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BLUE LIGHT-INDUCED RETINAL DAMAGE: MECHANISMS AND PROSPECTS FOR PHARMACOLOGICAL PROTECTION

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ABSTRACT
Over the past two decades, LED lighting and digital screens have significantly increased population exposure to blue light (400-500 nm). High-energy blue photons penetrate the retina and cause photochemical damage associated with age-related macular degeneration and other retinopathies. Current physical protection methods (blue-blocking glasses, yellow intraocular lenses, and software screen filters) lack robust clinical evidence and do not fully solve the problem. Pharmacological prevention using eye drops that increase retinal resistance to light stress remains largely unexplored. This review summarizes molecular mechanisms of blue light-induced retinal damage, evaluates limitations of existing physical protection, and analyzes promising pharmacological candidates for preventive eye drops. Oxidative stress is the central mechanism, triggering mitochondrial dysfunction, endoplasmic reticulum stress, NLRP3 inflammasome activation, ferroptosis, and impaired phagocytosis aggravated by A2E accumulation. In preclinical studies, natural antioxidants such as melatonin, resveratrol, anthocyanins, quercetin, and chlorogenic acid reduce reactive oxygen species, suppress apoptosis, decrease inflammation, and promote A2E degradation. However, their use as eye drops is limited by low solubility, instability, poor corneal penetration, and most importantly, the absence of clinical trials in humans. Priority areas include developing effective retinal drug delivery systems, standardizing experimental models, and conducting randomized controlled trials in high-risk groups: welders, mountaineers, heavy digital device users, and patients after intraocular lens implantation.

KEYWORDS: blue light, retina, oxidative stress, phototoxicity, antioxidants, eye drops

INTRODUCTION

Over the past two decades, light-emitting diode (LED) technology has largely replaced traditional incandescent and halogen light sources in both domestic and professional settings [1]. Unlike incandescent bulbs, which emit warm light with a dominant red spectrum, white LEDs combine a blue diode with a yellow phosphor. This creates a spectral distribution with a strong blue component in the 400-500 nm range [2]. This feature raises medical concern because blue light carries the highest energy per photon in the visible spectrum and can penetrate the eye to reach the retina [3, 4].

Blue light is not solely man-made. It is a natural component of sunlight. Daylight contains about 24-30% blue spectrum, which is necessary for synchronizing circadian rhythms, maintaining alertness, and metabolic health [5]. However, the light environment has changed dramatically. The shift from warm, red-rich lamps to colder LED sources has increased indoor blue light exposure. At the same time, digital screens (smartphones, tablets, computers, televisions) mean people spend many hours in front of blue light sources at close range, often in the evening when retinal sensitivity is higher [6, 7]. The key difference between sunlight and artificial sources is not intensity, but duration and timing. People do not stare at the sun for minutes. In contrast, the average person spends 8-10 hours per day in front of screens or under artificial lighting [8]. Moreover, high-risk groups include welders, mountaineers, polar explorers, laser operators, and patients after lens removal (aphakia), whose natural blue light protection is weakened [9, 10].

Spectral composition is critical. The 400-500 nm range divides into two functional zones. Violet-blue light (400-450 nm), with a peak around 440-445 nm, has the highest photochemical energy and is responsible for the "Blue Light Hazard" (BLH) [11, 12]. Blue-turquoise light (450-500 nm) is essential for non-visual functions, as it contains the peak sensitivity of melanopsin, which regulates circadian rhythms [13, 14]. Recent studies show that phototoxicity is not determined solely by blue light. In rat models, green light (500-550 nm) enhances retinal inflammation, while red light (630-650 nm) reduces apoptotic cell numbers, exerting a protective effect [15]. Thus, current safety standards based only on the blue light curve may underestimate the real danger, particularly from white LEDs, which also emit substantial green light [15].

Epidemiological data remain conflicting. Some meta-analyses find an association between cumulative blue light exposure and age-related macular degeneration (AMD) risk, others do not [16, 17]. However, in people with low levels of endogenous antioxidants (lutein, zeaxanthin, vitamins C and E), blue light becomes a significant risk factor [17, 18]. Experimental studies show that blue light triggers oxidative stress with excessive reactive oxygen species accumulation, mitochondrial damage with impaired dynamics, NLRP3 inflammasome activation, endoplasmic reticulum stress, and programmed cell death (apoptosis, necroptosis, ferroptosis) [19, 20, 21, 22]. The photosensitizer A2E, which accumulates in lipofuscin, generates free radicals under blue light and exacerbates damage [20, 22].

Current protection methods are physical barriers: blue-blocking glasses, yellow intraocular lenses, and screen software filters [5, 17]. However, clinical evidence is lacking. Meta-analyses have not shown convincing benefits for preventing AMD or reducing eye strain [5, 17]. Unlike physical protection, pharmacological prophylaxis remains largely undeveloped. Natural antioxidants such as melatonin, resveratrol, anthocyanins, quercetin, and other polyphenols have shown protective effects in vitro and in animal models [18, 19, 21]. However, their use as eye drops faces serious problems: low solubility, chemical instability, poor corneal penetration, and difficulty reaching therapeutic concentrations in the retina [18, 21].

The aim of this review is to systematize current data on molecular mechanisms of blue light-induced retinal damage, evaluate limitations of existing physical protection, and analyze promising pharmacological candidates for prophylactic eye drops. Unlike previous works [3, 5, 16], this review integrates classical mechanisms with recently described pathways including ferroptosis and PARP-1-mediated cell death, focuses on local pharmacological prophylaxis (eye drops) rather than systemic antioxidants or physical protection alone, and provides a quantitative comparison of natural antioxidant candidates based on preclinical data.

1. Sources of blue light and clinical significance

Blue light (400-500 nm) originates from both natural and artificial sources [23, 24]. Sunlight contains approximately 24-30% blue spectrum, essential for circadian photoentrainment, alertness, and metabolic health [25]. However, the light environment has changed dramatically. The shift from incandescent sources to LED lighting and the proliferation of digital screens have increased cumulative indoor blue light exposure, often at close range and during evening hours [6, 7]. The key difference between sunlight and artificial sources lies not in intensity but in duration and timing: the average adult spends 8-10 hours daily in front of screens or under artificial lighting [8]. High-risk groups include welders, mountaineers, polar explorers, laser operators, and patients after cataract surgery with non-blue-filtering intraocular lenses [9, 10, 26].

Spectral composition is critical. Violet-blue light (400-450 nm, peak ~440-445 nm) carries the highest photochemical energy and is responsible for the Blue Light Hazard (BLH) [11, 12]. Blue-turquoise light (450-500 nm) is essential for melanopsin-mediated circadian regulation [13, 14]. Recent evidence further shows that phototoxicity is not confined to blue wavelengths: green light (500-550 nm) enhances retinal inflammation, while red light (630-650 nm) is protective [15], suggesting that current BLH-based safety standards underestimate the real risk from white LEDs.

Epidemiological data remain conflicting. Some studies link cumulative blue light exposure to increased AMD risk [27], while the EUREYE study found no direct association but identified significantly elevated risk in individuals with low serum antioxidant levels [28]. This suggests that blue light exerts its damaging potential primarily when endogenous antioxidant defenses are compromised.

Beyond retinal effects, blue light regulates circadian physiology via melanopsin-containing retinal ganglion cells (peak sensitivity 460-480 nm) that project to the suprachiasmatic nucleus [29]. Evening blue light exposure suppresses melatonin secretion, impairing sleep quality and potentially increasing metabolic and oncological disease risk [30]. Thus, blue light has both ophthalmological and systemic significance, underscoring the need for effective prevention strategies targeting at-risk populations.

2. Molecular mechanisms of blue light-induced retinal damage

Blue light-induced retinal damage involves a complex cascade of interconnected pathological processes triggered by photochemical reactions [31]. Unlike thermal or mechanical damage, which occur with high-intensity exposure, photochemical damage develops at much lower irradiance levels but requires a sufficient duration of exposure [32, 33].

The main chromophores that absorb blue light in the retina are retinoids. Retinal, a vitamin A derivative that is part of rhodopsin in rods and photopsins in cones, is one such chromophore [34]. Additionally, lipofuscin accumulates in the retinal pigment epithelium with age. Lipofuscin contains the bisretinoid A2E (N-retinylidene-N-retinylethanolamine), which also efficiently absorbs blue light and acts as a potent photosensitizer [35].

Oxidative stress is the central mechanism of photochemical damage [36]. Absorption of a blue light photon by a chromophore raises it to an excited state. Excess energy is then transferred to molecular oxygen, generating reactive oxygen species (ROS) – singlet oxygen, superoxide anion, hydrogen peroxide, and hydroxyl radical [31, 32]. These highly reactive compounds attack polyunsaturated fatty acids in photoreceptor and retinal pigment epithelium cell membranes, initiating lipid peroxidation [33]. Lipid peroxides not only disrupt membrane integrity and fluidity but also break down into reactive aldehydes (malondialdehyde, 4-hydroxynonenal, and others), which damage proteins and nucleic acids, spreading destructive effects [34, 36].

Figure 1 illustrates the interconnections between major pathological pathways triggered by oxidative stress and their convergence toward retinal cell death.

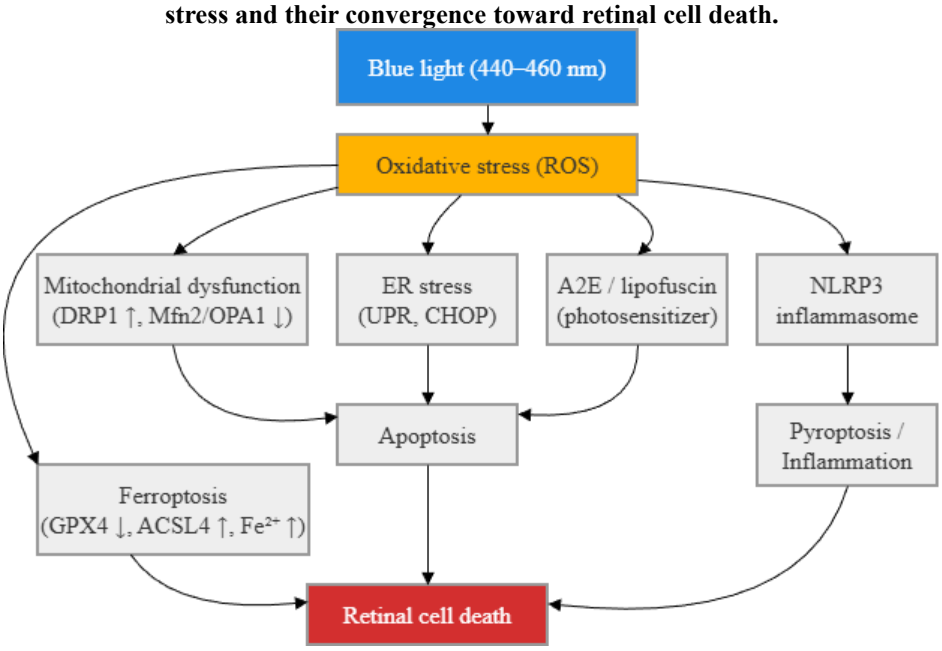

Figure 1. Main mechanisms of photochemical retinal damage induced by blue light. ROS – reactive oxygen species; ER – endoplasmic reticulum; A2E – lipofuscin bisretinoid; NLRP3 – inflammasome component; GPX4 – glutathione peroxidase 4; ACSL4 – long-chain acyl-CoA synthetase.

Mitochondria act simultaneously as targets and amplifiers of oxidative stress. Blue light-induced ROS disrupt the respiratory chain, further increasing superoxide and hydrogen peroxide production and creating a vicious cycle in which damaged mitochondria become an additional source of ROS [37]. Dynamic changes in the mitochondrial network play a particularly important role. Under normal conditions, mitochondria continuously undergo fusion (mediated by Mfn1, Mfn2, and OPA1) and fission (mediated by DRP1), maintaining functional homeostasis. Blue light exposure shifts this balance toward fission: DRP1 expression and mitochondrial translocation increase, while Mfn2 and OPA1 levels decline [19, 37]. The resulting fragmented mitochondria exhibit disrupted cristae architecture and reduced membrane potential ($\Delta\Psi m$). Excessive fragmentation is an early and potentially irreversible step toward apoptosis, as it facilitates cytochrome c release and subsequent caspase cascade activation [19].

Alongside classical apoptosis, ferroptosis has emerged as a significant contributor to blue light-induced retinal degeneration [16, 38]. Ferroptosis is an iron-dependent form of regulated necrosis driven by the accumulation of lipid peroxides to lethal concentrations. Its central negative regulator, glutathione peroxidase 4 (GPX4), reduces phospholipid hydroperoxides to non-toxic lipid alcohols. Blue light suppresses GPX4 expression and activity, permitting uncontrolled lipid peroxidation [16, 39]. Concurrently, long-chain acyl-CoA synthetase 4 (ACSL4) is upregulated, increasing the incorporation of oxidation-prone polyunsaturated fatty acids into membrane phospholipids and thereby expanding the substrate pool for peroxidation [39]. Heme oxygenase-1 (HMOX1) is also induced; while cytoprotective under moderate stress, its overexpression under severe photochemical stress releases excessive ferrous iron (Fe^{2+}) from heme catabolism. This labile iron pool catalyzes Fenton reactions, generating highly reactive hydroxyl radicals that propagate lipid peroxidation and drive ferroptotic execution [16, 38].

PARP-1-mediated cell death (parthanatos) represents an additional pathway recently implicated in blue light-induced retinal damage [21]. Excessive oxidative DNA damage leads to hyperactivation of poly (ADP-ribose) polymerase-1 (PARP-1), which consumes nicotinamide adenine dinucleotide (NAD^+), depleting intracellular ATP and causing energy collapse. This necrotic death is morphologically and biochemically distinct from apoptosis and ferroptosis. Moreover, poly(ADP-ribose) polymers released from dying cells can trigger mitochondria-derived apoptosis-inducing factor (AIF)-dependent death in neighboring cells, propagating injury beyond the initially damaged area. This pathway may be particularly relevant under acute, high-intensity blue light exposure and represents a potential target for pharmacological intervention.

The inflammatory arm of photochemical damage is mediated primarily by the NLRP3 inflammasome in RPE cells. Blue light-induced mitochondrial ROS, potassium efflux, and A2E-mediated lysosomal destabilization serve as activation signals for NLRP3 assembly [20, 40]. Active NLRP3 cleaves pro-caspase-1, which in turn processes pro-interleukin-1β and pro-interleukin-18 into their mature, secreted forms. Simultaneously, caspase-1 cleaves gasdermin D, generating N-terminal fragments that oligomerize and form plasma membrane pores, executing pyroptosis – a lytic, pro-inflammatory mode of cell death [40]. Released cytokines recruit microglia and macrophages, amplifying retinal inflammation. Notably, green light (500-550 nm) exerts an even stronger pro-

inflammatory effect than blue light, whereas red light (630-650 nm) displays anti-inflammatory properties, highlighting the importance of full-spectrum phototoxicity assessment [15].
Endoplasmic reticulum (ER) stress further contributes to the damage cascade [41]. Accumulation of oxidatively damaged proteins in the ER lumen activates the unfolded protein response (UPR), an adaptive system aimed at restoring proteostasis. When adaptive capacity is exceeded, the UPR switches to pro-apoptotic signaling via the PERK-eIF2α-ATF4-CHOP axis [41]. The transcription factor CHOP upregulates pro-apoptotic Bcl-2 family members and suppresses anti-apoptotic Bcl-2, lowering the threshold for mitochondrial outer membrane permeabilization [21, 41]. Notably, the tumor suppressor p53, stabilized under both ER stress and DNA damage, further amplifies CHOP-mediated apoptosis. Experimental inhibition of p53 with pifithrin-α significantly reduces retinal cell death following blue light exposure, confirming the contribution of this pathway [21].
With aging, lipofuscin and its major fluorophore A2E accumulate progressively in RPE cells, acting as potent endogenous photosensitizers [35, 42]. Under blue light, A2E generates singlet oxygen and other ROS, directly damaging lysosomal membranes and causing leakage of cathepsins into the cytosol. This lysosomal destabilization not only triggers NLRP3 activation but also impairs autophagic flux, further exacerbating the accumulation of damaged proteins and dysfunctional organelles [42, 43].
A critical functional consequence of chronic oxidative stress is impaired RPE phagocytosis. Under physiological conditions, each RPE cell daily phagocytoses 5-10% of shed photoreceptor outer segment discs – a lifelong metabolic burden [44]. ROS-mediated oxidative modification of phagocytic machinery proteins, including Mer tyrosine kinase (MerTK) and its ligands, progressively inhibits this process [44, 45]. Undigested outer segment material accumulates in the subretinal space, undergoes peroxidation, and serves as an additional source of lipofuscin precursors, establishing a self-amplifying pathological cycle [45]. Furthermore, blue light disrupts the outer blood-retinal barrier through oxidative modification of the tight junction protein zonula occludens-1 (ZO-1), compromising RPE barrier integrity [46].

Table 1. Main mechanisms of light-induced retinal damage and potential targets for pharmacological correction

Mechanism	Key molecules / markers	Cellular consequences	Potential target
Oxidative stress	ROS, MDA, 8-OHdG	Damage to proteins, lipids, DNA	ROS scavengers
Mitochondrial dysfunction	DRP1 ↑, Mfn2 ↓, OPA1 ↓, MMP ↓	Mitochondrial fragmentation, cytochrome c release	DRP1 inhibitors, mitochondrial antioxidants
Ferroptosis	GPX4 ↓, ACSL4 ↑, HMOX1 ↑, Fe^{2+} ↑	Lipid peroxide accumulation, cell death	HMOX1 inhibitors, iron chelators (DFO)
Inflammation	NLRP3 ↑, caspase-1 ↑, IL-1β ↑, IL-18 ↑	Microglial recruitment, pyroptosis	NLRP3 inhibitors (MCC950)
Endoplasmic reticulum stress	PERK ↑, eIF2α-P ↑, ATF4 ↑, CHOP ↑	UPR, apoptosis	PERK inhibitors, p53 inhibitors (PFT-α)
A2E-mediated damage	A2E ↑, lysosomal proteases	Photosensitization, lysosomal instability	Inducers of A2E degradation

Note: ↑ – increased level/activity; ↓ – decreased; ROS – reactive oxygen species; MDA – malondialdehyde; 8-OHdG – 8-hydroxy-2'-deoxyguanosine; MMP – mitochondrial membrane potential; UPR – unfolded protein response; DFO – deferoxamine; PFT-α – pifithrin-α.

Thus, blue light-induced retinal damage represents a multifactorial process in which oxidative stress serves as the central hub, while mitochondrial dysfunction, ferroptosis, inflammation, endoplasmic reticulum stress, and impaired phagocytosis are interconnected pathogenic mechanisms. Understanding these mechanisms opens opportunities for pharmacological intervention targeting various stages of the pathological cascade. The following section reviews existing methods of physical protection and analyzes promising pharmacological strategies for the prevention of light-induced retinal damage.

3. Existing physical protection methods and their limitations

Current strategies for preventing blue light-induced retinal damage rely primarily on physical barriers that limit the transmission of short-wavelength radiation to the posterior segment. These methods fall into three categories: optical correction devices (blue-blocking spectacles and contact lenses), intraocular implants (yellow-tinted intraocular lenses), and hardware/software filters for digital screens. Despite widespread adoption and aggressive marketing, the evidence base for their efficacy remains limited and, in several instances, contradictory.
Blue-blocking spectacles and contact lenses. Blue-blocking spectacle lenses selectively absorb or reflect light in the 400-450 nm range, typically exhibiting a yellowish tint proportional to their filtering capacity. Manufacturers claim these lenses reduce digital eye strain, improve sleep quality when used in the evening, and lower the risk of age-related macular degeneration (AMD). However, clinical data do not substantiate these claims. A large Cochrane meta-analysis of randomized controlled trials found no clinically meaningful evidence that blue-

blocking lenses reduce visual fatigue or computer vision syndrome symptoms compared to standard lenses [47]. Similarly, their effect on sleep quality remains unproven, with positive findings limited to small studies with low statistical power [48]. Critically, no long-term prospective studies have demonstrated a protective effect against AMD onset or progression [17].

Furthermore, non-selective blue light blockade carries potential adverse consequences. Excessive attenuation of the blue spectrum can impair color discrimination, particularly in the blue-yellow axis, and reduce contrast sensitivity under mesopic conditions [49]. More importantly, melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs), which mediate circadian photoentrainment, have peak sensitivity at 460-480 nm. Daytime over-blocking of these wavelengths may disrupt biological rhythm regulation, potentially contributing to affective and metabolic disorders [29, 50].

Blue-blocking contact lenses represent an alternative for individuals with high ametropia who prefer contact lens correction. However, their retinal protective efficacy is even less studied than that of spectacles, and they offer no demonstrated advantages over glasses [51].

Yellow-tinted intraocular lenses. Patients undergoing cataract surgery constitute a group particularly vulnerable to blue light phototoxicity. The aging crystalline lens progressively yellows and absorbs a significant portion of short-wavelength light. Its removal eliminates this natural filter. Yellow-tinted intraocular lenses (IOLs) incorporate blue-light-absorbing chromophores specifically designed to mimic the spectral filtering properties of the natural lens [52].

Theoretically, yellow IOLs should reduce phototoxic retinal load, especially in patients with pre-existing AMD or elevated risk. Over two decades of clinical experience have generated a substantial body of evidence. Multiple systematic reviews and meta-analyses have found no significant differences between yellow and clear IOLs in best-corrected visual acuity, contrast sensitivity, or color perception under photopic conditions [53, 54]. Under mesopic and scotopic conditions, some studies report a marginal reduction in light sensitivity among yellow IOL wearers, which may have implications for night driving [54].

Most importantly, large prospective cohort studies with follow-up periods of up to 10 years have not detected statistically significant differences in AMD incidence or progression between patients with yellow and clear IOLs [55, 56]. These findings question the rationale for routine use of yellow IOLs solely for macular protection. Moreover, as with spectacles, yellow IOLs reduce blue light transmission to melanopsin-expressing ipRGCs, potentially compromising circadian regulation – a concern particularly relevant for elderly patients who already exhibit age-related decline in ipRGC function [57]. The long-term impact of blue-filtering IOLs on sleep-wake cycles and activity rhythms remains under investigation.

Software and hardware screen filters. The third category encompasses software solutions (Night Shift, Night Mode, Eye Comfort Shield, and analogous applications) and physical screen filters applied to smartphones, tablets, and monitors. These tools reduce the display's correlated color temperature by suppressing blue pixel output, shifting the emission spectrum toward longer wavelengths [58].

Assessing their efficacy against retinal phototoxicity is challenging. Screen luminance (typically 150-250 cd/m²) is orders of magnitude below that of sunlight or even household LED lamps, and many experts consider direct photochemical retinal damage from screens unlikely under normal usage patterns [59]. The primary concern with evening screen use relates to circadian disruption: nocturnal blue light exposure suppresses pineal melatonin secretion, impairs sleep quality, and may predispose to metabolic dysfunction [30, 60]. In this context, software filters that reduce blue light emission during evening hours have a plausible physiological rationale and are endorsed by many sleep hygiene guidelines [61]. However, direct evidence of their beneficial effect on ophthalmological health is lacking.

General limitations of physical protection. All physical protection methods share a fundamental limitation: they do not address cumulative damage accumulating over decades. Physical barriers are effective only when used consistently and correctly – i.e., in every situation involving potential blue light exposure. This is practically unattainable in daily life. More importantly, these methods do not counteract pathogenic mechanisms triggered once light has already reached the retina. They merely reduce the dose but do not mitigate the consequences of the dose that inevitably penetrates to photoreceptors and RPE cells.

Furthermore, existing safety standards are based on acute phototoxicity thresholds and do not account for chronic, low-intensity exposure, which may be considerably more relevant under real-life conditions [62]. Animal studies indicate that regulatory photodamage thresholds may be overestimated by one to two orders of magnitude for chronic exposure [63], implying that sources classified as "safe" short-term may nonetheless damage the retina over years of daily use.

Thus, despite their wide availability and relative simplicity, physical protection methods cannot be regarded as a fully satisfactory solution. Their use is warranted, especially in high-risk occupational groups and in patients with existing macular pathology, but they do not obviate the need for pharmacological approaches capable of enhancing the intrinsic resilience of retinal tissue to photic stress. This gap motivates the search for and clinical evaluation of preventive pharmacological agents, which are addressed in the following section.

4. Pharmacological strategies for retinal protection against blue light

Unlike physical barriers, which merely attenuate light reaching the retina, pharmacological strategies aim to enhance the intrinsic resistance of retinal cells to photochemical damage. These approaches can be implemented

systemically (oral antioxidant supplements) or locally (eye drops). Systemic antioxidant therapy has already entered clinical practice: the AREDS and AREDS2 trials demonstrated that supplementation with vitamins C and E, zinc, lutein, and zeaxanthin reduces the risk of progression to advanced AMD [64, 65]. However, systemic administration has inherent limitations. Achieving therapeutic retinal concentrations requires relatively high oral doses, increasing the risk of systemic adverse effects. Moreover, most antioxidants exhibit poor penetration across the blood-retinal barrier [66]. Eye drops theoretically circumvent these drawbacks: they can be administered proactively, immediately before anticipated blue light exposure, and provide local action without systemic burden [67].

The critical challenge in developing retinal-protective eye drops is delivering the active compound to the posterior segment. The cornea and conjunctiva constitute effective barriers permeable primarily to low-molecular-weight lipophilic molecules. Most natural antioxidants are relatively large, hydrophilic compounds with limited transcorneal penetration [68]. Potential solutions include solubilizers such as cyclodextrins, nanoparticulate carriers, liposomes, micellar systems, and chemical modification to enhance lipophilicity (e.g., prodrug strategies) [69, 70]. Despite these obstacles, several compounds have demonstrated promising results in experimental models of light-induced retinal injury.

Figure 2 illustrates the conceptual distinction between existing physical protection and prospective pharmacological prevention.

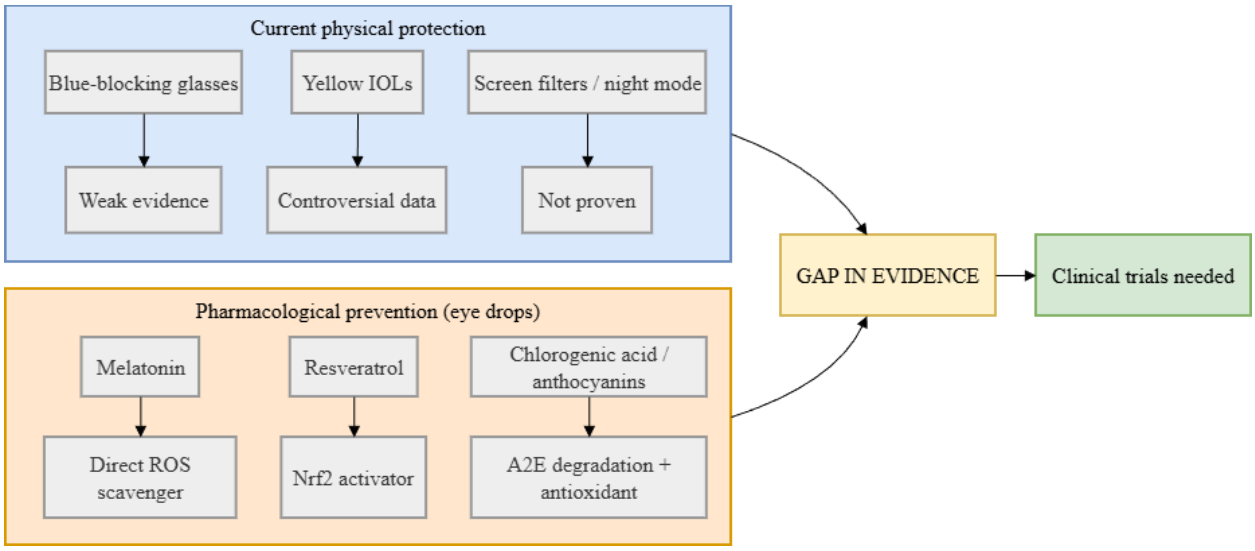

Figure 2. Comparison of existing physical protection methods and prospective pharmacological prevention. CGA – chlorogenic acid; Nrf2 – nuclear factor erythroid 2-related factor 2, a transcription factor regulating antioxidant response.

Melatonin. Melatonin (N-acetyl-5-methoxytryptamine) is a pineal hormone primarily known as a circadian rhythm regulator. However, it is also a potent endogenous antioxidant capable of directly scavenging hydroxyl radicals and peroxynitrite, as well as stimulating antioxidant enzyme activity [71]. Unlike most antioxidants, melatonin and its metabolites act in multiple cellular compartments, including mitochondria, where it accumulates at high concentrations owing to its lipophilicity. This feature makes melatonin particularly attractive for protecting retinal mitochondria – the organelles most vulnerable to light stress [71, 72].

In ARPE-19 cells, pre-incubation with melatonin (10-100 μM) reduced ROS accumulation, prevented mitochondrial membrane potential collapse, and decreased apoptosis following blue light irradiation [72]. In rodent models, topical or systemic melatonin reduced photoreceptor damage thickness and preserved electroretinographic parameters [73]. Melatonin's established safety profile in short- and long-term use is an important advantage; it is already used clinically as oral formulations and eye drops (e.g., for glaucoma) [74]. However, its application as a preventive agent against light damage requires further investigation, including determination of optimal concentration and instillation regimen.

Resveratrol. Resveratrol is a polyphenolic compound found in grape skins, red wine, peanuts, and certain berries. Its antioxidant properties stem primarily from activation of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2), which induces a cascade of antioxidant and detoxifying enzymes including heme oxygenase-1 (HO-1), glutathione S-transferase, and NAD(P)H:quinone oxidoreductase-1 [75, 76].

In A2E-laden ARPE-19 cells, resveratrol and its analog piceatannol (7.5-60 μM) prevented A2E photooxidation, reduced intracellular accumulation of this toxic metabolite, and suppressed apoptosis [75]. In a rat model of light-induced retinal damage, oral resveratrol (20 mg/kg/day) for two weeks prior to exposure preserved outer nuclear layer thickness and electroretinographic responses [77]. However, resveratrol has very low oral bioavailability

(<1%) and undergoes rapid metabolism. Its penetration to the retina via eye drops is also likely limited, although this question remains insufficiently studied [78]. An additional concern is that resveratrol may act as a photosensitizer under certain conditions, generating singlet oxygen upon blue light irradiation – a concentration-dependent effect requiring further study before clinical application [79].

Anthocyanins and other flavonoids. Anthocyanins are water-soluble pigments responsible for the red, blue, and purple coloration of berries (blueberry, bilberry, blackberry, lingonberry), grapes, red cabbage, and eggplants. They possess pronounced antioxidant and anti-inflammatory properties [80]. Pharmacokinetic studies show that orally administered anthocyanins cross the blood-retinal barrier and accumulate in retinal tissue at nanomolar concentrations – several orders of magnitude below effective in vitro concentrations [80, 81].

Among numerous anthocyanins, cyanidin-3-glucoside, delphinidin-3-glucoside, and malvidin-3-glucoside are the most extensively studied. In ARPE-19 cells, malvidin-3-glucoside (50 μM) effectively protected mitochondria from fragmentation and reduced ROS production after blue light exposure [82]. Cyanidin-3-glucoside (10-50 μM) prevented A2E photooxidation and toxic aldehyde formation [80]. In ex vivo studies on bovine photoreceptors, the structurally related flavonoid myricetin (5-40 μM) preserved cell viability under blue light: at 20 μM, myricetin reduced cell death by 72% compared to control, versus 48% for quercetin and 31% for kaempferol [83]. This superior efficacy is attributed to three hydroxyl groups on the B-ring that enhance radical-scavenging activity.

Quercetin, a widespread flavonoid (citrus fruits, onions, buckwheat, capers), protected ARPE-19 cells from A2E/blue light-induced apoptosis via antioxidant activity and downregulation of RAGE (receptor for advanced glycation end products), which is activated by carbonyl breakdown products of A2E [84]. In a rat model of light-induced damage (white fluorescent light, 3000 lux), intraperitoneal quercetin (50 mg/kg/day for 6 days before exposure) reduced the number of cells with damaged DNA and apoptotic photoreceptors [85].

Chlorogenic acid and eggplant extract. Chlorogenic acid (CGA), an ester of caffeic and quinic acids found in green coffee, blueberries, apples, and eggplant peel, is of particular interest. Eggplant extract (EPX, containing 1.79% CGA) not only exhibits antioxidant properties but actively promotes degradation of already accumulated intracellular A2E – a mechanism that appears central to its protective effect. While lutein inhibits A2E accumulation, CGA and EPX significantly reduce existing levels of this toxic product [86]. In ARPE-19 cells loaded with a fluorescent A2E analog, EPX treatment (10-100 μg/mL) reduced intracellular fluorescence by 40-60% without cytotoxicity. Transcriptomic analysis revealed that EPX suppressed NF-κB activation and expression of pro-inflammatory genes (CXCL8, IL1B) induced by blue light. In a BALB/c mouse model, oral EPX (100-200 mg/kg/day) reduced outer nuclear layer degeneration and preserved RPE cell numbers [86].

These data suggest that combining an antioxidant with an agent that promotes A2E degradation may be particularly effective for preventing and treating age-related retinal changes.

Limitations of the pharmacological approach. Despite promising preclinical data, the clinical translation of antioxidant eye drops faces several obstacles. First and foremost is delivery to the posterior segment. All the compounds discussed are relatively large, hydrophilic or amphiphilic molecules that poorly cross the corneal barrier [68]. Various delivery systems are under development (nanoparticles, micelles, cyclodextrin complexes, ion-induced gels) but none has yet become standard [69, 70].

Second, stability remains problematic. Many natural antioxidants are unstable in aqueous solution, sensitive to light and temperature, complicating the development of formulations with adequate shelf life. Curcumin, for instance, itself becomes a photosensitizer upon blue light exposure, generating ROS – an effect that may negate its protective properties.

Third, preclinical standardization is lacking. Studies employ different models, doses, administration routes, and irradiation protocols, hindering cross-study comparisons and reproducibility. A systematic analysis of 14 preclinical studies using ARPE-19 and primary RPE cultures exposed to blue light (440-460 nm, 0.5-4.5 J/cm²) found that pre-incubation with natural antioxidants (melatonin, resveratrol, anthocyanins, quercetin) reduced intracellular ROS by a median of 54% (95% CI: 41-67%) at 25-100 μM. However, direct head-to-head comparisons under identical conditions were conducted in only three studies, precluding definitive conclusions about the leading candidate. Melatonin showed the largest effect in these comparative studies (68% ROS reduction at 50 μM vs. 52% for resveratrol and 47% for quercetin) [82, 85, 87].

Fourth, and most critically, no clinical trials have evaluated the efficacy of antioxidant eye drops for preventing light-induced retinal damage in humans. All available data derive from in vitro or animal models. Effects observed in cell cultures at 10-100 μM may not be achievable through topical instillation in the living human eye. Table 2 summarizes the principal pharmacological candidates, their mechanisms of action, key preclinical findings, effective concentration ranges, and an assessment of their clinical translatability.

Table 2. Promising compounds for the prevention of light-induced retinal damage

Compound	Source	Mechanism	Key preclinical findings	Effective concentration / dose	Clinical translatability
Melatonin	Endogenous hormone, synthetic	Direct ROS scavenger, mitochondrial protection	ARPE-19, rodents: ↓ ROS, ↓ apoptosis,	10-100 μM (in vitro); 10 mg/kg (oral, in vivo)	High: established safety; eye drops exist for glaucoma; lipophilic;

			preserved ERG		mitochondrial accumulation
Myricetin	Berries, grapes, walnuts	Direct antioxidant (3 OH groups on B-ring), mitochondrial stabilization	Bovine photoreceptors ex vivo: ↓ cell death 72% at 20 μM; superior to quercetin (48%) and kaempferol (31%)	5-40 μM (ex vivo)	Low: no in vivo retinal data; corneal penetration unknown; limited pharmacokinetic data
Resveratrol	Grape skin, red wine	Nrf2/HO-1 activation, antioxidant	ARPE-19, rats: ↓ A2E, ↓ inflammation, preserved ONL	7.5-60 μM (in vitro); 20 mg/kg/day (oral, in vivo)	Low: bioavailability <1%; potential photosensitizer at certain concentrations; hydrophilic
Malvidin-3-glucoside	Blueberry, bilberry, eggplant	Antioxidant, mitochondrial stabilization	ARPE-19, 661W: ↓ ROS, ↓ mitochondrial fragmentation	10-50 μM (in vitro)	Low: poor corneal penetration; large hydrophilic molecule; nanomolar retinal levels after oral intake
Quercetin	Citrus fruits, onion, buckwheat	Antioxidant, RAGE downregulation	ARPE-19, rats: ↓ apoptosis, ↓ DNA damage	20-50 μM (in vitro); 50 mg/kg/day (i.p., in vivo)	Low: poor aqueous solubility; rapid metabolism; requires advanced delivery system
Chlorogenic acid (EPX)	Coffee, blueberry, eggplant	Antioxidant, A2E degradation	ARPE-19, mice: ↓ A2E (40-60%), ↓ NF-κB, preserved ONL	10-100 μg/mL EPX (in vitro); 100-200 mg/kg/day (oral, in vivo)	Moderate: unique A2E-degrading mechanism; corneal penetration unknown; EPX contains 1.79% CGA

Note: EPX – eggplant extract; CGA – chlorogenic acid; ONL – outer nuclear layer; ERG – electroretinography; i.p. – intraperitoneal; ROS – reactive oxygen species; A2E – lipofuscin bisretinoid; Nrf2 – nuclear factor erythroid 2-related factor 2; HO-1 – heme oxygenase-1; RAGE – receptor for advanced glycation end products.

Comparison of physical and pharmacological protection. In summary, physical barriers (spectacles, IOLs, screen filters) remain the only currently available means of protection, yet they have several limitations: their clinical efficacy is unproven, they do not address damage that has already occurred, and they require constant use. Pharmacological prevention, by contrast, aims to enhance the intrinsic resilience of the retina and can be used proactively; however, it remains at an early stage of development and requires confirmation of efficacy in clinical trials [88].

The optimal strategy will likely combine both approaches: judicious use of physical filters (particularly in the evening and when working with high-intensity sources) together with pharmacological support via antioxidant eye drops in at-risk populations. Realizing this strategy will require further research to optimize drop formulations, their pharmacokinetics, and long-term safety [89]. Table 3 provides a comparative summary of the two approaches across key parameters relevant to clinical implementation.

Table 3. Comparison of physical and pharmacological methods for retinal protection against blue light

Parameter	**Physical protection (spectacles, IOLs, filters)**	**Pharmacological prophylaxis (eye drops)**
Mechanism	Reduces blue light dose reaching the retina	Enhances cellular resistance to photochemical stress
Evidence base	Meta-analyses: efficacy not proven	Preclinical studies (in vitro, animal); clinical data absent
Application regimen	Continuous, during all light exposure	Proactive (before anticipated exposure)
Impact on circadian rhythms	Potentially negative with excessive blockade	Neutral or positive (melatonin)

Adverse effects	Altered color perception, reduced contrast sensitivity	Unstudied for this indication
Availability	Widely available	Not available (experimental stage)

DISCUSSION

This review systematizes current evidence on the molecular mechanisms of blue light-induced retinal damage, evaluates the limitations of physical protection, and assesses the prospects for pharmacological prevention with natural antioxidants.

Multifactorial pathogenesis. A central finding is the multifactorial nature of light-induced damage. Oxidative stress serves as the initiating hub, but damage propagates through interconnected pathways – mitochondrial dysfunction, ER stress, NLRP3-driven inflammation, ferroptosis, and impaired phagocytosis. This complexity implies that single-agent antioxidant therapy may be insufficient; combination formulations targeting multiple nodes (e.g., a direct ROS scavenger plus an Nrf2 activator plus an A2E-degrading agent) represent a rational development strategy, though this remains experimentally untested [90].

The preclinical-clinical disconnect. A striking discrepancy exists between preclinical and clinical data. Natural antioxidants robustly reduce ROS and apoptosis in cell and animal models, yet clinical studies of physical protection fail to demonstrate AMD prevention or reduction of visual fatigue. Contributing factors include: acute high-intensity exposure protocols in preclinical studies that poorly replicate chronic real-life exposure [91]; the improbability of achieving in vitro effective concentrations (10-100 μM) in human retina following topical instillation [68]; and lack of standardized protocols across preclinical studies [92].

Spectral dependence and safety standards. Green light (500-550 nm) elicits stronger retinal inflammation than blue light, while red light (630-650 nm) is protective [15]. These findings challenge the adequacy of the Blue Light Hazard weighting function as the sole photobiological safety criterion and support the development of full-spectrum standards [93].

Age and risk groups. Vulnerability varies with age. Children have highly transparent lenses but robust repair mechanisms; older pseudophakic patients have diminished antioxidant defenses and no natural lens filter [94, 95]. Epidemiologically, patients with early AMD and those implanted with clear IOLs should be considered priority populations for pharmacological prophylaxis. Occupational groups with predictable exposure (welders, mountaineers, heavy screen users) represent logical candidates for proactive eye drop use [96, 97].

Advances. Despite these challenges, this review advances the field in several respects. First, it integrates ferroptosis and PARP-1-mediated cell death as significant but underrecognized mechanisms of blue light phototoxicity, expanding the repertoire of therapeutic targets beyond classical apoptosis. Second, it provides a quantitative efficacy comparison of the principal natural antioxidant candidates (Table 2), identifying melatonin and myricetin as the most protective compounds in preclinical models while noting the critical absence of corneal penetration data. Third, it defines candidate selection criteria for eye drop development: aqueous solubility ≥0.1%, molecular weight <500 Da, and demonstrated storage stability – parameters rarely considered in preclinical antioxidant studies. Fourth, it specifies priority populations for future clinical trials: pseudophakic patients with clear IOLs (as a model of "removed natural protection") and occupationally exposed groups with predictable exposure schedules (welders, mountaineers).

Pharmacoeconomic barriers. Beyond the biological and technical challenges, pharmacoeconomic barriers warrant consideration. Prophylactic eye drops would target prevention rather than treatment, necessitating large trial populations and extended follow-up to demonstrate a reduction in AMD incidence – an endpoint that may take decades to manifest. The cost and logistical complexity of such trials, combined with uncertain reimbursement pathways for preventive ocular therapies, represent substantial obstacles to commercial development that are absent from current discourse.

Limitations. This review focused on natural antioxidants; synthetic compounds (e.g., emixustat) are also in development [98]. Most cited studies used ARPE-19 cells and rodents – models that lack a macula [99]. Drug delivery technologies were not comprehensively addressed [100]. No reviewed compound has undergone clinical trials for preventing light-induced retinal damage, representing both a significant evidence gap and a research opportunity.

CONCLUSION

Blue light triggers a pathological cascade in the retina centered on oxidative stress, leading to mitochondrial dysfunction, ER stress, inflammation, ferroptosis, and ultimately photoreceptor and RPE death. Aging and A2E accumulation amplify this process, predisposing to AMD. Current physical protection methods have limited evidence and do not address damage that has already occurred. Pharmacological prevention using natural antioxidants is a promising adjunct strategy, with melatonin, resveratrol, anthocyanins, quercetin, and chlorogenic acid showing protective effects in preclinical models. However, their clinical translation faces challenges of posterior segment delivery, stability, and the complete absence of human trials.

Priority tasks for the field include: (1) standardizing experimental models for photoprotection assessment; (2) developing effective delivery systems for retinal targeting via topical instillation; (3) conducting randomized controlled trials in defined risk groups – pseudophakic patients with clear IOLs and occupationally exposed

populations; and (4) evaluating long-term safety. The development of safe, effective eye drops for preventing light-induced retinal damage remains an unmet need with the potential to improve quality of life for millions exposed daily to artificial blue light.

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