Review Article

Reactive oxygen species and oxidative stress in ocular disease: from molecular mechanisms to targeted therapies

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ABSTRACT

Background: Reactive oxygen species and oxidative stress are increasingly recognized as central drivers in the development of major ocular diseases, including cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy. The eye's unique environment—continuous light exposure, high oxygen tension, and abundant photosensitizers—renders it particularly vulnerable to ROS-mediated damage. This narrative review aims to synthesize current evidence on the molecular mechanisms of oxidative stress in ocular disease and highlight emerging therapeutic approaches.

Methods: Targeted searches of PubMed, Scopus, and Google Scholar for literature published between 2000 and June 2025 were conducted. Keywords included "oxidative stress", "reactive oxygen species", "ocular disease", "cataract", "age-related macular degeneration", "glaucoma", and "diabetic retinopathy". Only English-language, peer-reviewed articles were considered. Relevant primary studies, clinical trials, reviews, and experimental reports were selectively incorporated, with an emphasis on recent publications and high-impact contributions to the field.

Results: Evidence consistently demonstrates that ROS induce lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and disruption of redox-sensitive cellular signaling pathways across ocular tissues. In cataracts, oxidation of crystalline proteins and glutathione depletion are primary drivers of lens opacification. In age-related macular degeneration, mitochondrial dysfunction and lipofuscin accumulation promote retinal pigment epithelium degeneration and neovascularization. Glaucoma involves both trabecular meshwork oxidative injury, contributing to elevated intraocular pressure, and mitochondrial-driven retinal ganglion cell apoptosis. In diabetic retinopathy, hyperglycemia-induced ROS overload activates pathogenic pathways, leading to microvascular damage and neuronal dysfunction. Clinical and experimental studies support antioxidant therapies as adjunctive strategies, with the strongest evidence for Age-Related Eye Disease Study-based formulations in age-related macular degeneration and promising results for agents such as Coenzyme Q10 in glaucoma and sulforaphane in diabetic retinopathy. For cataracts, supplementation trials have yielded mixed outcomes and surgery remains the definitive treatment.

Conclusions: Oxidative stress represents a unifying mechanism in the pathogenesis of vision-threatening ocular diseases. Antioxidant-based interventions show potential, particularly when integrated with existing treatment regimens, but their translation into routine practice remains limited by heterogeneous trial results and the absence of robust biomarkers for patient selection. Future research should focus on precision antioxidant therapy, leveraging stage-specific interventions, novel delivery systems, and pathway-targeted compounds, to transform ocular care from reactive management toward prevention.

KEYWORDS

oxidative stresses, oxidative injury, oxidative dna damage, active oxygen species, reactive oxygen species, cataracts, age-related macular degeneration, glaucomas, diabetic retinopathies, antioxidant, mitochondrial dysfunctions

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INTRODUCTION

Reactive oxygen species (ROS) are highly reactive molecules generated as byproducts of normal aerobic metabolism. These include oxygen-derived free radicals, such as superoxide anion and hydroxyl radical, and non-radical oxidants like hydrogen peroxide [1, 2]. Under physiological conditions, endogenous antioxidant systems—including enzymatic defenses such as superoxide dismutase, catalase, and glutathione peroxidase, along with non-enzymatic antioxidants like vitamins C and E—neutralize ROS and maintain redox homeostasis [1, 3]. Oxidative stress arises when ROS production overwhelms these defense mechanisms, leading to oxidative modification of lipids, proteins, nucleic acids, and other macromolecules [3–7]. This imbalance is increasingly recognized as a unifying mechanism underlying tissue degeneration and chronic disease across organ systems.

The eye is uniquely susceptible to oxidative stress because of its constant exposure to ultraviolet and visible light, high oxygen tension, and abundance of photosensitizers and polyunsaturated fatty acids (PUFAs) within ocular tissues [1, 5]. Even modest increases in ROS can trigger a cascade of structural and functional impairments, including lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction [2, 3, 6, 7]. These processes promote apoptosis, inflammatory signaling, and pathological angiogenesis, which in turn drive the onset and progression of major vision-threatening diseases such as cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) [6–9]. Collectively, these ocular disorders account for the majority of global blindness and visual impairment, highlighting the critical importance of understanding and addressing oxidative stress as a common pathogenic denominator in their development [9, 10].

The global burden of ocular disease continues to rise with aging populations and increasing prevalence of diabetes and hypertension. Cataracts remain the leading cause of blindness worldwide, while AMD is the most common cause of irreversible central vision loss in older adults [9, 10]. Glaucoma, a progressive optic neuropathy, is projected to affect more than 110 million individuals by 2040, and DR remains the most common microvascular complication of diabetes, contributing significantly to vision loss in working-age adults [9, 11]. Epidemiological studies further strengthen the association between oxidative stress and DR, highlighting its role as a unifying mechanism across both vascular and neuronal compartments [12]. Despite extensive investigation, large-scale trials and meta-analyses have not demonstrated consistent benefit of antioxidant supplementation in preventing cataract progression, underscoring the ongoing need for mechanism-based strategies [13, 14].

The clinical significance of oxidative stress is reflected by ongoing trials of antioxidant supplementation across AMD and DR, suggesting that redox modulation is increasingly recognized as a therapeutic target [9, 15]. Mounting evidence implicates oxidative stress not only in the initiation but also in the amplification of these diseases, suggesting that redox-targeted therapies could play an important role in prevention and management [2, 6, 9, 13].

This narrative review synthesizes current knowledge on the molecular mechanisms of ROS-induced ocular injury—including lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and dysregulation of redox-sensitive cellular signaling pathways. We then examine disease-specific roles of oxidative stress in cataracts, AMD, glaucoma, and DR, and appraise the evidence for antioxidant-based therapeutic strategies and emerging redox-targeted interventions aimed at preserving vision.

METHODS

Targeted searches of PubMed, Scopus, and Google Scholar were conducted between January 2000 and June 2025. Keywords included “oxidative stress”, “reactive oxygen species”, “ocular disease”, “cataract”, “age-related macular degeneration”, “glaucoma”, and “diabetic retinopathy”. Articles published in English were considered. Eligible records included peer-reviewed original studies, clinical trials, experimental reports, case series, meta-analyses, and narrative or systematic reviews. References in relevant articles were screened to identify additional sources. Literature was selectively included based on relevance to ocular disease mechanisms and antioxidant-related therapeutic strategies. The findings from the literature search are presented below, structured into mechanistic insights, disease-specific roles of oxidative stress, and current or emerging therapeutic approaches.

RESULTS and DISCUSSION

Mechanisms of Reactive Oxygen Species -induced Ocular Damage

ROS compromise ocular homeostasis via a range of biochemical mechanisms that target membrane lipids, structural and enzymatic proteins, genomic material, and redox-sensitive signaling pathways [1, 3, 5]. The cumulative burden of these injuries disrupts cellular integrity and function across multiple ocular compartments, laying the foundation for degenerative and vascular pathologies that threaten vision [1, 4, 6].

Lipid Peroxidation

Cellular membranes enriched in PUFAs are exceptionally vulnerable to ROS-mediated peroxidation due to the high reactivity of bis-allylic hydrogen atoms. Hydroxyl radicals and related ROS abstract these hydrogens, initiating a chain reaction that generates lipid peroxyl radicals and lipid hydroperoxides [2, 3]. These unstable intermediates destabilize membrane structure and yield cytotoxic aldehydes such as malondialdehyde and 4-hydroxynonenal. Persistent accumulation of lipid peroxides can trigger ferroptosis—an iron-dependent, non-apoptotic form of cell death increasingly identified in ocular disease [3, 12].

Elevated lipid peroxidation markers have been detected with aging in the crystalline lens, and experimental evidence suggests that ferroptotic loss of lens epithelial cells may contribute to cataractogenesis [2, 16]. Lipid-derived aldehydes are also capable of forming covalent adducts with proteins and DNA, amplifying injury and activating pro-apoptotic and autophagic signaling pathways [2, 3]. These effects are particularly destructive in PUFA-rich retinal photoreceptors and lens fiber cells, where increased malondialdehyde levels have been documented in diabetic cataractous lenses under hyperglycemia-induced oxidative stress [12, 17].

Protein Oxidation

Proteins serve as both the structural scaffolding and catalytic machinery of ocular tissues, and ROS-induced modifications can irreversibly compromise these roles. Oxidative insults manifest as side-chain oxidation, peptide backbone fragmentation, and formation of carbonyl groups or disulfide crosslinks. In the lens, crystalline proteins oxidation—particularly via thiol group modification—drives aggregation of these proteins into high-molecular-weight complexes that scatter light and diminish transparency [1].

Under physiological conditions, oxidized proteins are recognized, ubiquitinated, and degraded by the proteasome [1]. However, sustained oxidative stress can overwhelm this clearance system, resulting in the accumulation of dysfunctional proteins. In the retinal pigment epithelium (RPE) such aggregates include lipofuscin, a lipoproteinaceous pigment that accumulates with chronic oxidative load and contributes to pathogenesis of AMD [6]. Nitration of tyrosine residues by peroxynitrite produces 3-nitrotyrosine, a widely used biomarker of oxidative protein injury that is elevated in multiple ocular diseases [5, 7].

DNA Damage

Nuclear and mitochondrial DNA in ocular cells is susceptible to ROS-mediated injuries, including base modifications, single- and double-strand breaks, and DNA-protein crosslinks [4]. The oxidative adduct 8-hydroxy-2'-deoxyguanosine (8-OHdG) serves as a hallmark of such damage and correlates with increased oxidative burden in ocular pathology [4, 18]. DNA injury can initiate cell cycle arrest or apoptosis in cell populations essential for vision, such as retinal neurons and lens epithelial cells [4, 12].

Although base excision repair and nucleotide excision repair pathways act to restore genomic integrity [1, 4], their efficiency declines with age and chronic oxidative exposure permits mutation accumulation [6, 12]. In the RPE, mitochondrial DNA damage exacerbates bioenergetic deficits and accelerates AMD progression [6]. Similarly, oxidation-induced DNA injury in lens epithelial cells undermines viability and contributes to cataract development [2, 16].

Mitochondrial Dysfunction

Mitochondria are both primary sources and key targets of ROS. During oxidative phosphorylation, electron leakage from the respiratory chain partially reduces oxygen to superoxide [3, 5, 6]. Under pathological conditions, excessive ROS damage mitochondrial DNA, respiratory complexes, and membrane lipids, impairing adenosine triphosphate (ATP) synthesis and prompting the release of pro-apoptotic factors [3, 6].

Compromised mitochondria exacerbate oxidative stress through increased ROS production, establishing a self-amplifying injury cycle [3, 6]. High-energy demand ocular cells such as photoreceptors, RPE, and retinal ganglion cells (RGCs) are particularly vulnerable [6, 12]. In glaucoma, mitochondrial oxidative injury in RGCs contributes directly to apoptosis and optic nerve degeneration [4, 7, 19]. In AMD, mitochondrial dysfunction in the RPE is associated with elevated ROS levels and impaired cellular resilience [6]. In DR, hyperglycemia accelerates mitochondrial superoxide generation in retinal endothelial and pericyte cells, promoting microvascular cell loss [1, 12].

Disrupted of Cellular Signaling Pathway

Beyond direct macromolecular damage, ROS perturb redox-sensitive signaling networks that regulate antioxidant defenses, inflammatory responses, and angiogenesis. The Keap1-Nrf2 pathway represents a central cytoprotective mechanism: oxidative modification of Keap1 cysteine residues releases Nrf2, allowing its nuclear translocation and induction of detoxifying and antioxidant enzymes such as glutathione S-transferase, NAD(P)H quinone oxidoreductase, and heme oxygenase-1 [2, 8].

Age-related decline or chronic impairment of Nrf2 signaling has been documented in the RPE, correlating with increased susceptibility to AMD-related degeneration [6, 8]. Concurrently, ROS can aberrantly activate stress-responsive kinases (p38 mitogen-activated protein kinase [MAPK], c-Jun N-terminal kinase [JNK]), transcription factors (nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]), and pro-inflammatory cascades, leading to cytokine production and vascular endothelial growth factor upregulation [1, 9, 12]. These changes foster chronic inflammation and pathological angiogenesis, as observed in AMD and DR [4, 9, 12].

Oxidative stress also disrupts autophagy and induces endoplasmic reticulum stress; for example, in glaucomatous trabecular meshwork (TM) cells, ROS-driven protein misfolding triggers the unfolded protein response, compromising tissue homeostasis [4, 19]. Collectively, these signaling alterations shift the ocular microenvironment toward a pro-degenerative, pro-inflammatory, and pro-angiogenic state [1, 6, 9, 12]. Table 1 summarizes the major pathways through which ROS drive ocular damage, including lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and disruption of cellular signaling.

Oxidative Stress in Ocular Disease

Cataracts

Cataracts, the opacification of the crystalline lens, remain the leading global cause of blindness. Oxidative stress is a central driver of its pathogenesis, arising from chronic exposure of the crystalline lens to ROS generated by both metabolic processes and environmental ultraviolet (UV) radiation. Under physiological conditions, the lens maintains transparency through a robust antioxidant network, including glutathione (GSH), ascorbate, and enzymatic defenses [1].

Table 1. Summary of the mechanisms of ROS-Induced Ocular Damage

Mechanism	Key Facts
Lipid Peroxidation [2, 3, 12, 16, 17]	ROS attack polyunsaturated fatty acids in cell membranes, forming lipid hydroperoxides and toxic aldehydes (e.g., 4-hydroxynonenal, malondialdehyde). Persistent peroxidation can trigger ferroptosis, contributing to cataractogenesis and retinal degeneration.
Protein Oxidation [1, 5, 6, 7, 8]	ROS induce side-chain oxidation, crosslinking, and carbonyl formation in proteins. In the lens, crystalline proteins oxidation drives protein aggregation and lens opacity; in the RPE, oxidized proteins accumulate as lipofuscin, fueling AMD progression.
DNA Damage [1, 2, 4, 6, 12, 16, 18]	ROS cause base modifications such as 8-hydroxy-2'-deoxyguanosine, strand breaks, and mitochondrial DNA lesions. DNA injury impairs retinal neurons and lens epithelial cells, with reduced repair efficiency under chronic oxidative stress.
Mitochondrial Dysfunction [3, 4, 5, 6, 12, 19]	ROS damage mitochondrial DNA and respiratory complexes, impair ATP synthesis, and release apoptotic factors. Dysfunctional mitochondria exacerbate ROS generation, harming RPE, photoreceptors, and retinal ganglion cells.
Disrupted Signaling Pathways [1, 2, 4, 6, 8, 9, 12, 19]	ROS dysregulate Nrf2, MAPK, NF-κB, and VEGF pathways, driving inflammation, angiogenesis, and impaired antioxidant defenses. Endoplasmic reticulum stress and defective autophagy worsen glaucomatous trabecular meshwork damage and AMD pathology.

Abbreviations: ROS, reactive oxygen species; RPE, retinal pigment epithelium; AMD, age-related macular degeneration; DNA, deoxyribonucleic acid; ATP, adenosine triphosphate; Nrf2, Nuclear factor erythroid 2–related factor 2; MAPK, mitogen-activated protein kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF, Vascular endothelial growth factor.

With aging or under risk conditions such as sustained UV exposure, diabetes, and hypertension, ROS generation increases while antioxidant reserves decline. This redox imbalance promotes oxidative modification of lens epithelial cells and crystalline proteins, particularly via methionine and cysteine oxidation. Such modifications lead to disulfide bond formation, S-glutathionylation, and aggregation of crystalline proteins of lens into high-molecular-weight complexes that scatter light [1, 2].

GSH depletion, a biochemical hallmark of cataractogenesis, renders crystalline proteins highly susceptible to irreversible cross-linking. In parallel, lipid peroxidation in lens fiber cell membranes disrupts membrane integrity, contributing to fiber disorganization and optical aberrations. Clinical studies consistently report elevated protein carbonyl content and reduced GSH levels in human cataractous lenses, correlating with cataract severity [2]. In diabetes, hyperglycemia-induced ROS accelerate oxidation of lens epithelial cells and crystalline proteins, an effect compounded by protein glycation and osmotic stress. Oxidative injury to lens proteins and membranes precedes clinically visible opacities, indicating that ROS-mediated damage is an initiating, rather than secondary, event in cataract development [1].

Age-related macular degeneration

AMD is a progressive macular disorder and the primary cause of irreversible central vision loss in older adults. Oxidative stress is a key pathogenic factor in both the atrophic (dry) and neovascular (wet) forms of AMD. The macula is highly susceptible to oxidative injury due to its elevated oxygen consumption, dense concentration of PUFAs, and continuous light exposure [1].

In early AMD, extracellular deposits known as drusen accumulate between the RPE and Bruch's membrane. These deposits contain oxidized proteins, lipids, and lipofuscin, a pigment generated from incomplete degradation of photoreceptor outer segments. Lipid peroxidation accelerates lipofuscin formation, while excessive ROS within the RPE promote debris accumulation beyond the degradative capacity of cell [1].

Mitochondrial DNA damage, protein aggregation, and oxidative injury to Bruch's membrane impair nutrient and waste materials exchange, undermining photoreceptor support [6]. In advanced dry AMD, these processes culminate in RPE cell death and geographic atrophy; in wet AMD, oxidative stress stimulates vascular endothelial growth factor upregulation, driving choroidal neovascularization. Clinical and experimental studies consistently demonstrate elevated oxidative biomarkers, such as 8-OHdG and carboxyethylpyrrole adducts, alongside reduced macular antioxidant levels in eyes with AMD [4, 9, 12, 18]. Genetic risk factors, including complement factor H polymorphisms, may amplify oxidative inflammation and accelerate disease progression [7, 9].

Glaucoma

Glaucoma encompasses a group of optic neuropathies characterized by progressive RGC loss and optic nerve head damage. While elevated intraocular pressure (IOP) remains the primary modifiable risk factor, oxidative stress plays a critical role in compromising both pressure-dependent and pressure-independent aqueous humor drainage pathways [4, 7, 19–21].

In the anterior segment the TM, a sieve-like tissue regulating aqueous humor outflow, is directly exposed to ROS in the aqueous humor, including hydrogen peroxide and superoxide [1]. Chronic oxidative insult induces TM cell loss, cytoskeletal reorganization, and extracellular matrix stiffening, thereby increasing outflow resistance and elevating IOP [4, 7]. Peroxynitrite-mediated reduction of nitric oxide bioavailability further impairs TM relaxation, exacerbating outflow dysfunction. Histological studies in glaucoma patients reveal higher oxidative DNA damage and reduced antioxidant capacity in TM tissue compared to controls [4, 7].

In the posterior segment, RGCs are particularly susceptible to mitochondrial oxidative injury due to their high energy demand. Mitochondrial dysfunction in RGCs and supporting glia contributes directly to apoptosis and optic nerve degeneration [4, 19]. Even in normal-tension glaucoma, oxidative stress—often triggered by ischemia-reperfusion injury from vascular dysregulation (e.g., Flammer syndrome)–can damage the optic nerve head despite "normal" IOP [1, 7, 22]. Elevated nitrotyrosine levels in glaucomatous optic nerve head reflect protein nitration by ROS, while depletion of antioxidants such as GSH and superoxide dismutase increases neuronal vulnerability [4, 7, 19]. Hence oxidative stress in glaucoma acts via dual mechanisms: degeneration of the TM leading to ocular hypertension, and direct RGC injury driving optic nerve atrophy [4, 7, 19–21].

Diabetic Retinopathy

DR is a microvascular complication of diabetes in which chronic hyperglycemia induces oxidative stress-mediated damage to the retina's vascular and neural components. Excess glucose metabolism accelerates mitochondrial superoxide production, overwhelming the electron transport chain and causing electron leakage [1].

This oxidative overload activates multiple interlinked pathogenic pathways: (1) the polyol pathway, which consumes NADPH and depletes GSH; (2) formation of advanced glycation end products (AGEs) with activation of receptor for AGE; (3) hyperactivation of protein kinase C isoforms; and (4) the hexosamine biosynthetic pathway [1, 17, 23]. Each pathway either generates ROS directly or is potentiated by oxidative stress, establishing a self-reinforcing cycle. ROS-driven protein kinase C activation promotes vascular permeability and dysregulated blood flow, while AGEs alter protein function and stimulate pro-inflammatory signaling. Retinal endothelial cells and pericytes undergo apoptosis under combined hyperglycemia and ROS exposure, leading to capillary dropout, microaneurysm formation, and breakdown of the blood-retina barrier. Concurrent activation of NF-κB promotes leukostasis and cytokine release, contributing to diabetic macular edema. The neuronal retina also suffers ROS-induced synaptic and glial dysfunction, compounding visual decline [12, 15, 17, 23].

A particularly challenging aspect of DR pathophysiology is "metabolic memory", whereby ROS-induced epigenetic modifications perpetuate oxidative injury even after glycemic control is restored [1, 12]. Clinically, elevated oxidative biomarkers and reduced retinal antioxidants are consistently reported in patients with DR, underscoring oxidative stress as a unifying mechanistic link between hyperglycemia and progressive retinal injury [12, 17, 18, 24].

Table 2 summarizes the major oxidative stress mechanisms, representative biomarkers, and supporting clinical or experimental evidence for cataracts, AMD, glaucoma, and DR. This tabular overview highlights the shared pathogenic themes, such as lipid peroxidation, mitochondrial dysfunction, and impaired antioxidant defenses, as well as disease-specific features, including crystalline proteins oxidation in cataracts, drusen-associated oxidative debris in AMD, trabecular meshwork injury in glaucoma, and metabolic pathway activation in DR. By condensing these findings, the table provides a clear snapshot of how oxidative stress unifies diverse ocular pathologies while shaping their distinct clinical manifestations [1, 2, 4, 6, 7, 9, 12, 14–24].

Table 2. Summary of oxidative stress mechanisms in major ocular diseases

Disease	Key oxidative stress mechanisms	Representative biomarkers/ findings	Clinical and experimental findings
Cataracts [1, 2, 14, 16]	Crystalline proteins oxidation, GSH depletion, lipid peroxidation in lens fibers	↑ Protein carbonyls, ↑ MDA, ↓ GSH in cataractous lenses	Oxidative damage precedes opacities; diabetes accelerates oxidative crystalline proteins injury
Age-Related Macular Degeneration [4, 6, 9, 12, 18]	Lipid peroxidation, mitochondrial DNA damage, impaired Nrf2 signaling, VEGF upregulation	↑ 8-OHdG, ↑ carboxyethylpyrrole adducts, ↑ lipofuscin	Oxidative debris in drusen, RPE mitochondrial dysfunction, complement gene variants worsen oxidative injury
Glaucoma [4, 7, 19, 20, 21]	Trabecular meshwork oxidative damage → impaired outflow; retinal ganglion cell mitochondrial dysfunction → apoptosis; nitric oxide/peroxynitrite imbalance	↑ Nitrotyrosine, ↑ oxidative DNA damage, ↓ antioxidant enzymes (SOD, GSH)	Oxidative stress implicated in both IOP elevation and RGC loss (including normal-tension glaucoma)
Diabetic Retinopathy [12, 15, 17, 18, 23, 24]	Hyperglycemia → mitochondrial ROS overproduction; polyol, AGE/RAGE, PKC, hexosamine pathways; NF-κB activation	↑ ROS, ↑ AGEs, ↑ inflammatory cytokines, ↓ retinal antioxidants	Oxidative stress drives microvascular damage, neuronal dysfunction, and "metabolic memory" despite glycemic control

Abbreviations: GSH, reduced glutathione; MDA, malondialdehyde; DNA, deoxyribonucleic acid; Nrf2, Nuclear factor erythroid 2–related factor 2; VEGF, Vascular endothelial growth factor; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; RPE, retinal pigment epithelium; SOD, superoxide dismutase; IOP, intraocular pressure; RGC, retinal ganglion cell; AGE, advanced glycation end-product; RAGE, receptor for advanced glycation end-product; PKC, protein kinase C; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species.

Therapeutic Approaches

Age-Related Macular Degeneration

In AMD, oxidative damage to the RPE and photoreceptors is a pivotal driver of disease progression. The landmark Age-Related Eye Disease Studies (AREDS and AREDS2) provided the first large-scale clinical evidence that targeted antioxidant supplementation can slow, though not reverse, disease progression. In AREDS, a formulation containing high doses of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg), and copper (2 mg) reduced the 5-year risk of progression from intermediate to advanced AMD by approximately 25% [10]. AREDS2 refined the formula, replacing beta-carotene with lutein (10 mg) and zeaxanthin (2 mg), which improved safety by reducing lung cancer risk in smokers and potentially enhanced efficacy [10]. The clinical benefit is attributed to reduced oxidative injury in the macula via free radical neutralization and stabilization of photoreceptor and RPE cell function. Although AREDS-based supplementation does not restore lost vision, it remains an evidence-based adjunct for patients with intermediate or advanced dry AMD, representing a validated oxidative stress-targeted intervention [10].

Beyond nutritional formulations, several emerging oxidative stress-modulating strategies are under investigation. These include Nrf2 activators such as sulforaphane, which protect the RPE, and photoreceptors that upregulate the Nrf2/HO-1 pathway and reduce oxidative injury in ischemia-reperfusion models [11]. In addition, mitochondria-targeted antioxidants such as MitoQ concentrate ROS scavenging at the primary site of production. In a preclinical rat model of retinal ischemia-reperfusion injury, MitoQ improved retinal function, reduced ROS generation, and modulated the SIRT1/Notch1/NADPH oxidase pathway [13]. While clinical trials are pending, these approaches may complement established supplementation regimens.

Glaucoma

In glaucoma, oxidative stress contributes directly to retinal ganglion cell (RGC) apoptosis and optic nerve degeneration, even in the context of well-controlled IOP. Coenzyme Q10 (CoQ10), a mitochondrial cofactor and lipid-soluble antioxidant, has emerged as a promising neuroprotective agent in this context. CoQ10 sustains mitochondrial electron transport and scavenges free radicals, thereby preserving ATP production while limiting oxidative damage to lipids, proteins, and DNA [19, 20, 21].

Preclinical studies demonstrate that CoQ10 protects retinal cells against oxidative stress in vitro and in vivo, preventing mitochondrial depolarization and cell death [25]. In optic nerve head astrocytes, CoQ10 was further shown to inhibit oxidative stress, restore mitochondrial mass, and improve bioenergetic function [26]. Early clinical and translational findings also suggest that adding oral or topical CoQ10 (often combined with vitamin E for enhanced bioavailability) to standard IOP-lowering therapy may improve retinal function as assessed by visual evoked potentials over 6-12 months [19–21]. While larger randomized controlled trials are still required, current evidence supports CoQ10 as a promising adjunctive neuroprotective strategy aimed at countering oxidative injury in glaucoma.

Other investigational agents include citicoline, which supports mitochondrial integrity and neuronal membrane stability, and Ginkgo biloba extract, that demonstrates antioxidant and vasoregulatory effects in both preclinical and early clinical models. Recent reviews highlight that citicoline and CoQ10 may act synergistically in retinal protection, reinforcing the role of combined antioxidant-based approaches in glaucoma management [27].

Diabetic Retinopathy

Chronic hyperglycemia in diabetes drives persistent oxidative stress in the retina, making antioxidant therapy an attractive adjunct to metabolic control. Epidemiological data indicate that higher dietary intake of antioxidant vitamins, including vitamin C, vitamin E, and carotenoids, is associated with a reduced risk of developing DR [12, 17, 18, 24]. Clinical trials and systematic reviews of oral antioxidant supplementation have produced mixed but generally supportive findings, with some studies showing stabilization of retinal pathology in mild-to-moderate non-proliferative DR [15, 17, 18]. A recent systematic review assigned a Level IIB recommendation for antioxidant supplementation as a consideration in DR management [15]. The proposed mechanisms include attenuation of ROS production, preservation of retinal vascular integrity, and reduction of inflammatory mediator expression [18, 21, 23]. Nevertheless, glycemic and blood pressure control remain the primary interventions; antioxidant therapy is best viewed as a supportive measure that may slow progression by mitigating oxidative injury.

Preclinical research is also exploring Nrf2 pathway activation as a therapeutic target in DR. Sulforaphane attenuates high-glucose-induced oxidative stress, reduces inflammatory cytokine expression, and inhibits NLRP3 inflammasome activation in retinal Müller cells and diabetic rat retinas [23]. In parallel, polyphenol-based compounds like resveratrol have shown potential in reducing retinal oxidative load and improving microvascular integrity in experimental diabetes, yet translation to clinical benefit remains under investigation [28–30].

Cataracts

Although oxidative stress is a central mechanism in age-related cataract formation [31, 32], large randomized controlled trials, including the AREDS study [10] and subsequent Cochrane meta-analyses [14], have failed to demonstrate a preventive or therapeutic benefit from systemic antioxidant supplementation. Observational studies, such as the Blue Mountains Eye Study, have linked high dietary intake of vitamins C and E, beta-carotene, and zinc to reduced incidence of nuclear cataracts [31]. However, neither the AREDS trial [10] nor subsequent Cochrane reviews [14] or more recent clinical evaluations [9, 15] have found significant effects of beta-carotene, vitamin C, or vitamin E supplementation on cataract onset or progression. Cataract surgery thus remains the definitive treatment for vision restoration. Experimental approaches, including topical antioxidant formulations and gene therapies designed to enhance crystalline lens antioxidant enzyme expression, are under investigation but are not yet clinically applicable.

Novel experimental approaches include gene therapy to upregulate endogenous antioxidant enzymes such as glutathione peroxidase and superoxide dismutase in lens epithelial cells, and small-molecule inhibitors of lens protein oxidation, both of which have shown potential in delaying crystalline lens opacification in animal models [16]. While still far from clinical translation, these strategies highlight the ongoing pursuit of mechanism-based cataract prevention.

This narrative review provides a comprehensive and integrative overview of oxidative stress across four major vision-threatening diseases—cataracts, AMD, glaucoma, and diabetic retinopathy—highlighting shared molecular mechanisms and emerging therapeutic opportunities. A particular strength lies in the emphasis on both mechanistic insights (lipid peroxidation, mitochondrial dysfunction, redox signaling) and translational approaches (AREDS formulations, CoQ10, sulforaphane, novel delivery systems), supported by recent literature up to 2025. However, as a narrative rather than a systematic review, the selection of studies was not exhaustive and may be subject to selection bias. The lack of formal quality assessment or meta-analysis also limits the ability to draw firm conclusions about therapeutic efficacy. Despite these limitations, the synthesis identifies clear knowledge gaps and provides direction for future research, particularly in the development of robust oxidative stress biomarkers, stage-specific antioxidant strategies, and innovative delivery platform. Looking ahead, several avenues warrant further exploration to translate oxidative stress research into clinical benefit. First, the development of reliable, non-invasive biomarkers would enable earlier detection and more precise monitoring of oxidative injury across ocular diseases. Second, stage-specific antioxidant strategies are needed, as timing and disease context may determine whether redox modulation is protective or ineffective. Third, advances in drug delivery—including nanoparticle carriers, sustained-release implants, and high-bioavailability topical agents—hold promise for improving bioavailability and targeting of antioxidant therapies. Finally, rigorous, long-term clinical trials of pathway-specific compounds, such as Nrf2 activators and mitochondrial-targeted antioxidants, are essential to determine efficacy and safety. Together, these efforts could establish oxidative stress modulation as a meaningful adjunct to current standards of care in ophthalmology.

CONCLUSIONS

Oxidative stress emerges as a central, unifying mechanism in the pathogenesis of cataracts, AMD, glaucoma, and diabetic retinopathy, acting through lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and disruption of redox-sensitive pathways. Current clinical evidence supports antioxidant-based interventions only in specific contexts, most notably AREDS formulations in AMD, while surgery, intraocular pressure control, and systemic metabolic management remain the standards of care for cataracts, glaucoma, and diabetic retinopathy, respectively. The main implication for ophthalmology is that oxidative stress provides a mechanistic framework for understanding disease overlap and offers a rationale for adjunctive therapies, but it is not yet sufficient to alter frontline management. Recognition of this biology may nevertheless inform future therapeutic design and improve strategies for preserving vision.

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