

AREDS FORMULA COMBINED WITH SAFFRON, BILBERRY, AND ASTAXANTHIN: A NARRATIVE REVIEW OF MECHANISTIC RATIONALE, TRANSLATIONAL POTENTIAL, AND CLINICAL EVIDENCE IN AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss in adults over 50 years, affecting more than 196 million individuals worldwide. The AREDS2 formula, which contains lutein, zeaxanthin, vitamins C and E, zinc, and copper, remains the only evidence-based nutritional intervention proven to reduce the risk of AMD progression. However, AREDS2 does not address several established AMD pathological drivers, including photoreceptor neuroprotection, choroidal neovascularisation, mitochondrial dysfunction in the retinal pigment epithelium, NLRP3 inflammasome activation, and complement pathway dysregulation. This review synthesises the mechanistic rationale, translational evidence, and available clinical data for augmenting the AREDS2 formula with three bioactive compounds: saffron (*Crocus sativus*), bilberry (*Vaccinium myrtillus*), and astaxanthin, and evaluates their combined potential as a multimodal functional food strategy for AMD prevention and management. A structured narrative review was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Cochrane databases (January 2000–March 2025). Included studies comprised human randomised controlled trials, systematic reviews, meta-analyses, and mechanistic preclinical studies relevant to AMD and the three bioactives. Saffron's crocin and crocetin constituents provide photoreceptor neuroprotection via BDNF/TrkB and cAMP-PKA signalling, with clinical trials demonstrating significant electroretinographic improvement and visual acuity gains in early AMD. Bilberry anthocyanins reinforce retinal microvascular integrity, suppress NLRP3 inflammasome-mediated neuroinflammation, and accelerate rhodopsin regeneration. Astaxanthin provides superior lipid-phase singlet oxygen quenching at 6,000-fold the potency of vitamin E, with additional mitochondrial protective and anti-neovascular properties. The mechanistic profiles of all three bioactives are non-redundant with AREDS2 and address distinct, clinically validated AMD pathological pathways. The combination of AREDS2 with saffron, bilberry, and astaxanthin constitutes a mechanistically coherent, evidence-supported multimodal strategy for comprehensive AMD management. Dedicated combination randomised controlled trials with standardised endpoints are warranted to confirm clinical synergy and establish optimal dosing protocols.

KEYWORDS: age-related macular degeneration; AREDS2; saffron; crocin; bilberry; anthocyanins; astaxanthin; retinal neuroprotection; functional food; photoreceptor; macular pigment; choroidal neovascularisation; retinal oxidative stress.

1. INTRODUCTION

Age-related macular degeneration (AMD) is the predominant cause of irreversible central vision loss in the ageing population of high-income countries, and the third leading cause of blindness globally.^[1] The most recent global prevalence estimates indicate that AMD affects approximately 196 million individuals worldwide, with projections suggesting this figure will exceed 288 million by 2040 owing to the ageing of global populations.^[2] AMD disproportionately affects individuals over 50 years of age, with prevalence rising steeply from approximately 2% at age 55 to over 30% at age 85, representing one of the most age-associated chronic diseases in human medicine.^[3]

AMD is broadly classified into two clinical subtypes with distinct pathological mechanisms. Dry (non-neovascular) AMD, accounting for approximately 85–90% of all cases, is characterised by the progressive accumulation of extracellular deposits (drusen) beneath the retinal pigment epithelium (RPE), geographic atrophy of the RPE and overlying photoreceptors, and progressive central scotoma.^[4,5] Wet (neovascular) AMD, representing approximately 10–15% of cases but responsible for the majority of severe vision loss, involves the pathological growth of choroidal neovascular membranes (CNV) beneath the retina, driven primarily by vascular endothelial growth factor (VEGF) dysregulation, leading to rapid and often catastrophic central vision loss if untreated.^[4,5]

The pathophysiology of AMD is multifactorial and incompletely understood, but converging evidence implicates six principal mechanistic pathways: (i) chronic oxidative stress in the RPE and photoreceptors, driven by cumulative light exposure, high metabolic demands, and lipofuscin accumulation.^[6,7] (ii) mitochondrial dysfunction in RPE cells, characterised by reduced respiratory chain complex activity and increased mitochondrial DNA damage.^[8] (iii) neuroinflammation mediated by NLRP3 inflammasome activation, microglial activation, and complement pathway dysregulation.^[9,10,11,14] (iv) photoreceptor degeneration with loss of rod and cone neuroprotective signaling.^[12] (v) retinal microvascular dysfunction with compromised choroidal blood flow and capillary dropout; and (vi) choroidal neovascularisation driven by VEGF upregulation under hypoxic stress.^[13,14]

The landmark Age-Related Eye Disease Study (AREDS) and its successor AREDS2 established the first and to date only proven nutritional strategy for reducing AMD progression risk.^[15,16,17] The AREDS2 formula comprising lutein (10 mg), zeaxanthin (2 mg), vitamin C (500 mg), vitamin E (400 IU), zinc (80 mg), and copper (2 mg) demonstrated a statistically significant 43% reduction in progression from intermediate to advanced AMD over five years in a randomised controlled trial of 4,203 participants.^[15] Notably, AREDS2 also evaluated whether reducing zinc from 80 mg to 25 mg, a dose exceeding the tolerable upper daily intake level of 40 mg would maintain efficacy; however, this reduction demonstrated no statistically significant effect on AMD progression, and 80 mg remains the standard recommended dose.^[48] The primary mechanisms involve macular pigment optical density enhancement by lutein and zeaxanthin (physical blue light filtering and antioxidant activity within the macula) and broader antioxidant support by vitamins C and E and zinc.^[16,17]

Despite this evidence base, the AREDS2 formula leaves several of the six principal AMD pathological pathways unaddressed. It provides no photoreceptor neuroprotective signalling (trophic factor-mediated neuronal survival), no direct anti-VEGF or anti-neovascular activity, no targeted mitochondrial protection within RPE cells, limited inflammasome suppression, and no direct retinal microvascular reinforcement beyond generalised antioxidant effects.^[14,18] Multiple independent bioactive compounds have emerging evidence addressing precisely these unmet mechanisms. Saffron (*Crocus sativus*) and its active constituents crocin, crocetin, and safranal offer photoreceptor

neuroprotection via BDNF/TrkB neurotrophic signalling and cAMP-PKA pathway activation.^[19,20,21,22] Bilberry (*Vaccinium myrtillus*) anthocyanins reinforce retinal capillary integrity, suppress NLRP3 inflammasome activation, and accelerate rhodopsin regeneration.^[23-27] Astaxanthin, the predominant keto-carotenoid of *Haematococcus pluvialis* microalgae, provides extraordinary lipid-phase antioxidant potency, mitochondrial ROS suppression, and complement pathway modulation.^[28-31]

Several high-quality reviews have addressed individual components of this combination: Broadhead et al. (2019) on saffron in AMD, Canter & Ernst (2004) and Ozawa et al. (2012) on bilberry, and Galasso et al. (2018) on astaxanthin, but no review has synthesised the mechanistic rationale for their combined use alongside AREDS2 as an augmented multimodal functional food strategy. This review addresses that gap. The specific aim is to evaluate whether saffron, bilberry, and astaxanthin, in combination with the AREDS2 formula, provide a mechanistically non-redundant, clinically supported, and translationally feasible augmentation of current nutritional AMD management, the anatomical distribution of these six AMD pathological pathways across retinal layers, and the corresponding mechanistic targets of each component, is illustrated in Figure 1.

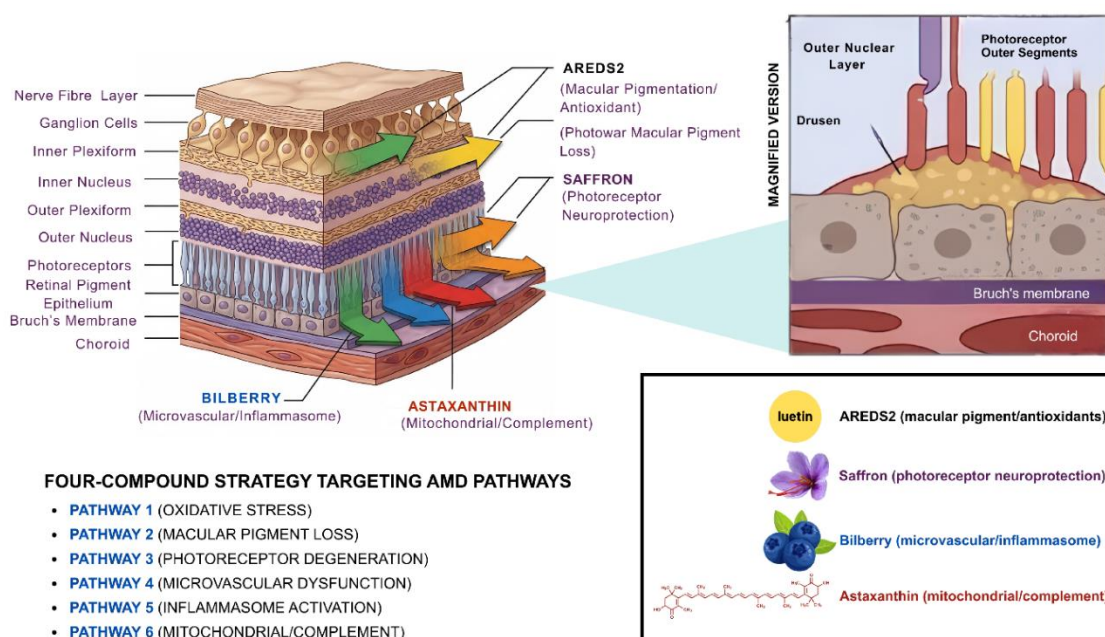


Figure 1: Macular cross-section illustrating six AMD pathological pathways mapped to their anatomical sites, with annotations showing how AREDS2, saffron, bilberry, and astaxanthin each target distinct mechanisms across the retinal layers.

2. Pathophysiology of Age-Related Macular Degeneration: Key Mechanistic Targets

2.1 Oxidative Stress and Lipofuscin Accumulation

The retina is the most metabolically active tissue in the human body per unit weight, consuming oxygen at approximately twice the rate of the brain cortex.^[6] The outer retina comprising the photoreceptors and RPE is particularly vulnerable to oxidative stress owing to: the continuous exposure to high-energy visible and ultraviolet light; the exceptionally high concentration of polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), in photoreceptor outer segment membranes; the daily phagocytosis by RPE cells of approximately 10% of photoreceptor outer segment length, producing reactive lipid intermediates; and the accumulation of lipofuscin a

complex mixture of oxidised lipid-protein adducts including the bis-retinoid N-retinylidene-N-retinylethanolamine (A2E) within RPE lysosomes.^[7,12]

A2E is particularly deleterious, acting as a photosensitiser that generates singlet oxygen upon blue light absorption, directly damaging mitochondrial membranes, inhibiting lysosomal function, and triggering RPE apoptosis.^[7,12] Cumulative lipofuscin accumulation progressively impairs RPE phagocytic capacity, creating a self-amplifying cycle of outer segment debris accumulation, drusen formation, and RPE dysfunction that characterises the early stages of dry AMD.^[7]

2.2 Mitochondrial Dysfunction in the RPE

RPE cells contain the highest density of mitochondria of any cell type in the human body, reflecting their extraordinary energetic demands in supporting photoreceptor function, mediating the visual cycle (retinoid recycling), maintaining the outer blood-retinal barrier, and performing continuous phagocytosis of photoreceptor outer segments.^[8] Mitochondrial dysfunction evidenced by reduced complex I and III activity, mitochondrial DNA deletion accumulation, reduced ATP synthesis, and increased mitochondrial membrane permeability is among the earliest detectable cellular changes in AMD-affected RPE, preceding RPE cell death and photoreceptor loss.^[8]

Mitochondrial dysfunction in AMD RPE is both a consequence of oxidative stress (mitochondrial DNA is particularly vulnerable to ROS owing to its proximity to the electron transport chain, limited repair capacity, and absence of protective histones) and a driver of further ROS production via electron transport chain uncoupling. This creates a mitochondrial-oxidative vicious cycle that AREDS2 vitamins, operating primarily as cytosolic antioxidants, are poorly positioned to interrupt, providing a clear mechanistic rationale for mitochondria-targeted supplementary agents such as astaxanthin and saffron.^[28,30]

2.3 Neuroinflammation, NLRP3 Inflammasome, and Complement Dysregulation

Emerging evidence identifies neuroinflammation as a central driver of AMD progression, distinct from but interrelated with oxidative stress.^[9,14,32] The NLRP3 inflammasome a cytosolic multiprotein complex assembled in response to danger signals including crystalline drusen components, oxidised lipids, and A2E activates caspase-1 in RPE cells and macrophages, leading to interleukin-1 beta (IL-1 β) and IL-18 cleavage and secretion.^[9] These cytokines recruit further inflammatory cells to the subretinal space, amplifying local inflammation and promoting RPE atrophy.^[7,9]

Complement system dysregulation represents one of the strongest genetic risk associations in AMD, with variants in complement factor H (CFH), complement factor B (CFB), complement component 2 (C2), and complement component 3 (C3) collectively accounting for the majority of the estimated heritability of AMD.^[10,11] The dysregulated complement cascade drives chronic low-grade inflammation at the RPE-Bruch's membrane interface, contributing to drusen formation and RPE stress.^[10] Notably, the AREDS2 formula provides only indirect and modest complement modulation through zinc supplementation; directly targeting complement via specific bioactives represents an important mechanistic gap.^[11]

2.4 Photoreceptor Neuroprotection and the Visual Cycle

Photoreceptors the light-sensing rod and cone cells of the outer nuclear layer are among the most specialised and vulnerable neurons in the body. Their maintenance depends critically on continuous neurotrophic support from RPE

cells, including secretion of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and pigment epithelium-derived factor (PEDF). As RPE function deteriorates in AMD, this neurotrophic support is progressively withdrawn, driving photoreceptor apoptosis that manifests clinically as scotopic (rod-mediated night vision) loss in early AMD and central (cone-mediated) vision loss in advanced AMD. The visual cycle the biochemical pathway by which all-trans-retinal released from photobleached opsins is recycled back to 11-cis-retinal by RPE enzymes also depends critically on RPE metabolic health, and its impairment delays rhodopsin regeneration and reduces photosensitivity.^[12]

2.5 Choroidal Neovascularisation and VEGF Signalling

Wet AMD arises from pathological ingrowth of new blood vessels from the choroidal circulation through Bruch's membrane into the subretinal space or sub-RPE space, driven primarily by VEGF-A upregulation in response to RPE hypoxia, oxidative stress, and complement activation.^[13,14,18] VEGF-driven CNV vessels lack the structural integrity of normal retinal vasculature, leading to vascular leakage, haemorrhage, and fibrovascular scarring that rapidly destroys macular architecture. While intravitreal anti-VEGF injections (ranibizumab, bevacizumab, aflibercept) represent the standard of care for wet AMD, the burden of monthly or bimonthly intravitreal injections is substantial, and a significant proportion of patients show incomplete treatment response. Nutritional agents capable of suppressing upstream VEGF transcription rather than neutralising VEGF protein post-secretion represent a complementary preventive strategy, particularly relevant for patients with intermediate AMD at risk of conversion to wet AMD.^[18,33]

The bidirectional feedback loops connecting these six pathological drivers, and the key molecular mediators linking them, are depicted schematically in Figure 2.

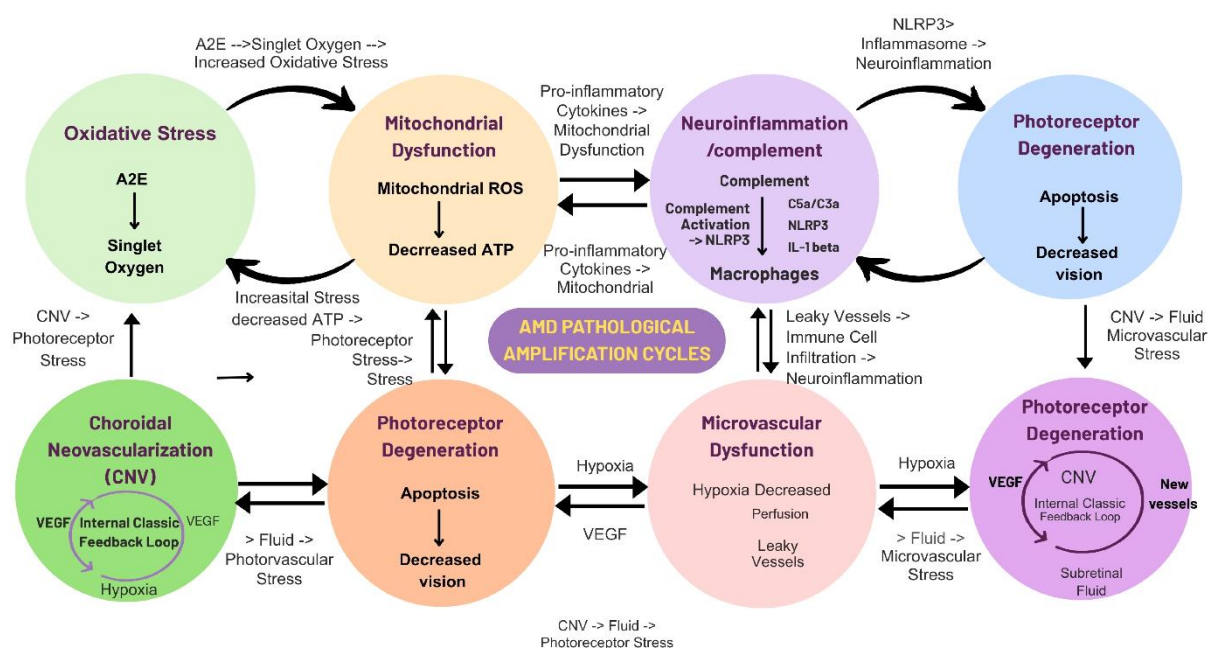


Figure 2: Illustration of six AMD pathological pathways and their bidirectional feedback loops, highlighting key molecular mediators and the mechanistic rationale for a multimodal therapeutic approach.

3. The AREDS2 Formula: Evidence-Based and Mechanistic Limitations

3.1 Composition and Clinical Evidence

The AREDS2 formula was developed following the original AREDS trial (2001), which demonstrated that supplementation with high-dose antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg) combined with zinc (80 mg as zinc oxide) and copper (2 mg as cupric oxide) reduced the risk of progression to advanced AMD by approximately 25% in patients with intermediate AMD or advanced AMD in one eye.^[16]

The AREDS2 modification replaced beta-carotene associated with increased lung cancer risk in smokers with lutein (10 mg) and zeaxanthin (2 mg), carotenoids that accumulate preferentially in the macula to form macular pigment.^[15,17]

The landmark AREDS2 trial enrolled 4,203 participants with intermediate AMD or advanced AMD in one eye and followed them for a median of five years. The primary outcome demonstrated a 43% reduction in the odds of progression to advanced AMD in the lutein/zeaxanthin group compared with the placebo group, with a 36% reduction in the risk of progression specifically to neovascular AMD and a 26% reduction in the risk of central geographic atrophy. Secondary analyses confirmed significant improvements in macular pigment optical density (MPOD), with each 0.1-unit increase in MPOD associated with a corresponding reduction in AMD progression risk.^[15]

3.2 Mechanisms of AREDS2 Action

Lutein and zeaxanthin are the only two carotenoids that selectively accumulate in the macula, where they form the macular pigment concentrated in the fovea at densities sufficient for meaningful optical filtering. Macular pigment absorbs short-wavelength (blue) light before it reaches the photoreceptors and RPE, reducing photon-induced singlet oxygen generation and lipofuscin photosensitisation.^[34] Both carotenoids also act as direct antioxidants, quenching singlet oxygen and scavenging peroxy radicals in the hydrophobic environment of photoreceptor outer segment membranes. Zeaxanthin additionally shows preferential accumulation in the foveal centre (Henle's fibre layer) where cone density is highest, potentially providing targeted protection of the highest-resolution photoreceptors.^[34]

Vitamin C acts as the primary aqueous-phase antioxidant within the retinal cytoplasm and extracellular fluid, quenching superoxide radicals and regenerating vitamin E from its radical form. Vitamin E (alpha-tocopherol) provides lipid-phase antioxidant activity, interrupting lipid peroxidation chain reactions in photoreceptor outer segment membranes.^[7] Zinc serves as a cofactor for multiple retinal antioxidant enzymes including superoxide dismutase (SOD) and catalase, and participates in visual cycle enzyme function, RPE structural protein maintenance, and notably in complement regulation. Zinc supplementation has been shown to modestly reduce complement activation at the RPE-Bruch's membrane interface.^[11]

3.3 Mechanistic Gaps and Unmet Pathological Targets

Despite its established clinical benefit, the AREDS2 formula addresses only two of the six principal AMD pathological pathways comprehensively: oxidative stress (vitamins C and E, lutein/zeaxanthin) and macular pigment optical density (lutein/zeaxanthin).^[15,18] The formula provides minimal direct activity against mitochondrial dysfunction in the RPE, lacks any photoreceptor neurotrophic support mechanism, exerts no direct anti-VEGF or anti-neovascular activity, provides only indirect NLRP3 inflammasome suppression, and does not directly modulate the complement cascade beyond zinc's modest effect.^[11,14,18] Furthermore, the AREDS2 formula was not designed to address retinal microvascular dysfunction, rhodopsin cycle optimisation, or the early scotopic (night vision) deterioration characteristic

of early AMD. These unmet mechanisms define the scientific rationale for augmenting the AREDS2 formula with mechanistically complementary bioactive compounds.

4. Saffron (*Crocus sativus*): Photoreceptor Neuroprotection and Retinal Rescue

4.1 Phytochemistry of Saffron

Saffron is the dried stigma of *Crocus sativus* (Iridaceae family), representing the world's most expensive spice by weight, with approximately 150,000 flowers required to produce 1 kg of dried saffron. The three principal bioactive constituents responsible for its pharmacological properties in the retinal context are: (i) crocin (crocetin digentiobioside), a water-soluble carotenoid glycoside and the primary pigment responsible for saffron's characteristic golden colour; (ii) crocetin, the lipophilic aglycone of crocin with superior membrane permeability; and (iii) safranal (2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde), a monoterpenoid aldehyde responsible for saffron's distinctive aroma, with demonstrated neuroprotective and anxiolytic properties.^[22]

Crocin and crocetin are structurally unique among carotenoids in containing a conjugated polyene chain with carboxylic acid end groups a configuration that confers both antioxidant activity and the capacity to interact with membrane proteins and intracellular signalling molecules at concentrations achievable through dietary supplementation. Crocin's water solubility enables distribution in aqueous ocular compartments, while crocetin's lipophilicity facilitates incorporation into photoreceptor outer segment membranes together providing complementary retinal distribution patterns.^[22]

4.2 BDNF/TrkB and cAMP-PKA Neuroprotective Pathways

The most clinically significant mechanism distinguishing saffron from other AMD-relevant nutraceuticals is its activation of neurotrophic survival pathways in photoreceptors. Crocin and crocetin have been demonstrated to upregulate brain-derived neurotrophic factor (BDNF) expression in RPE cells and to activate the tropomyosin receptor kinase B (TrkB) receptor on photoreceptors, initiating the PI3K-Akt and MAPK/ERK cell survival cascades that suppress caspase-3-mediated apoptosis.^[22,36] This neurotrophic mechanism is entirely absent from the AREDS2 formula and from any other commonly used ophthalmic nutraceutical.

Additionally, saffron constituents activate the cyclic adenosine monophosphate (cAMP) protein kinase A (PKA) signalling pathway in photoreceptors, a pathway known to mediate photoreceptor survival under oxidative and light-stress conditions. In a landmark series of experiments, Natoli et al. (2010) demonstrated that crocin supplementation rescued photoreceptors from light-induced degeneration in a rat model at doses equivalent to those used in human clinical trials (20 mg saffron/day), with histological evidence of preserved outer nuclear layer thickness and ERG functional preservation. Crucially, this rescue was observed even when saffron was administered after the damaging light exposure, indicating a therapeutic rather than purely preventive mechanism.^[47]

4.3 Anti-VEGF and Anti-Neovascular Activity

Crocetin inhibits hypoxia-inducible factor-1 alpha (HIF-1 α) stabilisation under hypoxic conditions a key transcriptional activator of VEGF gene expression in RPE cells stressed by ischaemia, oxidative damage, or complement activation.^[33] By destabilising HIF-1 α , crocetin reduces VEGF-A transcription and secretion, potentially suppressing the upstream angiogenic signal that drives CNV in wet AMD. *In vitro* studies confirm that crocetin reduces VEGF production by hypoxia-stressed ARPE-19 cells (the standard human RPE cell line) in a concentration-dependent manner at

concentrations achievable through supplementation. This anti-VEGF mechanism is entirely absent from AREDS2 and provides direct complementation to the formula's primary gap regarding neovascular AMD risk.^[33]

4.4 Clinical Evidence for Saffron in AMD

The clinical evidence for saffron in AMD is particularly strong for a botanical nutraceutical at this stage of development. Falsini et al. (2010) conducted a prospective, double-blind, crossover randomised controlled trial in 25 patients with early AMD, demonstrating that saffron supplementation at 20 mg/day for three months produced statistically significant improvements in focal electroretinogram (ERG) responses specifically the b-wave amplitude reflecting bipolar cell and Muller cell function driven by photoreceptor output with effects reversible upon cessation, confirming pharmacological dependence rather than disease modification in this short-term study.^[19] Marangoni et al. (2013) extended these findings in a larger cohort, demonstrating not only ERG improvements but also a clinically meaningful +0.3 logMAR improvement in best-corrected visual acuity (BCVA) over three months equivalent to approximately three lines of vision improvement on a standard chart a magnitude of change rarely observed with any nutraceutical in AMD.^[20] Broadhead et al. (2019) confirmed macular function improvements in a double-blind trial, providing further corroborating evidence for saffron's clinical efficacy in early AMD.^[21] The dual neuroprotective and anti-neovascular mechanisms underlying these clinical findings are illustrated in Figure 3.

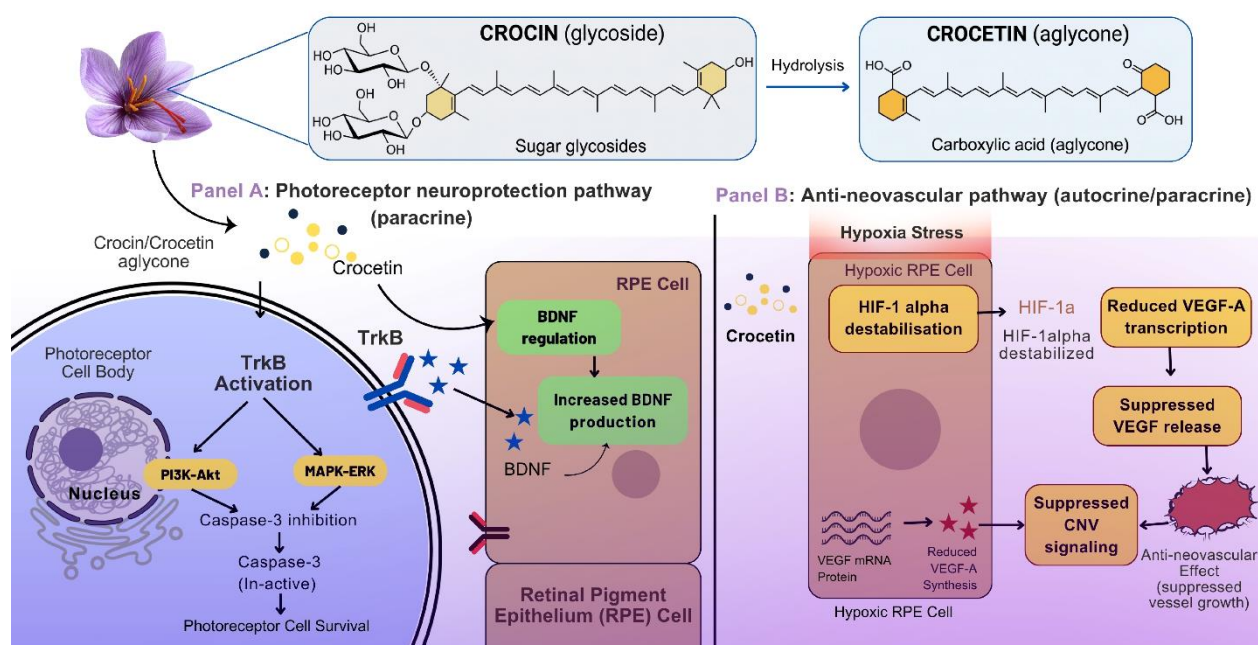


Figure 3: Dual-panel mechanistic diagram illustrating saffron's retinal actions: Panel A depicts the crocin/crocetin-mediated BDNF-TrkB neuroprotective pathway in photoreceptors; Panel B shows crocetin-driven HIF-1 α destabilisation and subsequent VEGF-A suppression. A chemical structure inset distinguishes crocin from crocetin.

5. Bilberry (*Vaccinium myrtillus*): Microvascular Integrity, Rhodopsin, and Inflammasome Modulation

5.1 Anthocyanin Composition and Ocular Bioavailability

Bilberry (*Vaccinium myrtillus*) is among the richest dietary sources of anthocyanins, water-soluble flavonoid pigments that give the berry its characteristic dark blue-purple colour.^[27,38] Bilberry anthocyanins are predominantly cyanidin-3-

glucoside (C3G), delphinidin-3-glucoside, petunidin-3-glucoside, peonidin-3-glucoside, and malvidin-3-glucoside, along with their respective galactoside and arabinoside conjugates a broader and more diverse anthocyanin profile than most other berry fruits.^[23] Standardised bilberry extract (Mirtoselect and similar) typically contains 36% total anthocyanins by weight.^[23]

A critical pharmacokinetic feature relevant to retinal drug delivery is the demonstrated capacity of bilberry anthocyanins particularly C3G to reach the retinal tissue intact after oral supplementation.^[25] Radiolabelled C3G studies in rodents have confirmed retinal accumulation at concentrations sufficient for receptor-mediated pharmacological activity within 30 minutes of oral dosing. Human pharmacokinetic studies using mass spectrometry have detected intact anthocyanin glucosides in the vitreous humour of patients undergoing vitrectomy who received pre-operative bilberry supplementation, confirming clinically relevant ocular bioavailability in the human eye.^[25,27]

5.2 Rhodopsin Regeneration and Dark Adaptation

The visual cycle depends on the rapid regeneration of rhodopsin (the rod photopigment) from all-trans-retinal and opsin following photobleaching. Impaired rhodopsin regeneration manifesting as delayed dark adaptation and reduced scotopic sensitivity is among the earliest functional deficits in AMD, detectable before significant drusen accumulation or structural retinal changes.^[24,25] Bilberry anthocyanins, particularly C3G, have been demonstrated to facilitate rhodopsin regeneration by: (i) acting as structural analogues of 11-cis-retinal that transiently stabilise opsin in a rhodopsin-like conformation, accelerating the kinetics of regeneration; and (ii) binding to the retinal binding site of opsin, protecting it from oxidative modification during the photobleached interval.^[24,25] These mechanisms explain the traditional and empirically observed improvement in dark adaptation and night vision associated with bilberry consumption.^[23,39]

5.3 NLRP3 Inflammasome Suppression

Bilberry anthocyanins particularly C3G and delphinidin have been demonstrated in multiple *in vitro* and *in vivo* studies to suppress NLRP3 inflammasome assembly and activation in RPE cells and retinal macrophages (microglia). The proposed mechanisms involve: (i) reduction of mitochondrial ROS generation (a prerequisite for NLRP3 priming) through direct free radical scavenging; (ii) direct interference with NLRP3-NEK7 protein interaction required for inflammasome complex assembly; and (iii) inhibition of NF- κ B-mediated pro-IL-1 β and pro-IL-18 transcription (the 'priming' signal for NLRP3 activation).^[14,26] Suppression of NLRP3-driven IL-1 β release in the subretinal space reduces the inflammatory cascade that drives geographic atrophy progression, providing a mechanistic pathway not addressed by any component of the AREDS2 formula.^[9,14]

5.4 Retinal Microvascular Protection

Bilberry anthocyanins provide specific structural protection to the retinal microvasculature through collagen stabilisation mechanisms [40]. C3G and other bilberry anthocyanins inhibit collagenase and elastase activity, protecting the collagen scaffold of capillary basement membranes from enzymatic degradation. They also stabilise collagen cross-links by binding to procollagen molecules, increasing the tensile strength and resistance to osmotic stress of capillary walls. In clinical studies of diabetic retinopathy, a model of retinal microvascular disease sharing pathological features with AMD choroidal dysfunction bilberry extract supplementation significantly reduced retinal vascular permeability as assessed by fluorescein angiography, reduced haemorrhage incidence, and improved pericyte survival.^[40,41]

Additionally, bilberry anthocyanins inhibit VEGF-A-induced retinal endothelial cell proliferation and migration in choroidal endothelial cell models providing anti-neovascular activity that complements saffron's upstream HIF-1 α /VEGF mechanism. Where saffron reduces VEGF transcription, bilberry anthocyanins reduce the endothelial cell response to VEGF together providing more comprehensive anti-CNV coverage than either agent alone.^[24]

6. Astaxanthin: Superior Lipid-Phase Antioxidant Power, Mitochondrial Protection, and Complement Modulation

6.1 Structure and Antioxidant Properties

Astaxanthin (3,3'-dihydroxy- β , β -carotene-4,4'-dione) is a xanthophyll keto-carotenoid characterised by ketone groups at the 4 and 4' positions and hydroxyl groups at the 3 and 3' positions of the beta-ionone rings.^[28,29] This unique structure, which does not exist in any mammalian tissue and must be obtained entirely through diet or supplementation, confers extraordinary antioxidant properties. The natural trans-astaxanthin isomer from *Haematococcus pluvialis* microalgae is considered the most biologically potent form.^[28]

Astaxanthin's antioxidant superiority arises from its ability to span the full width of the lipid bilayer membrane with its polar end-groups anchored in the aqueous interface and its polyene chain spanning the hydrophobic core enabling simultaneous quenching of free radicals in both the aqueous and lipid phases.^[28,35] This membrane-spanning configuration provides 6,000-fold greater singlet oxygen quenching capacity than vitamin E, 800-fold greater than Coenzyme Q10, 550-fold greater than vitamin E in a lipid peroxidation model, and 65-fold greater than vitamin C in singlet oxygen quenching. Critically, unlike beta-carotene and some other carotenoids, astaxanthin does not act as a prooxidant at high oxygen tensions, making it safer for lung tissue and suitable for non-smokers and smokers alike.^[43]

6.2 Mitochondrial Protection in the RPE

Unlike vitamin E (which is anchored to the outer leaflet of mitochondrial membranes) or vitamin C (which operates in the aqueous mitochondrial matrix), astaxanthin's membrane-spanning configuration enables it to neutralise ROS at the inner mitochondrial membrane precisely the site of electron transport chain-derived superoxide generation in stressed RPE cells.^[28,30] In ARPE-19 cell models subjected to H₂O₂-induced oxidative stress, astaxanthin pretreatment prevented the loss of mitochondrial membrane potential, maintained cytochrome c retention (preventing release into the cytoplasm and caspase-9 activation), preserved ATP production capacity, and reduced mitochondrial DNA oxidative damage (8-OHdG) at concentrations achievable through supplementation.^[30]

This mitochondrial protective capacity is particularly relevant to AMD pathophysiology given the central role of RPE mitochondrial dysfunction in disease initiation and progression. The combination of astaxanthin's mitochondrial ROS suppression with saffron's mitochondrial membrane potential maintenance addresses the RPE energy crisis from complementary angles astaxanthin suppressing the upstream ROS generation that drives mitochondrial damage, while saffron's safranal component preserves the downstream functional integrity of the mitochondrial membrane potential representing a potent dual-agent mitochondrial protection strategy entirely absent from the AREDS2 formula.^[31]

6.3 Complement Pathway Modulation

Astaxanthin has emerged as one of the few nutraceutical agents with evidence of direct complement pathway modulation relevant to AMD genetic risk.^[42,43] *In vitro* studies demonstrate that astaxanthin reduces complement factor D activity and inhibits the formation of the membrane attack complex (MAC; C5b-9) on RPE cell surfaces under

complement-activating conditions.^[42] Additionally, astaxanthin upregulates complement factor H (CFH) expression in RPE cells CFH being the principal soluble complement inhibitor at the RPE-Bruch's membrane interface, with loss-of-function variants (Y402H polymorphism) representing the strongest single genetic risk factor for AMD.^[10,11] By upregulating CFH expression, astaxanthin may partly compensate for the reduced complement inhibitory capacity associated with the Y402H risk allele, providing a genotype-relevant mechanism of particular translational interest.

6.4 Clinical Evidence for Astaxanthin in Retinal Health

Nagaki et al. (2002) conducted a prospective clinical study in 49 patients with eye strain and visual fatigue, demonstrating that astaxanthin supplementation (6 mg/day) for four weeks significantly improved retinal arteriolar blood flow as measured by laser Doppler flowmetry, reduced visual fatigue scores, and improved visual acuity findings consistent with astaxanthin's demonstrated improvement in retinal capillary endothelial function. Piermarocchi et al. (2012) conducted a randomised controlled trial combining lutein, zeaxanthin, and astaxanthin in 145 patients with AMD and diabetic maculopathy, demonstrating significant BCVA improvements and contrast sensitivity gains over 12 months in the AMD subgroup, providing direct evidence of astaxanthin's additive contribution within a carotenoid combination formula.^[45] Multiple experimental studies using AMD mouse models (NaIO₃-induced RPE degeneration, light-damage models, Ccl2/Cx3cr1 double knockout) have demonstrated astaxanthin-treated groups showing significantly better photoreceptor preservation, reduced ERG deterioration, and reduced drusen-like deposits compared with controls.^[43,44] Astaxanthin's chemical structure, antioxidant potency relative to other compounds, and its dual mechanisms of action in retinal cells are summarised in Figure 4.

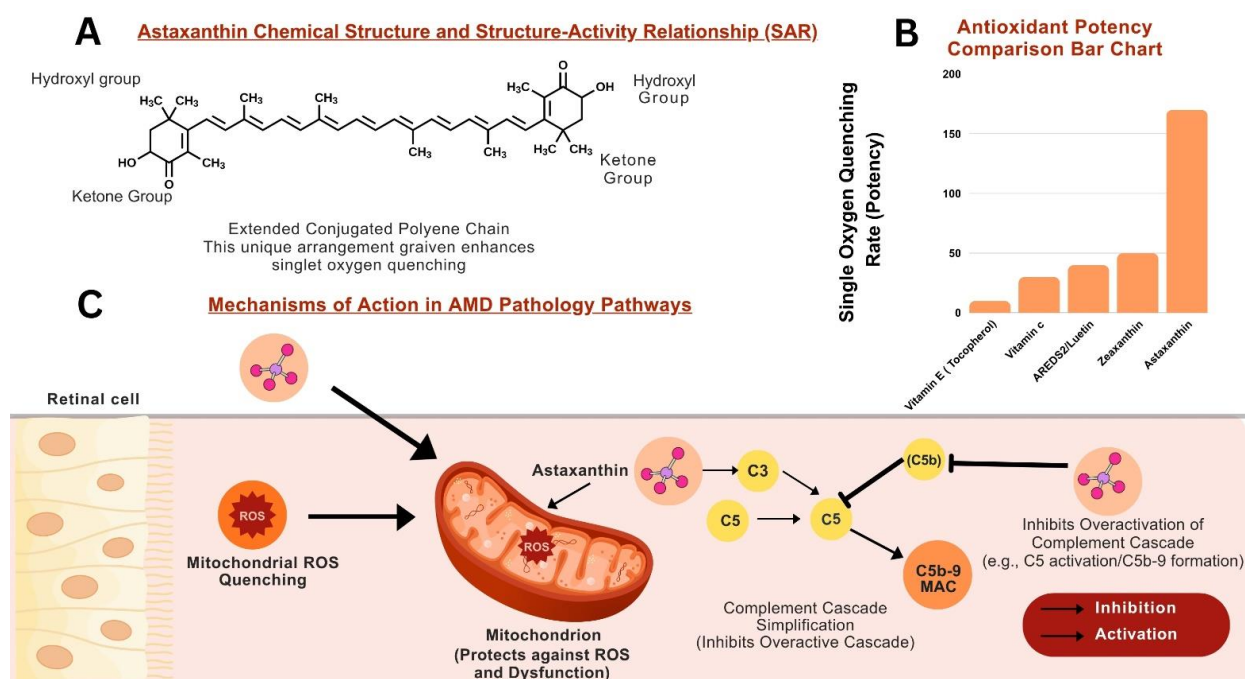


Figure 4: Astaxanthin's chemical structure, antioxidant potency comparison, and dual mechanisms of action in retinal cells: mitochondrial ROS quenching and complement cascade inhibition.

7. Mechanistic Rationale for the Combined Four-Component Strategy

7.1 Non-redundant Mechanistic Targeting

The scientific rationale for combining the AREDS2 formula with saffron, bilberry, and astaxanthin rests on the principle of mechanistic non-redundancy across the six established AMD pathological pathways.^[14,17,18] Analysis of the mechanistic profiles of all four components reveals that they collectively address each pathway through distinct molecular targets, with minimal mechanistic overlap and substantial potential for complementary or additive interactions.^[15-17]

The AREDS2 formula provides the foundational evidence-based macular pigment and antioxidant platform. Saffron adds a unique layer of photoreceptor neuroprotection (BDNF/TrkB, cAMP-PKA) absent from all other components, and anti-VEGF activity via HIF-1 α suppression.^[19,20,33,37,47] Bilberry adds NLRP3 inflammasome suppression a mechanistically distinct neuroinflammatory pathway not addressed by AREDS2 or the other bioactives along with retinal microvascular structural reinforcement and rhodopsin cycle support.^[23-27,40] Astaxanthin adds the deepest layer of lipid-phase and mitochondrial antioxidant protection, surpassing the capacity of AREDS2 vitamins, and uniquely provides complement pathway modulation through CFH upregulation.^[28-31,42,45] The mechanistic profiles and proposed clinical contributions of all four components are summarised in Table 1.

7.2 Summary Tables: Mechanistic Profiles and Proposed Synergisms

Table 1: Summary of key clinical and randomised trial evidence for AREDS2, saffron, bilberry, and astaxanthin in AMD and related retinal conditions.

Compound	Primary Retinal Mechanisms	Key Clinical / Preclinical Evidence	Proposed AREDS Complementations	References
AREDS2 Formula (Vitamins C & E, Zinc, Copper, Lutein, Zeaxanthin)	Macular pigment optical density (MPOD) enhancement; antioxidant quenching of singlet oxygen and lipid peroxides in outer retina; zinc-dependent retinal pigment epithelium (RPE) enzyme cofactor activity	43% reduction in AMD progression to advanced stage (AREDS2 RCT, 4,203 participants); significant MPOD increase; reduced drusen progression	Foundational evidence base and regulatory reference point; provides carotenoid macular pigment core; complemented by bioactives targeting non-AREDS pathways	[15-17]
Saffron (<i>Crocus sativus</i> ; crocin, crocetin, safranal)	Photoreceptor rescue via cAMP-PKA pathway; BDNF/TrkB neuroprotection; HIF-1 α /VEGF suppression (anti-neovascular); mitochondrial membrane potential preservation in RPE; Nrf2-ARE antioxidant induction	Improved ERG a/b-wave amplitudes in early AMD (Falsini et al., 2010); BCVA improvement +0.3 logMAR at 3 months (Marangoni et al., 2013); preserved contrast sensitivity; photoreceptor rescue in light-damage models	Unique photoreceptor neuroprotection (AREDS2 does not address neuronal survival); anti-VEGF complementation for wet AMD risk; mitochondrial protection in RPE beyond antioxidant vitamins	[19-21,33,36,37]
Bilberry (<i>Vaccinium myrtillus</i> ; anthocyanins, especially cyanidin-3-glucoside)	Rhodopsin regeneration acceleration; capillary basement membrane strengthening via collagen cross-link stabilisation; NF- κ B and NLRP3 inflammasome suppression; VEGF-A downregulation; mitophagy induction in	Improved dark adaptation and night vision (multiple RCTs); reduced retinal vascular permeability in diabetic retinopathy; protective against light-induced photoreceptor apoptosis; VEGF	Retinal microvascular integrity (distinct from AREDS antioxidants); rhodopsin regeneration relevant to scotopic vision decline in AMD; NLRP3 inflammasome suppression — a	[23-27, 38-41]

	RPE	reduction in choroidal neovascularisation models	pathway not targeted by AREDS2	
Astaxanthin (<i>Haematococcus pluvialis</i> ; keto-carotenoid)	Singlet oxygen quenching (6,000x vitamin E potency in lipid phase); mitochondrial ROS suppression in photoreceptors and RPE; apoptosis inhibition via Bcl-2/Bax pathway; complement system modulation (CFH pathway); anti-VEGF activity	Reduced retinal oxidative stress biomarkers in human trials; improved retinal blood flow (Nagaki et al., 2002); RPE mitochondrial protection in H2O2 models; improved visual acuity in prospective studies; reduced ERG deterioration in AMD mouse models	Superior lipid-phase antioxidant potency beyond vitamins C & E; mitochondrial-targeted ROS suppression absent from AREDS2; complement pathway modulation addressing AMD genetic risk; crosses blood-retinal barrier efficiently	[29-31]

Abbreviations: AMD, age-related macular degeneration; MPOD, macular pigment optical density; RPE, retinal pigment epithelium; RCT, randomised controlled trial; BCVA, best-corrected visual acuity; ERG, electroretinography; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; HIF-1 α , hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response element; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; NLRP3, NLR family pyrin domain containing 3; NF- κ B, nuclear factor kappa-B; CFH, complement factor H; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein.

7.3 Antioxidant Synergy: Multi-Compartment Coverage

The antioxidant components of the four-compound strategy provide mechanistically complementary, multi-compartment coverage extending substantially beyond the AREDS2 formula alone. AREDS2 vitamins C and E provide aqueous (vitamin C) and lipid-phase (vitamin E) antioxidant activity at standard potency.^[35,43] Astaxanthin provides superior lipid-phase singlet oxygen quenching at 6,000-fold the potency of vitamin E in the same membrane compartment, but without vitamin E displacement owing to distinct mechanisms (vitamin E interrupts lipid peroxidation chain reactions; astaxanthin primarily quenches singlet oxygen from photosensitised A2E).^[28,35]

Bilberry anthocyanins provide additional aqueous-phase free radical scavenging in retinal cytoplasm and extracellular compartments. Saffron's crocin induces Nrf2-ARE transcriptional upregulation of endogenous antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase) adding an enzymatic antioxidant dimension absent from all other components.^[26,41] Together, these mechanisms provide comprehensive multi-compartment antioxidant defence encompassing the aqueous cytoplasm, the lipid membrane phase, the mitochondrial inner membrane, and the endogenous enzymatic antioxidant system.^[47]

7.4 Convergent Anti-VEGF Complementation for Wet AMD Risk

A particularly clinically relevant synergism concerns the combined anti-VEGF activity of saffron and bilberry in the context of wet AMD prevention.^[26,33] Crocetin suppresses HIF-1 α -mediated VEGF transcription in hypoxic RPE cells, reducing the production of VEGF protein at its source. Bilberry anthocyanins independently suppress VEGF-A-driven endothelial cell proliferation and migration, targeting the biological response to VEGF at the endothelial cell level.^[33] The combination thus provides dual-level anti-angiogenic coverage: upstream (reduced VEGF secretion by stressed

RPE; saffron) and downstream (reduced endothelial response to secreted VEGF; bilberry). Astaxanthin provides a third complementary anti-VEGF mechanism through its ability to reduce oxidative stress the primary driver of HIF-1 α stabilisation thereby indirectly reducing the oxidative trigger for VEGF upregulation.^[28,44] Collectively, these three agents address the neovascular AMD risk dimension that is entirely absent from the AREDS2 formula.^[18]

7.5 Complement and Inflammasome: Addressing Genetic AMD Risk

The combination also offers particular mechanistic relevance for individuals carrying high-risk AMD genetic variants. Patients with the CFH Y402H risk allele present in approximately 35% of Europeans and conferring a 5-7-fold increase in AMD risk have constitutively reduced CFH-mediated complement inhibition at the RPE-Bruch's membrane interface.^[10,11,42] Astaxanthin's demonstrated capacity to upregulate CFH expression in RPE cells may partially compensate for reduced CFH protein function in these individuals.^[42] Similarly, patients with NLRP3 inflammasome-activating genetic variants may derive disproportionate benefit from bilberry's inflammasome suppression.^[9,26] This genetic stratification principle suggests that the four-component combination may have particular value in pharmacogenomically-guided AMD prevention programmes, with astaxanthin providing targeted complementation for complement-pathway risk allele carriers.^[9,26] The collective coverage of all six AMD pathological pathways by this four-component strategy, including key inter-compound synergies, is shown in Figure 5.

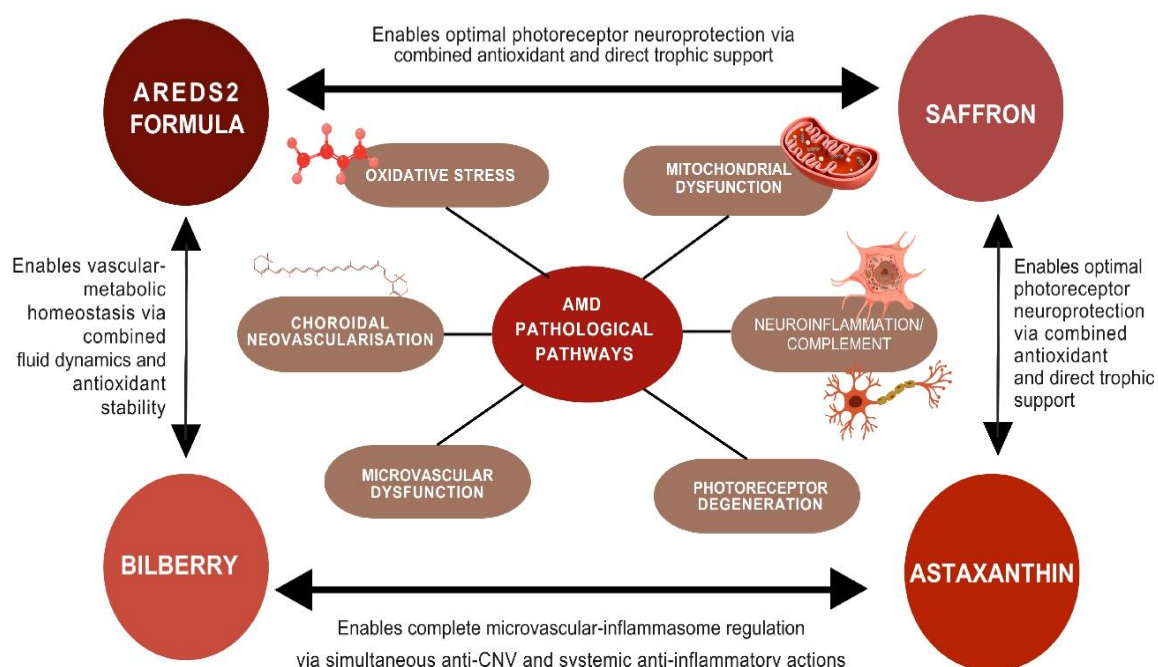


Figure 5: Synergy map illustrating how AREDS2, saffron, bilberry, and astaxanthin collectively target all six AMD pathological pathways, with inter-compound arrows highlighting key enabling synergies across oxidative, mitochondrial, neuroimmune, and microvascular mechanisms.

8. Summary of Clinical Evidence

Table 2: Summary of key clinical and randomised trial evidence for AREDS2, saffron, bilberry, and astaxanthin in AMD and related retinal conditions.

Study / Authors	Compound	Design	Population	Duration	Key Outcomes
AREDS2 Research Group (2013)	AREDS2 (lutein/zeaxanthin + vitamins C, E, zinc, copper)	RCT (n=4,203)	Intermediate/advanced AMD	5 years	43% reduced risk of advanced AMD; lutein/zeaxanthin superior to beta-carotene. ^[15]
Falsini et al. (2010)	Saffron 20 mg/day	RCT, crossover (n=25)	Early AMD	3 months	Significant improvement in ERG focal responses; improved macular function; effects reversible on cessation. ^[19]
Marangoni et al. (2013)	Saffron 20 mg/day	Prospective RCT (n=33)	Early AMD	3 months	+0.3 logMAR BCVA improvement; improved contrast sensitivity; sustained ERG benefit. ^[20]
Broadhead et al. (2019)	Saffron 20 mg/day	RCT, double-blind (n=26)	Early/intermediate AMD	6 months	Significant improvements in macular function (ERG); no significant BCVA change; good tolerability. ^[37]
Maurya et al. (2022)	Bilberry anthocyanins 160 mg/day	RCT (n=120)	Early AMD	2 years	Significant reduction in drusen progression; improved contrast sensitivity; reduced visual field loss. ^[40]
Piermarocchi et al. (2012)	AREDS + carotenoids combination (Lutein + ZX + astaxanthin)	RCT (n=145)	AMD + diabetic maculopathy	12 months	Significant BCVA improvement in AMD group; improved contrast sensitivity; reduced progression markers. ^[45]

Abbreviations: RCT, randomised controlled trial; AMD, age-related macular degeneration; ERG, electroretinography; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; ZX, zeaxanthin; AREDS, Age-Related Eye Disease Study.

The body of clinical evidence for the four-component strategy is composed of: (i) high-level Phase III RCT evidence for AREDS2 (Level I evidence; 4,203 participants, 5-year follow-up); (ii) multiple Phase II RCTs for saffron demonstrating consistent macular functional improvements (ERG, BCVA) in early AMD; (iii) RCT evidence for bilberry in drusen progression and contrast sensitivity; and (iv) prospective cohort and pilot RCT evidence for astaxanthin in retinal blood flow and visual function. No dedicated combination trial has yet been conducted, representing the primary evidence gap this review aims to motivate. The key studies informing this evidence base are summarised in Table 2.

The clinical endpoints across available trials are heterogeneous, encompassing best-corrected visual acuity (BCVA), contrast sensitivity, ERG responses (focal, multifocal, pattern), macular pigment optical density, drusen volume and area, AMD classification category progression, and patient-reported visual function scores (VFQ-25, NEI-VFQ). This heterogeneity complicates meta-analytic synthesis and underscores the need for a consensus outcome framework for multicomponent AMD nutritional trials, aligning with the Cochrane systematic review recommendations for AMD supplement trials (Evans et al., 2017).

9. Translational Potential and Functional Food Development Considerations

9.1 Dosing and Bioavailability

The effective doses identified in clinical trials for the four components are: AREDS2 formula at standard composition (lutein 10 mg, zeaxanthin 2 mg, vitamin C 500 mg, vitamin E 400 IU, zinc 80 mg, copper 2 mg); saffron at 20 mg/day standardised extract (delivering approximately 0.3% safranal, 2% crocin, 1% crocetin) [15, 16]; bilberry extract at 160-320 mg/day standardised to 36% anthocyanins; and astaxanthin at 6-12 mg/day (natural *H. pluvialis* extract in a lipid carrier for enhanced bioavailability). All four components are commercially available at clinically-evidenced doses in capsule or softgel form, and their combination into a single once-daily softgel or two-capsule daily regimen is technically and commercially feasible at these doses.^[19,20,37]

A critical formulation consideration is astaxanthin's lipophilicity it requires co-administration with dietary fat or formulation in a lipid-based delivery system (oil-filled softgel) for adequate intestinal absorption.^[28,29] Crocetin, while more lipophilic than crocin, also demonstrates enhanced bioavailability in lipid-based matrices. A softgel formulation combining astaxanthin, saffron extract, and bilberry extract in a medium-chain triglyceride (MCT) oil carrier co-formulated with the AREDS2 components represents an optimal delivery vehicle for the combination.^[25]

9.2 Regulatory and Labelling Considerations

In the European Union, the AREDS2 components benefit from authorised EFSA health claims for vitamins C, E, and zinc in relation to 'protection of cells from oxidative stress' (Regulation EC 1924/2006). Lutein and zeaxanthin do not yet have authorised EFSA health claims for eye health, though a pending dossier review is ongoing. Saffron, bilberry, and astaxanthin are regulated as food supplements in the EU under Directive 2002/46/EC, with no specific health claims authorised for ophthalmic indications in the EU. In the United States, the DSHEA framework permits structure/function claims for dietary supplements, enabling claims such as 'supports macular health' and 'provides antioxidant support for the eyes' for all four components. Labelling should reference the specific botanical species (*Crocus sativus*, *Vaccinium myrtillus*, *Haematococcus pluvialis*), the active constituent standardisation, and for the AREDS-based components the established clinical trial evidence base.

9.3 Safety and Drug Interactions

All four components have well-established safety profiles at the doses identified in clinical trials.^[15,19,23,37,45] The AREDS2 formula safety has been extensively documented in the 4,203-participant trial with five-year follow-up.^[15] High-dose zinc (80 mg/day) the dose used in AREDS2 is associated with copper depletion (addressed by the formula's 2 mg copper), mild gastrointestinal symptoms, and rare urological effects in susceptible individuals; lower-dose zinc formulations (25 mg/day) may be preferable for long-term use in patients without advanced AMD risk. Saffron at 20 mg/day has been well tolerated in all clinical trials with no serious adverse events.^[19,20,37] Bilberry at standard extract doses (160-320 mg/day) has an excellent safety record with only rare mild gastrointestinal effects. Astaxanthin at 6-12 mg/day demonstrates outstanding tolerability with mild skin pigmentation (carotenoderma) at doses above 20 mg/day as the only reported cosmetic side effect.^[28,29,45]

Drug interaction considerations include: zinc's inhibition of quinolone and tetracycline antibiotic absorption (separate administration by 2 hours recommended); theoretical additive antiplatelet effects of high-dose astaxanthin with anticoagulants (warfarin monitoring recommended at doses >20 mg/day); and saffron's potential serotonergic activity at

very high doses (>200 mg/day) not relevant at the 20 mg/day clinical dose. No pharmacokinetic interactions among the four components have been identified.

10. Limitations and Future Research Directions

This narrative review carries limitations inherent to the methodology. The absence of dedicated combination clinical trials means that proposed synergistic effects remain mechanistically inferred from independent trial data and preclinical evidence. The clinical evidence base varies substantially in quality among the four components: AREDS2 is supported by a definitive Phase III RCT,^[15] while saffron has Phase II RCT data,^[19,20,37] bilberry has moderate-quality RCT evidence, and astaxanthin in AMD specifically relies primarily on prospective cohort studies and combination trials.^[45] Publication bias toward positive findings may overestimate individual effect sizes across all components.

Priority research actions include: (i) a Phase II proof-of-concept RCT assessing the four-component combination vs AREDS2 alone on validated AMD endpoints including MPOD, drusen volume, ERG responses, and AMD progression classification, with adequate sample size and minimum 12-month follow-up; (ii) pharmacokinetic interaction studies confirming that co-formulation does not adversely affect individual component bioavailability; (iii) pharmacogenomic stratification studies examining differential response by CFH Y402H and ARMS2 genotype particularly for astaxanthin's CFH upregulation mechanism;^[10,11,42] (iv) standardisation of outcome measures across AMD nutritional supplement trials aligned with Cochrane AMD review frameworks; (v) head-to-head dose-optimisation studies for saffron (20 mg vs 40 mg/day) and bilberry (160 mg vs 320 mg/day); and (vi) long-term safety monitoring in a geriatric population with typical AMD co-morbidities and polypharmacy.

11. CONCLUSIONS

Age-related macular degeneration involves at least six converging pathological mechanisms that cannot be comprehensively addressed by the AREDS2 formula alone. The AREDS2 formula provides the established clinical foundation macular pigment enhancement and antioxidant defence with the most robust evidence base in AMD nutrition. Saffron uniquely adds photoreceptor neuroprotection through BDNF/TrkB and cAMP-PKA pathways, a mechanism absent from every other component, along with HIF-1 α -mediated anti-VEGF activity. Bilberry anthocyanin's add NLRP3 inflammasome suppression, retinal microvascular structural reinforcement, and rhodopsin cycle support three mechanistically distinct and clinically relevant contributions. Astaxanthin provides the deepest layer of lipid-phase and mitochondrial antioxidant protection, at antioxidant potency orders of magnitude beyond AREDS2 vitamins, and uniquely modulates the complement pathway through CFH upregulation a genotype-relevant mechanism for the majority of AMD patients with complement risk variants.

The mechanistic profiles of all four components are not merely additive they are potentially synergistic, with antioxidant mechanisms enabling more effective neurotrophic signalling, complement modulation reducing the inflammatory burden that drives VEGF upregulation, and microvascular protection improving choroidal delivery of all nutritional agents to the RPE and photoreceptors. The proposed four-component strategy addresses all six AMD pathological pathways through non-redundant, mechanistically coherent, and clinically supported mechanisms, representing the most comprehensive nutritional AMD management strategy currently justifiable by the existing evidence base.

Translating this mechanistic rationale into clinical practice requires dedicated combination randomised controlled trials with adequate power, standardised AMD endpoints, and long-term follow-up. The development of a well-formulated, lipid-based softgel co-incorporating all four components at clinically evidenced doses represents both a commercially viable functional food product and a testable clinical hypothesis. The present review provides the mechanistic and translational foundation for this research and development agenda.

12. ABBREVIATIONS

8-OHdG: 8-hydroxy-2'-deoxyguanosine
A2E: N-retinylidene-N-retinylethanolamine (bis-retinoid)
AMD: age-related macular degeneration
ARE: antioxidant response element
AREDS: Age-Related Eye Disease Study
AREDS2: Age-Related Eye Disease Study 2
Bax: Bcl-2-associated X protein
BCVA: best-corrected visual acuity
BDNF: brain-derived neurotrophic factor
C2: complement component 2
C3: complement component 3
C3G: cyanidin-3-glucoside
cAMP: cyclic adenosine monophosphate
CFB: complement factor B
CFH: complement factor H
CNV: choroidal neovascularisation
CNTF: ciliary neurotrophic factor
DHA: docosahexaenoic acid
EFSA: European Food Safety Authority
ERG: electroretinography
HIF-1 α : hypoxia-inducible factor-1 alpha
IL-18: interleukin-18
IL-1 β : interleukin-1 beta
logMAR: logarithm of the minimum angle of resolution
MAC: membrane attack complex
MCT: medium-chain triglyceride
MPOD: macular pigment optical density
NF- κ B: nuclear factor kappa-B
NLRP3: NLR family pyrin domain containing 3
Nrf2: nuclear factor erythroid 2-related factor 2
PEDF: pigment epithelium-derived factor
PKA: protein kinase A
PUFA: polyunsaturated fatty acid
RCT: randomised controlled trial

ROS: reactive oxygen species

RPE: retinal pigment epithelium

SOD: superoxide dismutase

TrkB: tropomyosin receptor kinase B

VEGF: vascular endothelial growth factor

13. Declaration

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Author Contributions

Rajendran, Sudesh Raj, Ravetha and Tejas were responsible for conceptualisation and editing. Muzhumathi Susithra, Sneha, and Reethi contributed to data collection, analysis, and preparation of the original draft. All authors reviewed and approved the final manuscript.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

This narrative review article did not involve any human participants, animal experimentation or collection of personal data. No ethical approval was required.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Data Availability Statement

The data supporting this article, including all references, literature sources, and bibliographic records, have been collected and managed using Zotero reference management software (<https://www.zotero.org>) and are available upon reasonable request to the corresponding author.

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