tezel et al., 2007). For example, activation of the innate immune system via lipopolysaccharide injection into the brain leads to an acute, increase in oxidative stress and degeneration of dendrites (Milatovic et al., 2004). It is known that IOP elevation can activate microglia to release inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-12 (De Hoz et al., 2018; González et al., 2014), which leads to the production of nitric oxide and ROS (De Hoz et al., 2018; Wang et al., 2014). Indeed, it has been recently shown that individuals with POAG had higher serum levels of IL-6, and the ratio of IL-6/IL-10 levels could be potentially useful in discriminating POAG severity (Ulhaq et al., 2021). Whilst the immune response can be initially neuroprotective, an overactive immune response may induce RGC death via direct activation of apoptotic pathways.

A role for glial cells in glaucoma pathogenesis has long been recognized, with age-related activation of optic nerve astrocytes strongly associated with connective tissue remodelling and glaucomatous damage (Hernandez, 2000, 1997) in human glaucoma (Johnson et al., 2000; Minckler, 1981) and preclinical models of elevated IOP (Inman and Horner, 2007). Astrocytes produce a range of molecules including NO, TNF-α, cytokines (IL-6), and endothelins that are potentially directly or indirectly neurotoxic to RGC axons (Johnson et al., 2011; Neufeld, 1997; Yuan and Neufeld, 2000). In addition to astrocytes, retinal macroglia, and Müller cells can also be activated by oxidative stress (Bringmann et al., 2009). Reactive Müller glia could increase the susceptibility of RGCs to stress signals and contribute to disease progression. Indeed, it has been shown that TNF-α is upregulated by Müller cells and glia through EphrinB/EphB signaling in models of elevated IOP (Cueva Vargas et al., 2015; Liu et al., 2018).

Microglia are resident immune cells and play an important role in the innate immune response. However, the activation of microglia can damage RGCs due to their ability to secrete TNF-α, cytokines and ROS (Hanisch and Kettenmann, 2007). Guttenplan et al. (2020) showed that by inhibiting the microglial secretions of TNF-α, complement 1q and IL-1α, it could prevent the formation of neuroinflammatory reactive astrocytes and was neuroprotective against optic nerve crush. Studies have shown activation of microglia in early disease in DBA/2 J mice (Bosco et al., 2011). Ebneter et al. (2010) found in a laser photocoagulation model of IOP elevation in the rat, that microglia activation was associated with axonal damage. Bosco et al. treated DBA/2 J mice with minocycline to reduce microglial activation, which resulted in improved axonal transport and increased RGC survival (Bosco et al., 2008). A deficiency in chemokine fractalkine receptor Cx3cr1 enhanced the neurotoxic effects of microglia activation, leading to greater RGC loss in a mouse model of glaucoma (Wang et al., 2014). Recently, Aires et al. (2019) demonstrated that blocking microglial adenosine A_{2A} receptors decreased microglial proliferation and release of pro-inflammatory mediators in response to elevated hydrostatic pressure in retinal cells. Liddelow et al. (2017) showed that microglia are important in mediating the transition of a subtype of reactive astrocytes (A1) from a protective to a neurotoxic phenotype by secreting TNF-α, complement 1q and IL-1α. Thus, modulating the neuroinflammatory sequalae of age and IOP-related stress may help to restore oxidative balance.

3. Neuroprotective strategies to modulate oxidative stress

Environmental factors, including nutrition can have a profound effect on cellular health. Thus, the role of caloric restriction (CR) (Luo et al., 2020) and extrinsic antioxidants (Garcia-Medina et al., 2020) has been explored as preventive and therapeutic strategies in ageing and age-related disease.

CR has been reported to increase longevity and has potential benefits in injury and disease. CR causes life extension through mechanisms that involve different nutrient-signaling pathways, such as those of the mammalian target of rapamycin (mTOR), the insulin-like growth factor 1 (IGF-1), and the sirtuins. Sirtuins are a family of seven proteins (SIRT1–7) with different NAD^{+}-dependent enzymatic activities, expressed in several tissues (Luo et al., 2020). Importantly, Sirtuin 1 (SIRT1) is activated by the upregulation of endothelial nitric oxide synthase (eNOS), which is a very important effector of CR. SIRT1 has been associated with biogenesis and turnover of mitochondria, aging, oxidative stress, and neurodegenerative diseases such as glaucoma (Zhou et al., 2018). Recent evidence indicates that regulating SIRT3 can confer neuroprotection by reducing mitochondrial ROS production and oxidative stress in ageing (Xie et al., 2017) and neurodegenerative diseases including Parkinson's disease (Shen et al., 2020) and Huntington's disease (Naia et al., 2021). In the retina, SIRT3 deficiency has been linked to significant retinal dysfunction in a model of diabetes (Lin et al., 2019) and acute photo-stress (Ban et al., 2017) but there are yet to be studies on glaucoma. Thus, targeting sirtuins continues to be investigated for age-related diseases.

A lack of exogenous antioxidant supply in our modern diet can contribute to oxidative stress particularly in ageing (Martins et al., 2016). Indeed, plant-derived antioxidants such as resveratrol-like

compounds can stimulate sirtuins (Mayack et al., 2020), thus reducing oxidative stress. Given our growing understanding of the oxidative stress pathogenesis in glaucoma (McMonnies, 2018), there has been considerable interest in strategies to enhance the antioxidant system (Gauthier and Liu, 2016; Ramdas et al., 2012; Szwajgier et al., 2017) and to improve mitochondria function in glaucoma (Almasieh et al., 2012), particular focused on delivery of exogenous antioxidant sources. A range of potential exogenous antioxidants for glaucoma are starting to be tested. While many different models have been and continue to be developed (Martins et al., 2016), it is clear that for cross- study comparison, standardization of in vitro and in vivo preclinical models will be useful (Martins et al., 2016). Whilst many studies show potential benefit of botanical compounds (Richardson et al., 2017), for the majority of such compounds there remains significant gaps in understanding of their mechanism of action. This section will describe current progress, present the range of existing models that can act as a resource for comparative future work, and highlight challenges as well as opportunities regarding the use, screening and delivery of antioxidants in glaucoma.

3.1. Botanical derived antioxidant strategies

Plants are a large source of dietary intake of antioxidants (Fig. 2) (Kapravelou et al., 2015; Murray and Pizzorno, 2012), especially those containing pigments, such as chlorophyll, carotenes, flavonoids and other phenolic compounds; vitamins; dietary fiber; enzymes; and minerals, among other minor constituents (Gu et al., 2019; Konczak et al., 2009; Martins et al., 2016; Szwajgier et al., 2017; Tang et al., 2020). Important antioxidants (Ismail et al., 2017) and modulators of cell signaling can be found in vegetables, berries (Luís et al., 2018), nuts (Godos et al., 2017), coffee and tea (Gorjanović et al., 2017), and whole grains (Debelo et al., 2020). Researchers have therefore sought botanical compounds to yield novel antioxidants and better means to deliver exogenous antioxidants (Rupesinghe et al., 2016). Appropriate assessment of their suitability, effectiveness and mechanism of action will allow the field to rapidly translate exogenous antioxidant strategies to ameliorate many of the oxidative stress related diseases accumulating with age.

There is growing evidence of modulating neuroinflammation and oxidative stress in the brain with natural compounds for neuroprotection in a range of conditions (Kempuraj et al., 2021; W. Zhou et al., 2021). Luteolin, a polyphenol flavonoid, has been identified as a promising polyphenol by targeting oxidative stress and was protective of microglia in Parkinson's disease (Elmazoglu et al., 2020). Further, luteolin can suppress the neuroinflammatory response and may have a role as an anti-cancer agent (Imran et al., 2019), in Alzheimer's disease (Ali and Siddique, 2019; Daily et al., 2021), and potentially improve cognitive dysfunction (Yao et al., 2018). There are no current studies on luteolin and glaucoma, though there is evidence that flavonoids in general may have a role in improving visual function in people with glaucoma (Patel et al., 2015).

Whilst there is an emerging role of Nrf2 regulation in glaucoma, the activation of Nrf2 signaling have been studied widely in brain conditions to modulate oxidative stress. Ursolic acid, a natural compound derived from berries and fruit (Luo et al., 2019), has been shown to be neuroprotective in cerebral ischemia (Li et al., 2013) and traumatic brain injury (Ding et al., 2017). Curcumin, found in turmeric, and has been studied extensively in ageing (Zia et al., 2021) and Alzheimer's disease (Voulgaropoulou et al., 2019). Curcumin has been shown to activate the Nrf2/ARE pathway and can provide neuroprotection in traumatic brain injury (Dai et al., 2018), myocardial ischemia reperfusion injury (Li et al., 2015) and neonatal hypoxic-ischemic brain injury (Rocha-Ferreira et al., 2019). Building on this work, Davis et al. recently demonstrated significantly reduced RGC loss in two rat glaucoma models using topical curcumin nanocarriers (Davis et al., 2018).

Different plant species have been identified to be potentially neuroprotective and currently used to obtain active compounds for glaucoma treatment, including cannabinoids (e.g., cannabidiol), diterpenoids (e.g., ginkgolides), carotenoids (e.g., crocetin), and flavonoids (e.g., catechins, anthocyanins) (Table 3). Although many botanical compounds have been tested preclinically (Table 4), only a few have translated to clinical trials (Table 5). The compounds that have received the most attention for preclinical glaucoma models include resveratrol (Wang et al., 2019), froskolin (Cammalleri et al., 2020), and retinoic acid (Wang et al., 2017); and for clinical trials, ginkgolides and vitamin

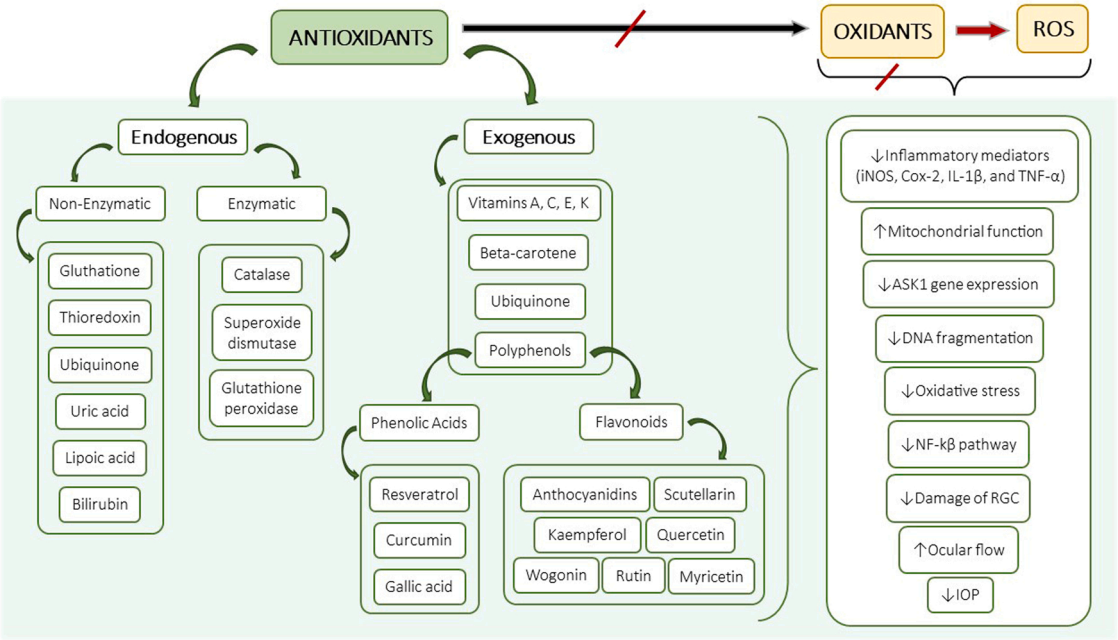

Fig. 2. Endogenous and exogenous antioxidants. Besides the endogenous antioxidant defenses that the human body develops to balance the excess of free radicals, there are also exogenous antioxidants supplied within the diet. These antioxidants act through different mechanisms, but are mainly ROS scavengers, reducing the oxidative stress. Red lines indicate how the imbalance or lack of antioxidants facilitate the oxidant effect.
Adapted from Simioni et al. (2018).

Table 3
Plant species currently used to obtain active compounds for glaucoma treatment.

Plants	Active compounds	Visual disorder	Findings
Ginkgo biloba	Ginkgolides A, B and C Bilobalide	Glaucoma	Antioxidant, mitochondria stabilization, vasorelaxation, blood viscosity reduction, anti-inflammation. (Ige and Liu, 2020; Kang and Lin, 2018)
Vaccinium myrtillus	Catechins Proanthocyanidins Kaempferol Quercetin Myricetin Hydroxycinnamic and hydroxybenzoic acids	Glaucoma	Antioxidant, anti-inflammatory. (Pires et al., 2020)
Rhus coriaria	γ-sitosterol Campesterol Stigmasta-5,24(28)-dien-3-ol.	Optic Nerve Injury	Neuroprotective, antioxidant, anti-inflammatory, IOP reduction. (Khalilpour et al., 2018)
Erigeron breviscapus	Scutellarin	Glaucoma	Apoptosis reduction (Downregulation of cleaved caspase-1, IL-18, and IL-1β). RGC survival and reduced microglial activation Inhibition of NLRP3 inflammasomes. (Zhu et al., 2018)
Panax ginseng	Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and Rg2	Glaucoma	Anti-inflammatory (reduction of cytokines and inflammation mediators). (Bae et al., 2015)
Crocus sativus L.	Crocin Crocetin	Glaucoma	Anti-inflammatory, antioxidant, anti-apoptotic (downregulate Bax, caspase-3). (Fernández-Albarral et al., 2019)
Prunella vulgaris	Rosmarinic acid	Glaucoma	IOP reduction, antioxidant, MDA production reduction. (Wu et al., 2017)
Ribes nigrum	Anthocyanins	Open-angle glaucoma (OAG)	Antioxidant, anti-inflammatory, ocular blood flow increase. (Yoshida et al., 2013)
Heliotropium indicum	Pyrrolizidine alkaloids Saponins Flavonoids	Acute and chronic glaucoma	Reduced intraocular pressure, anti-inflammatory, improved aqueous outflow. (Kyei et al., 2015)

E (alpha-tocopherol-acetate). These compounds are believed to improve mitochondrial activity and reduce oxidative stress. In addition to these neuroprotective properties, studies have also examined the IOP lowering benefits of botanical compounds as summarized in Tables 3, 4 and 5. Tables 4 and 5 synthesize key elements of preclinical and clinical studies, respectively, including administration route, dosage, time/-duration of the treatment, approach, and sample size.

3.2. Mechanisms of antioxidant strategy for glaucoma

Within mitochondria, antioxidants can exert beneficial effects via a number of pathways, including a direct electron-donating activity and indirect modulation of expression and action of a range of proteins (Garcia-Medina et al., 2020). For instance, the direct antioxidative effect of botanical compounds, such as quercetin, is mainly due to phenolic hydroxyl and catechol groups, which due to donation of hydrogen ions has high scavenging efficiency for free radicals (Ganie et al., 2011). Hormesis is an example of an indirect mechanism of antioxidants, whereby upregulation of enzymes involved in detoxification processes or overexpression of genes associated with repair pathways (Angeloni et al., 2020).

Zhu and coworkers (2018) examine *Erigeron breviscapus*, and show that the active compound scutellarin inhibits neuroinflammation through the NLRP3 inflammasome signaling pathway and reduced pro-apoptotic mediators in cell culture (Fig. 2). These effects were associated with the inhibition of poly ADP ribose polymerase-dependent mitochondrial dysfunction and the subsequent translocation of the apoptosis-inducing factor (AIF) pathway (Zhang et al., 2009). Other studies have confirmed that NLRP3 inflammasomes are activated in acute IOP elevation models (Chi et al., 2015, 2014; Zhu et al., 2018), and that the suppression of the Toll-like receptor 4/caspase-8/IL-1β axis is a potential therapeutic strategy against RGC death and glaucoma (Chi et al., 2014). Scutellarin reduces cell injury from IOP elevation to 60 mmHg for 30 min, an effect associated with reduced microglial activation (Zhu et al., 2018).

Crocins and crocetin extracted from Saffron (*Crocus sativus* L.) have been shown to reverse LPS-induced activation and proliferation of microglia, and reduce pro-inflammatory mediators (NO, iNOS, Cox-2, IL-1 β, and TNF-α), by suppressing NF-kβ activity (Fernández-Albarral et al., 2019; Lv et al., 2016; Nam et al., 2010) (Fig. 2). Crocin in PC-12 cells, blocks TNF-α-induced DNA fragmentation, and preserves mitochondrial membrane potential and ATP synthesis, thereby reducing ER stress (Zhang et al., 2015). Due to its powerful antioxidant activity, the extract of Saffron may also be useful for the treatment of brain neurodegenerative disorders and ocular diseases (Cordeiro et al., 2021).

Antioxidants can also impact cellular signaling pathways that modulate cell survival directly (Fig. 2). An example is signaling through the dedicator of cytokinesis 3 (Dock3) and apoptosis signal-regulating kinase 1 (ASK1). Dock3 is primarily expressed in RGCs, and appears to provide neuroprotection by inducing the degradation of N-methyl-D-aspartate and thereby reducing superoxide production (Namekata et al., 2013; Semba et al., 2014). ASK1 plays key roles in cellular responses to oxidative and ER stress and is strongly activated in response to various oxidants such as H_2O_2 (Katome et al., 2013). The deletion of the ASK1 gene prevents RGC death in various mouse models of glaucoma, including retinal ischemia and optic nerve injury (Katome et al., 2013; Kimura et al., 2017). Thus, using botanical antioxidants to modulate ASK1 and Dock3 expression in the retina is a potential therapeutic strategy for glaucoma.

3.3. Effective systemic delivery of exogenous antioxidants

Various antioxidant compounds taken orally might provide benefit throughout the body to broadly counteract age-related imbalance in oxidative stress. Such systemic delivery may also reach RGCs in sufficient quantities to reduce oxidative stress and/or help as electron carriers to modulate mitochondrial electron flow (Martins et al., 2016; Osborne et al., 2016). Natural products from plants, such as *Ginkgo biloba* (Ige and Liu, 2020), *Vaccinium myrtillus* (Pires et al., 2020; West et al., 2006), *Cannabis sativa* (Belyea et al., 2016), appear to improve mitochondrial function and cell signaling. Increased energy availability has been shown to improve vascular perfusion, reduce neuroinflammation, and enhance the resistance of RGCs to mechanical and ischemic stress (Geyman et al., 2018; Ige and Liu, 2020; Kim et al., 2020; Lascaratos et al., 2012). There is also a growing trend to combine several plant derived antioxidants for their synergetic effects (Bernardo-Colón et al., 2018; Cammalleri et al., 2020). However, when targeting cells in the central nervous system, such as the neurons affected in glaucoma, it is important to note that like other therapeutic compounds, antioxidants might not cross the blood neural barriers. Thus, systemic delivery may lead to poorer bioavailability in the eye than other organs, and so could

Table 4
Isolated antioxidant compounds and drugs used for treatment of visual disorders in in vivo preclinical models.

Compounds (Origin)	Visual disorder (model/ approach)	Animal (Gender/ age/*n*)	Dosage or Concentrations tested	Treatment (Time/duration) / Administration method	Findings (direct or indirect effects)
Tempol (Commercial)	Glaucoma (microbead/ viscoelastic injection-induced ocular hypertension)	C57BL/6 J mice Gender not reported 5–7 months-old $n = 12$/group	200 mg/kg/day	Acute (6 weeks) / Subcutaneously implanted minipumps	Reduced inflammation by decreased activation of NF-κB and cytokines (including IL-13 in the retina, and IL-4, IL-6, and IL-13 in the optic nerve) and transcriptional targets of NF-κB, such as TNF-α and IFN-γ. Reduced oxidative stress. Reduced ocular hypertension and neuron loss. (Yang et al., 2016)
Resveratrol (Commercial)	Age-related retinal neuropathy (aged zebrafish)	*Danio rerio* (wild-type of AB strain) Both sexes 19–23 months old $n = 8$/group	20 mg/L; 20 mg/L resveratrol+ 0.04% ethanol	Acute (1 and 10 days) / Immersion (10 h/day under dark condition and another 14 h under light condition with untreated water)	Activation of AMPK/ SIRT1/ PGC1α and inhibition of mTOR, leading to increased mitochondrial quality and enhanced energy metabolism (decreased mitochondrial fragmentation and increased autophagy/mitophagy). (Wang et al., 2019)
	Retinal Damage (N-methyl-D-aspartate (NMDA) 100 μM)	*Danio rerio* (wild-type of AB strain) Both sexes 3- to 6-month-old $n = 8$/group	50 mg/L resveratrol; 0.04% ethanol; 100 μM NMDA; 100 μM NMDA+ 50 mg/ L resveratrol	Acute (24 h) / Immersion (dark environment)	Activation of SIRT1 and reduced retinal damage potentially via mitochondrial sirtuins and OPA1 genes. (Sheng et al., 2018)
	Glaucoma (intracameral 25 ml hyaluronic acid 10 mg/ml)	Wistar rats Adult male $n = 12$/group	Riluzole (8 mg/kg/day); Resveratrol (10 mg/kg/day)	Acute (6 weeks) / Intraperitoneal injection	Reduced RGC loss. (Pirhan et al., 2016)
	Glaucoma (intracameral 7 μL magnetic micro-beads 9 μm diameter)	Sprague Dawley rats Adult male and 4–6 weeks old $n = 6$/group	20 mg/kg/day	Acute (4 weeks) / Intragastric administration	Retinal morphology improved. Reduced apoptotic cells. Reduced ROS production. Increased mitochondrial biogenesis and dynamics. (Zhang et al., 2018)
	Retinal ischemia (IOP to 110 mm Hg for 60 min)	Sprague Dawley rats Gender not reported 2–3 months old $n = 5$/group	250 mg/kg/day (three times, at 1 day before, at the time of, and 1 day after retinal injury)	Acute (3 days) / Intraperitoneal injection	Prevents RGC death, likely through inhibition of the Bax-caspase-3 dependent apoptotic pathway. Reduced reactive gliosis and decreased pro-inflammatory mediators. (Luo et al., 2018)
Gallic acid (Commercial)	Glaucoma (intracameral 0.1 mg/ml of α -chymotrypsin. IOP was higher than 20 mmHg)	New Zealand white rabbits Gender not reported 16–20 weeks of age $n = 6$/group	50 μL (10% w/v)	Acute (4 weeks) / Intracameral injections	Increasing retinal antioxidants. Reduction of oxidative stress. (Chou et al., 2017)
Salvianolic Acid A (Commercial)	Ischemia/Reperfusion model (increased IOP with saline solution (IOP no reported))	Sprague Dawley rats Males (150–200 g), age not reported $n = 40$/group	10 mg/kg/day	Acute (3 days) / Intraperitoneal injection	Reduced RGC apoptosis and astrocyte activation. Upregulate MAPK pathway. (Mao and Wu, 2019)
Vitamin C and Vitamin E (Commercial)	Ocular trauma (induced with a 26 psi blast of air)	C57BL/6 mice and Gulonolactone oxidase knock-out (Gulo–/–) mice Males 3–4 months of age, $n = 10$/group	100 mg/kg/day Vitamin C; 50 mg/kg/day Vitamin E	Acute (1 month) 1 month prior to injury and for the duration of the experiment / Orally	Decrease in ROS resulted in better axon preservation. (Bernardo-Colón et al., 2018)
Retinoic Acid (Commercial)	Retinal injury (intravitreal, Paclobutrazol-PBZ at 0.1, 1, or 5 ppm)	Zebrafish embryos (AB) $n = 15$/group	1 or 5 nM	2 hpf until 72 hpf / Immersion	Partial rescue of mitotic cells and eye size. Partial rescue of cone photoreceptors. (Wang et al., 2017)
Epigallocatechin-3-gallate (Commercial)	Optic nerve injury (Optic nerve crush-ONC)	Wistar rats Females 7 weeks old $n = 18$/group	25 mg/kg/day[a] and 2 mg/kg/day[b]	5 days from 2 days before ONC to 2 days after[a], and until the 28th day[b] / IP[a] and oral gavage[b]	Reduced both primary and secondary degeneration of RGCs. Increased NF-L in optic nerve. (Xie et al., 2010)
Quercetin (Commercial)	Glaucoma (IOP 18–33 mmHg, intracameral 5 μL of paramagnetic polystyrene microbeads)	Wistar rats 150–200 g Age and *n* not reported	2 μL (10 μM/week)	2 days before model induction continued for 4 weeks	Reduced RGC apoptosis. No change in IOP. Improved mitochondrial function and reduced mitochondria-mediated apoptosis. (Gao et al., 2017)
Wogonin (Commercial)	Optic nerve injury (Optic nerve crush-ONC)	Sprague-Dawley rats Adult male	30 mg/kg	Once, 10 min after ONC / Intraperitoneal injection	Reduced RGCs apoptosis. Inhibited activation of caspase-3, reduced pro-inflammatory cytokines, gliosis, and microglial

(*continued on next page*)

Table 4 (*continued*)

Compounds (Origin)	Visual disorder (model/ approach)	Animal (Gender/ age/*n*)	Dosage or Concentrations tested	Treatment (Time/duration) / Administration method	Findings (direct or indirect effects)
		10 weeks old $n = 36$/group			activation via inhibition of TLR4-NF-κB pathway. (Xu et al., 2016)
Forskolin (Commercial)	Glaucoma (topical instillation of 25 μL of 0.1% (w/v) dexamethasone, IOP 24.4 ± 1.1 mmHg)	New Zealand albino rabbits Adult male (2.0–2.5 kg) $n = 6$/group	Forskolin in situ gel (0.25 mg; 25 μL of 1% (w/v) suspension)	Once / Eye drop	Reduced IOP for 12 h. (Gupta et al., 2010)
Coenzyme Q10 (Commercial)	Light damage (UV-irradiated for 1 min, intensity of 14 mW/cm^2)	Wistar albino rats Adult (250–300 g) *n* not reported	0.2% CoQ10 in 10% Lutrol, 4 times daily	3 days / Eye drop	Protects retinal cells from serum starvation, chemical hypoxia, and apoptosis caused by UV- or γ-radiation by inhibiting mitochondrial permeability transition. (Lulli et al., 2012)
Kaempferol (Commercial)	Acute IOP (IOP elevated to 70 mmHg for 60 min)	C57BL/6 mice Female 6–8 weeks old $n = 5$/group	100 mg/kg/day	Once / Intragastrically	Reduced RGC death. Reduced caspase-3, caspase-8, and NLRP1/ NLRP3 inflammation activation. Reduced inflammatory cytokines production and oxidative stress. (J.B. Lin et al., 2019; C. Lin et al., 2019)
Ginsenoside Rg1 (Commercial)	Glaucoma (intracameral, 0.2 ml carbomer solution 0.3%; IOP >22 mm Hg for 4 weeks)	New Zealand white rabbits Male or female (2–2.5 kg) $n = 6$/group	0.1 ml (2.5 mg/kg)	Once per 3 days for 4 weeks / Intravitreal injection	Reduced RGC death. Reduced IOP and NO, MDA and SOD. (Wang et al., 2018)
Lutein (Commercial)	Acute Retinal ischemia/ reperfusion (ophthalmic artery occlusion with nylon monofilament)	C57BL/6 N mice Male mice 10–12 weeks old $n = 7$/group	0.2 mg/kg	1 h before and 1 h after reperfusion / Intraperitoneal injection	Reduced RGC death, reduced oxidative stress, NT and PAR expression. (Li et al., 2009)
Zeaxanthin (Commercial)	Glaucoma (elevated IOP, mutant model)	*Lrp2* (bugeye) zebrafish Sex not reported 1.5–3 years old $n = 10$–18/group	9.2nL (0.46 ng/μL)	Once / Eye Injection	Visual acuity significatively improved. (Saidi et al., 2015)
Nicotinamide (Commercial)	Glaucoma (mutant model, anterior chamber dysgenesis)	DBA/2 J (D2) mice Gender not reported 9 and 4-months-old $n = 8$/group	550 and 2000 mg/kg/day	3 months / Orally	Improved mitochondrial health and metabolism. Overexpression of Nmnat1 prevents axon and soma loss. (Williams et al., 2017c)
Coenzyme Q10 and (+)-α-tocopherol acetate (Commercial)	Retinal injury (intravitreal, 2 μL/eye of NMDA)	ddY mouse Male adult (36–43 g) $n = 5$–12/group	10 mg/kg/day (+)-α-tocopherol acetate;	14 days (starting 7 days before NMDA) / Orally	Coenzyme Q10 and α-tocopherol were synergic. Reduced oxidative stress. (Nakajima et al., 2008)
Forskolin/ Homotaurine/ Spearmint/B Vitamins	Glaucoma (intracameral 5 μL methylcellulose-MCE)	C57BL/6 mice Male or female 8 weeks old $n = 11$/group	19.3 mg/kg *Coleus forskohlii*; 14.5 mg/kg homotaurine; 86.7 mg/kg spearmint; 0.4 mg/kg vitamin B2; 0.4 mg/kg B6; 0.3 mg/kg B1; and 0.5 mg/kg B12	4 weeks (starting 2 weeks before MCE) / Orally	Reduced inflammatory markers and apoptosis. Lowered IOP. (Cammalleri et al., 2020)
Forskolin/ homotaurine/L-carnosine (Commercial)	Ischemia/reperfusion (IOP 80 mmHg for 50 min)	Wistar rats Male (280–330 g)	Forskolin 3 μL (0.6–6 nmol/ eye); homotaurine (0.059 μmol/eye); and L-carnosine (0.036 μmol/eye) alone or in combination	1 h before and following ischemia / Intravitreal injection	Reduced calpain activation and RGC death, via PI3K/Akt/GSK3-β pathway. (Russo et al., 2015)
Naringenin, Naringin, Hesperetin, Hesperidin, Rutin, and Quercetin (Commercial)	Retinal ischemia (ligature around optic nerve and posterior ciliary artery for 30 min)	Long–Evans rats Female (200–250 g) $n = 6$/group	10 mg/kg separately	Once right before the occlusion of central retinal arteries / Intraperitoneal injection	Enhance ocular blood flow and retinal function recovery when the flavonoid OH group increases from two to four. Potency declines with > 5 OH groups. Rutin showed the highest potency. (Chiou and Xu, 2004)

not reach specific and relevant sites of mitochondrial dysfunction within neurodegenerative disorders (Tsai et al., 2018; Yin et al., 2016). In fact, one of the major challenges in ophthalmic drug delivery is to overcome the physical and blood-ocular barriers of the eye (Tsai et al., 2018).

Strategies capable of targeting antioxidants to mitochondria would be preferential, as these can directly address their age-related increase specifically in mitochondrial dysfunction, which is the primary source of elevated reactive oxygen species. Excitingly, considerable progress has been made specifically in developing mitochondria-targeted molecules such as MitoQ, MitoVitE, MitoαLipoic acid, MitoPBN, and SS31, which will have broad applicability across ROS dependent age-related organ function. MitoQ, MitoVitE, MitoαLipoic acid, MitoPBN are molecules developed by conjugating antioxidant molecules to a positively charged lipophilic phosphonium cation. Their molecular moiety allows them to be highly attracted to mitochondrial matrix due to the charge difference, and reduces the mitochondrial dysfunction by scavenging free radicals

Table 5
Isolated antioxidant compounds and drugs used in clinical trials for glaucoma treatment.

Compounds (Origin)	Glaucoma sub-type (Additional information)	Severity/ visual field mean defect (MD) prior to treatment	Gender/age/ *n*	Dosage or Concentrations tested	Time of treatment / Administration method	Findings (direct or indirect effects)
GBE (Gingko biloba leaf extract)	NTG	bilateral with progressive damage MD: 11.40 ± 3.27 dB	11 males and 16 females 58–80 years-old $n = 27$	40 mg, 3 times per day Randomized/ controlled, cross over	4 weeks / Oral	Significant improvement in MD, no change to IOP, blood pressure, or heart rate. (Quaranta et al., 2003)
		Mean MD − 10.27	7 males and 8 females 18–80 years-old $n = 15$	80 mg 2x daily Randomized/ controlled	4 weeks / Oral	Mean peripapillary blood flow increased in volume, and velocity. (Park et al., 2011)
	NTG (retrospective study)	Mean MD − 5.25 ± 6.13	Males and Females 20–89 years-old $n = 103$	Unspecified	Self-reported duration 23.81 ± 10.36 (range, 6–59) months / Oral	Improvement to MD. (Shim et al., 2012)
	NTG (newly diagnosed)	BCVA > 35	Males and Females 18–90 years-old $n = 18$	40 mg, 3 times per day Randomized/ controlled, crossover	4 weeks / Oral	no significant differences observed. (Guo et al., 2014)
Vitamin E (alpha-tocopherol-acetate, commercial)	OAG ($n = 7$) Angle closure ($n = 5$)	Mean IOP, 20.62 (± 2.2) mmHg, 10/ 10, BCVA 55.5	Gender not reported mean 55.9 (± 12.1) years-old, $n = 12$	300 mg daily Randomized/ controlled	1 year / Oral	Visual field MD improved at 6 months. Posterior ciliary arteries pulsatility recued at 6 months. Ophthalmic artery resistivity lower in at 6 and 12 months. (Engin et al., 2007)
	OAG ($n = 4$) Angle closure ($n = 5$)	Mean IOP 20.95 (± 3.9) mmHg Mean BCVA 50	Gender not reported mean 57 (± 6.3) years-old, $n = 9$	600 mg daily Randomized/ controlled		
	POAG (n = 6), PEX (n = 13) (concurrent glaucoma filtration surgery)	Mean BCVA 55 (84–35)	10 males and 9 females, $n = 19$	300 mg daily Randomized/ controlled	2 months / Oral	No significant differences were observed. (Goldblum et al., 2009)
Epigallocatechin-gallate (commercial)	OAG	IOP > 21 mmHg MD > −10 dB	Males and Females 30–76 years-old $n = 18$	200 mg daily Randomized/ controlled, cross over	3 months / Oral	Small but significant improvement in retinal ganglion cell (pattern electroretinogram). (Falsini et al., 2009)
Anthocyanins (Black current)	OAG (2 years treatment by antiglaucoma drops before study)	MD > - 12 dB	Males and Females 20–80 years-old $n = 19$	25 mg daily Randomized/ controlled	1 year / Oral	Increased retinal blood flow was observed and ET-1 serum concentrations normalized. (Yoshida et al., 2013)
Brudysec 1.5 (commercial)	POAG	Non-severe	Males and Females 25–80 years-old $n = 31$	2x Brudysec 1.5 tablets daily Randomized/ controlled	3 months / Oral	Symptoms of dry-eyes were relived, IL-6 and TNF-α expression significantly decreased in tears. No changes to BCVA were noted. (Pinazo-duran et al., 2013)
Saffron (commercial)	POAG (6 months stable glaucoma, concurrent timolol /dorzolamide)	MD − 5.47 ± 1.5 BCVA 70 IOP 12.9 ± 3.7 mmHg	21 males and 13 females > 50 years-old $n = 34$	30 mg daily Randomized/ controlled	1 months / Oral	Significant Reduction in IOP during consumption period. (Pinazo-duran et al., 2013)
ICAPS R® – Alcon Laboratories (Vit A, B, C, E, lutein, Zeaxanthin); OFTAN MACULA® – Laboratorios Esteve (Vit A,B,C,E,lutein, Zeaxanthin, omega 3)	POAG (concurrent topical ocular hypotensive, Caucasian subjects, Glaucoma diagnosis 2 years previous the assessments)	Mean MD 5.54 (2.63) (ICAPS R®) and 5.30 (3.66) (OFTAN MACULA®)	ICAPS R®: 11 males and 15 females > 40 years-old $n = 26$ OFTAN MACULA® 10 males and 18 females > 40 years-old $n = 28$	5 tablets x weekly Randomized/ controlled	2 years / Oral	No significant differences were observed. (Garcia-Medina et al., 2015)
Vitamin A and Palmitate			8 males and 2 females	2x daily applications of	1 year / Oral	Reduction in dry-eye symptoms were observed and

(*continued on next page*)

Table 5 (*continued*)

Compounds (Origin)	Glaucoma sub-type (Additional information)	Severity/ visual field mean defect (MD) prior to treatment	Gender/age/ *n*	Dosage or Concentrations tested	Time of treatment / Administration method	Findings (direct or indirect effects)
	POAG: PGA[a] monotherapy for minimum 1 year prior (n = 23) NTG: PGA monotherapy for minimum 1 year prior (n = 7)	BCVA 45 ± 7 Mean IOP 15.8 ± 2.44 mmHg	35–71 years-old *n* = 310	vitamin A palmitate 0.1% Randomized/ controlled		treatment prevented decline in RGC density. (Cui et al., 2016)
Ginkgo biloba Optic Nerve Formula Retrobulbar and retinal capillary blood flow increased with treatment. (Harris et al., 2018)	OAG	BCVA > 60 Mean IOP 15.00 mmHg (0.68)	18 males and 24 females 30–70 years-old *n* = 42	1 tablet x daily (Optic Nerve Formula) Randomized, double blind, crossover	1 month / Oral	
CQ10 and Vit E	PEX (concurrent phacoemulsification and intraocular lens implantation)	Mean postoperative IOP of 13.7 ± 4.3 mmHg	29 males and 35 females 66–81 years-old *n* = 64	2x daily (100 mg CQ10, 500 mg Vitamin E TPGS) Randomized	1 month / Oral	Superoxide dismutase levels were lower in treatment groups. (Ozates et al., 2019)
Anthocyanins (*V. myrtillus* extract)	NTG (retrospective study	Mean MD: −6.44 ± 7.05	Males and Females 20–89 years-old *n* = 132	Self-reported treatment duration: 24.32 ± 10.43 (range, 6–53) months	treatment duration 24.32 ± 10.43 months / Oral	Mean BCVA for all eyes improved and mean Visual Field test scores improved. (Shim et al., 2012)
Nicotinamide (commercial)	POAG/NTG (*n* = 37) Angle closure (*n* = 8) PXF/PDG (*n* = 4)	Mean MD (placebo): − 5.46 dB (−7.20, −1.10) (nicotinamide): − 4.51 dB (−8.37, −1.84)	31 Males and 18 Females 65.5 ± 10.0 years-old *n* = 49	1.5 g daily for 6 weeks then 3.0 g daily for 6 weeks	12 weeks each of nicotinamide and placebo	Significant improvement in RGC function measured using electroretinography. (Hui et al., 2020)

[a] PGA: Prostaglandin analogs.

rapidly (Babizhayev, 2016; Yin et al., 2016). SS31 is a tetra-peptide which sequence allows it to target mitochondria, scavenge free radicals, including H_2O_2 and $ONOO^-$, and inhibit lipid peroxidation (Calkins et al., 2011; Yin et al., 2016). Due to their mitochondrial ROS reduction ability, molecules such as MitoQ and SS31 have been demonstrated to be promising candidates to treat oxidative stress in age-related diseases, such as Diabetes, Alzheimer, and Huntington (Bhatti et al., 2021; Calkins et al., 2011; Yin et al., 2016).

However, despite mounting evidence of the advantages of natural antioxidants, the lack of clinical translational highlights limitations, such as those related to biodistribution, solubility, low oral absorption, and systemic bioavailability (Buosi et al., 2020). For instance, Resveratrol bioavailability is relatively low (<1%) due to its rapid metabolism in the intestine and liver involving glucuronidated and sulfated compounds to generate key metabolites, trans-resveratrol-3-O-glucoronide and trans-resveratrol-resveratrol-3-sulfate, respectively, and elimination of these metabolites (Walle, 2011). The low stability and solubility of quercetin under oxidative conditions (e.g. in aerobic aqueous media) could decrease quercetin concentration by almost 98% (Makris and Rossiter, 2000; van der Woude et al., 2003). This effect of the food matrix has also been investigated for resveratrol bioavailability. Resveratrol-containing liquid formulations (either added or endogenous resveratrol) such as grape juice, vegetable juice, wine show similar absorption behavior; high-fat foods delayed absorption; and neither alcohol affected resveratrol bioavailability (la Porte et al., 2010). Furthermore, the antioxidant activity is also dose and time dependent. Considering the fact that rapid absorption and metabolism of resveratrol is often believed to be a potential limitation of its activity and biological effects, it remains to be seen whether maximizing any of these parameters is important for the clinical efficacy of resveratrol (Abu-Amero et al., 2016b). Due to the limited water solubility and bioavailability of natural antioxidants, formulations, and optimizations of these bioactive compounds, possibly including newly developed carriers, may be needed to achieve higher bioactivity and clinical efficacy. In this regard, nanotechnology enters into this scene as the central character to over-come the obstacles mentioned above.

3.4. Approaches for effective antioxidant delivery for glaucoma

For drug delivery to the eye for treatment of glaucoma, established ocular delivery routes include topical application, intravitreal (Doozandeh and Yazdani, 2016; Weng et al., 2017), subretinal (Ochakovski et al., 2017), subtenon (Ohira et al., 2015) or suprachoroidal (Himawan et al., 2019; Yeh et al., 2019) injections or systemic delivery through the vascular system (Himawan et al., 2019) are commonly used. Current drug delivery approaches for glaucoma and novel therapies are the subject of a number of excellent reviews by Lavik et al. (2011), Guglielmi et al. (2019), Lavik et al. (2011), and Kompella et al. (2020). The delivery of antioxidants as a treatment to RGCs, however, has very specific challenges, and current delivery approaches can limit the pharmaceutical action of antioxidants.

Due to the special physiological barriers and anatomical structures of the human eye, antioxidant delivery for the treatment of glaucoma can suffer from low efficiency and lack of specificity (Weng et al., 2017). Antioxidant delivery to the retina, choroid, and Bruch's membrane is challenging as the diseases affecting the posterior segment of the eye require long-term delivery at a higher dose. Furthermore, due to the presence of static barriers (sclera, retinal pigment epithelium (RPE), and multidrug resistance efflux pumps) treatment strategies such as oral, intraocular, and periocular have limited success (Bolla et al., 2020; Nayak and Misra, 2018). In addition, first pass metabolism leads to significant degradation before reaching the systemic circulation (Ratnam et al., 2006). Whilst topical delivery is excellent for IOP lowering medications (e.g. prostaglandin analogs, β-adrenergic blockers,

α-adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agonist) (Guglielmi et al., 2019) antioxidants are unstable in physiological media and topical ocular delivery of hydrophilic or hydrophobic antioxidants both encounter significant barriers in crossing the cornea. Consequently, these limitations highlight the need to design more appropriate antioxidant formulations for glaucoma treatment.

Excitingly much effort and progress are being made to overcome current delivery system limitations. These will be critical for advancing patient-friendly antioxidant treatment strategies Current intraocular drug delivery systems (DDS) can include microcarriers (1–1000 μm) (Arranz-Romera et al., 2019; Mietzner et al., 2020) and implants (> 1 mm), but of particular interest are nanocarriers (1–1000 nm), as they have the advantage of being able to be internalized by cells, to target efficient cellular drug delivery (Arranz-Romera et al., 2019; Bravo-Osuna et al., 2018). Nanosystems that carry, encapsulate or are conjugated with bioactive compounds act like a "Trojan Horse" by manipulating physicochemical properties (e.g. elemental composition, size, stability, surface charge, crystalline structure, chemical reactivity, solubility, physical and optical properties) (Huang and Chau, 2019), to optimise transport of antioxidants across physiological barriers. Nanocarriers (Fig. 3A) most commonly used to deliver bioactive compounds in the eye are nanoparticles (NPs) (Dillinger et al., 2018; Salama et al., 2017; Sánchez-López et al., 2018), liposomes (Fernando et al., 2018; Gómez-Ballesteros et al., 2019), nanocomposites (Sharma and Chauhan, 2020), and dendrimers (Lancina et al., 2017) (Table 6).

Emerging nanotechnology and nanomaterials-based strategies (Fig. 3A) have a range of customizable features that may be particularly suitable for delivery of antioxidants to RGCs (Fig. 3B). Potential benefits of nanotechnology include superior solubility and stability, improved epithelium permeability, enhanced tissue targeting, fewer side effects, sustained drug release (Fig. 3C and D), stimuli responsive release and bioadhesive enhancement (Meng et al., 2019; Sah et al., 2020; Weng et al., 2017) which can increase drug residence time on the ocular surface thereby increasing drug penetrance and ocular bioavailability (Cheng et al., 2019; Li et al., 2020; Mishra et al., 2017). These technologies are rapidly developing alongside identification of novel therapeutic drugs and will need to be considered for each potential antioxidant compound. A number of drugs including antioxidants (e.g., Resveratrol, and Quercetin) delivered using nanomedicine formulations are currently under preclinical investigation (Table 6).

Although, there has been significant growth in drug-delivery systems to the retina significant work remains to improve comfort, safety (bioaccumulation, degradation, excretion, production of unwanted metabolites, side effects, toxicity), efficacy and duration of therapy, using natural antioxidants as bioactive compounds.

4. Conclusions

Continued improvement in understanding the underlying genetic, cellular and molecular pathways of mitochondrial dysfunction, as well as the interplay between ageing, disease-specific genes and oxidative stress (Golpich et al., 2016) will help uncover viable therapeutic targets for glaucoma. In particular, restoring the feedback balance between neurotrophins, neuroinflammation and the antioxidant systems may be an important wholistic approach. To this end therapeutic strategies against oxidative stress in glaucoma are currently under active investigation, including identification of promising sustainable antioxidant compounds from native fruits, herbs and spices (Rupesinghe et al., 2016) and complementary nanocarriers to delivery enough to the back of the eye.

CRediT authorship contribution statement

PRCV and PRJ conceived of the review, coordinated, and written primarily by PRCV. All authors contributed written content and critical revisions to the paper and agreed with the final version.

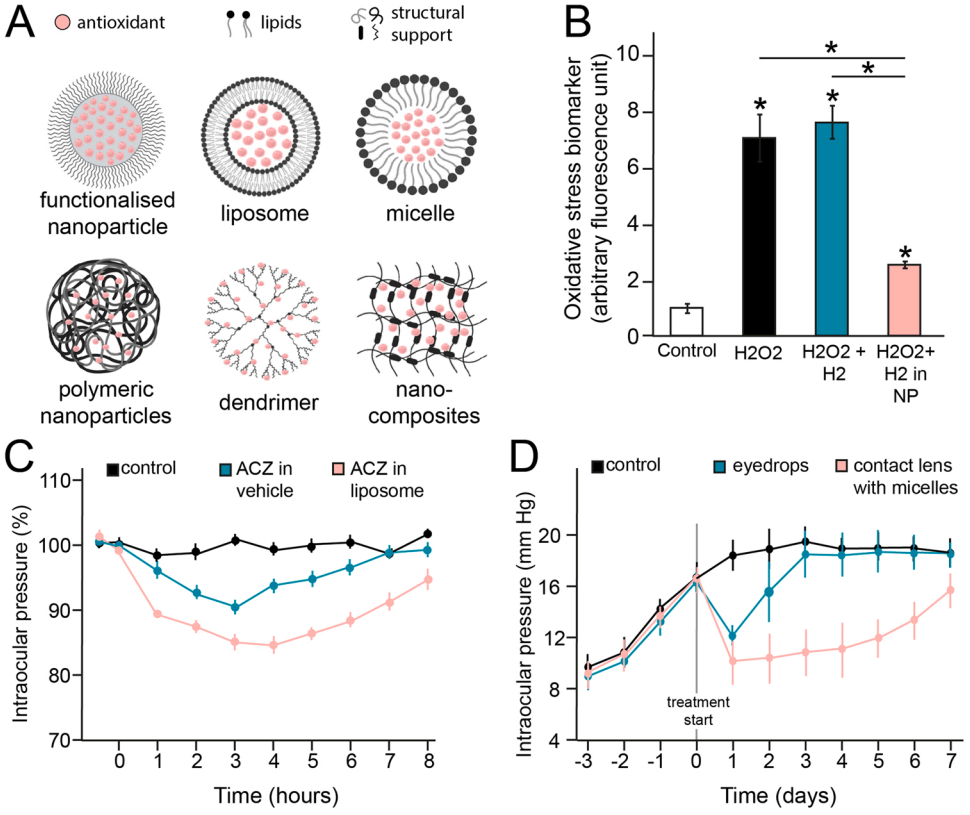

Fig. 3. Emerging nanomaterial-based strategies that could be developed for antioxidant delivery in glaucoma. (A) Most commonly used nanocarriers for treating visual impartment. The choice of nanoparticle will depend on a number of factors outlined in this review, which include the chemical properties of the antioxidant (e.g., hydrophobic vs. hydrophilic), carrying capacity and permeation of the nanoparticle and release dynamics of the antioxidant. Examples highlighting the advantages of these nanosystems include more efficient antioxidant activity (Cheng et al., 2019) (B), higher capacity to reduce intraocular pressure for a longer time period either by itself (Gómez-Ballesteros et al., 2019) (C), or in combination with contact lens exposure (Xu et al., 2019) (D). ACZ: acetazolamide. Graphs in B - D were modified from published material. Graphs in B - D were modified from published material. Some parts of this image were created in BioRender.com.

Table 6
Nanosystems currently used to deliver antioxidant compounds to treat glaucoma in preclinical models.

Nanosystem	Bioactive compounds	Features	Preclinical stage (model)	Administration method	Findings (direct or indirect effects)
Nanoparticles	Resveratrol (RES) and Quercetin (QUR)	Co-encapsulated resveratrol and quercetin in chitosan (CS) and PEG modified chitosan. d: 308 nm, PDI: 0.572	*In vivo* (normotensive rabbits)	Topical (drops)	RES and QUR loaded PEG modified NPs showed a synergistic IOP effect with increased ROs scavenging than RES and QUR alone. RES and QUR in PEG showed improved corneal permeation. (Natesan et al., 2017)
	Resveratrol (RES)	RES-loaded PEG-modified CS NPs. d: 129.8 nm, PDI: 0.351	*In vivo* (normotensive rabbits)	Topical (drops)	RES-loaded CS NPs has sustained RES release, crossed the ocular barriers, reached up to retinal choroid and reduced the IOP. (Pandian et al., 2017)
	Dorzolamide (DZ) hydrochloride and vitamin E-TPGS	Dorzolamide-loaded PLGA/vitamin E TPGS nanoparticles. d: 132.2 ± 24.3 nm, PDI: 0.180	*In vivo* (normotensive New Zealand albino rabbits)	Topical (drops)	Vitamin E TPGS as an emulsifier instead of PVA, a significant increase in drug encapsulation efficiency and corneal permeation with a sustained IOP-lowering effect was obtained. (Warsi et al., 2014)
	Curcumin	Curcumin-loaded TPGS micelles (CN) d: 16 nm, Dh: 17.9 nm, PDI: 0.10	*In vivo* (Induced OHT and pONT in adult male Dark Agouti rats) and *In vitro* (R28 cell line)	Topical (drops)	CN significantly reduced retinal ganglion cell loss in vivo, and increased R28 cell viability and protected against cobalt chloride induced hypoxia and glutamate induced toxicity. (Davis et al., 2018)
	SA-9	Bi-functional hybrid compound SA-9 loaded PLGA nanoparticles	*In vivo* (induced OHT in C57BL/6 J mice)	Topical (drops)	Reduced IOP, and demonstrated immediate broad-spectrum ROS scavenging activities followed by delayed NO release profile. (Amankwa et al., 2021).
Liposomes	Latanoprost/ thymoquinone (TQ).	Latanoprost/thymoquinone-loaded liposomes. d: 150.2 ± 9.46 nm, PDI: 0.48	*In vivo* (glaucoma was induced in New Zealand albino male rabbits)	Topical (drops)	Sustained drug release and showed the maximum IOP lowering effect up to 84 h. TQ improved retinal damage and decreased IOP. (Fahmy et al., 2018)
Dendrimers	Superoxide dismutase (SOD)	Boronic acid-rich dendrimer (BARD) conjugated with SOD d: 124 ± 9 nm, PDI: 0.30, ZP: 19.4 ± 1 mV	*In vivo* (Wistar rats, Ischemia reperfusion injury)	Intravitreal injection	Protected the RGCs from apoptosis, recovered the electrophysiological function of I/R rats, and it was not toxic. (X.Zhou et al., 2021)
Nanocomposites	Curcumin	*Hydrogel:* Thermosensitive chitosan-gelatin-based hydrogel containing curcumin-loaded (CUR-NPs) d: 161 ± 6.0 nm, PDI: 0.04 ± 0.023, ZP: − 23.79 ± 2.65	*In vivo* (New Zealand albino rabbits)	Topical (drops)	CUR-NPs decrease oxidative stress-mediated TM cell damage via decreasing inflammation, mitochondrial ROS production and apoptosis. (Cheng et al., 2019)
	Brimonidine tartrate and vitamin E	*In-situ gelling:* Brimonidine tartrate encapsulated vitamin E-tocopheryl polyethylene glycol succinate-polycaprolacton. d:243.4 ± 5.2 nm, PDI:0.103 ± 0.02, ZP:+ 3.23 ± 0.01 mV	*In vivo* (glaucoma was induced in White New Zealand)	Topical (drops)	Improved bioavailability, better permeation, better IOP lowering capacity compared with marketed eye drops till 8 h. (Sharma and Chauhan, 2020)

Particle size (d), zeta potential (ZP), polydispersity index (PDI), hydrodynamic diameter (Dh).

Conflict of interest

There is no conflict of interest.

Acknowledgements

The authors are grateful for funding support through the J. N. Peters Postdoctoral Fellowship (PRCV) and K. M. Brutton Bequest (PRCV) from the Faculty of Science, University of Melbourne, Australia.

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