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BEYOND AREDS2: NEXT-GENERATION NUTRITIONAL SUPPLEMENTS FOR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

Background: Age-related macular degeneration (AMD) remains the leading cause of irreversible vision loss in older adults worldwide. While the AREDS2 formula has represented the standard of care for nutritional supplementation in intermediate AMD, emerging evidence suggests that newer compounds may offer enhanced protection against disease progression.
Methods: This systematic review evaluates literature identified in PubMed, Scopus, and Web of Science up to July 2024. The analysis concentrates on clinical trials, observational research, and mechanistic studies concerning next-generation supplements for AMD, such as astaxanthin, resveratrol, flavonoids, and apocarotenoids.
Results: We identified 42 relevant studies demonstrating that novel compounds address limitations of the current AREDS2 formulation through superior antioxidant properties (astaxanthin exhibits 10-100 times greater potency than lutein), enhanced anti-inflammatory effects (resveratrol reduces mtROS by 50%), and improved mitochondrial protection. Apocarotenoids like crocetin and norbixin show enhanced bioavailability and retinal protection compared to traditional carotenoids. Combination approaches targeting multiple AMD pathways simultaneously appear most promising.
Conclusion: Current evidence indicates that these novel compounds, particularly when combined with specific carotenoids, may represent a significant advancement beyond the current AREDS2 formulation. Further clinical validation is necessary to establish optimal dosing protocols and long-term safety profiles, but the emerging evidence supports a shift toward personalized, mechanism-based supplementation strategies for AMD management.

KEYWORDS

Age-Related Macular Degeneration, Nutritional Supplements, Antioxidants, AREDS2, Astaxanthin, Resveratrol

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Introduction.

Age-related macular degeneration (AMD) is a multifactorial ocular condition marked by the progressive degeneration of the macular region of the retina, resulting in significant central vision loss. As the primary cause of visual impairment in developed countries among individuals aged 60 and older, AMD affects approximately 30 million people worldwide, with projections suggesting this number will increase to nearly 300 million by 2040 as global populations age [1]. The disease typically progresses from early stages (characterized by drusen and pigmentary changes) to intermediate stages, and ultimately to advanced forms including geographic atrophy (dry AMD) or choroidal neovascularization (wet AMD) [2, 3].

Since its introduction in 2013, the Age-Related Eye Disease Study 2 (AREDS2) formulation has been regarded as the benchmark nutritional supplement for AMD. The definitive AREDS2 composition includes vitamin C (500 mg), vitamin E (400 IU), lutein (10 mg), zeaxanthin (2 mg), zinc (80 mg), and copper (2 mg) [4]. This combination was shown to lower the risk of progression to advanced AMD by roughly 25% in patients with intermediate AMD or unilateral advanced disease [5, 4]. Notwithstanding these benefits, the formulation possesses notable drawbacks, including restricted effectiveness in late-stage AMD, possible safety issues related to high-dose zinc, and an incomplete scope of action against all pathological mechanisms implicated in AMD [6, 7].

The pathophysiology of AMD involves oxidative stress, persistent inflammation, mitochondrial impairment, and the deposition of toxic metabolites within the retinal pigment epithelium (RPE) and Bruch's membrane [8, 9]. Although the carotenoids lutein and zeaxanthin in AREDS2 counteract oxidative stress and filter blue light, they do not comprehensively mitigate inflammatory elements or offer complete protection against all variants of oxidative damage. This understanding has motivated the exploration of novel agents possessing strengthened antioxidant characteristics, anti-inflammatory capacities, and mitochondrial protective functions that might yield better safeguards against AMD progression [6, 10].

This review aims to critically appraise emerging data on advanced nutritional supplements for AMD, such as astaxanthin, resveratrol, flavonoids, and apocarotenoids like crocetin and norbixin. We assess their mechanistic foundations, preclinical data, and clinical potential while contrasting their efficacy with conventional lutein/zeaxanthin-based protocols. By amalgamating evidence from recent scientific publications, we present contemporary viewpoints on supplemental tactics that may more effectively target the complex pathogenesis of AMD and potentially decelerate its progression more efficiently than existing standard formulations [6, 11].

Methods

This comprehensive review followed a systematic approach to identify, evaluate, and synthesize relevant scientific literature on next-generation nutritional supplements for AMD. We conducted electronic searches of PubMed, Scopus, Web of Science, and Cochrane Library databases for articles published from January 2000 through July 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords including: "age-related macular degeneration," "AMD," "nutritional supplements," "antioxidants," "AREDS2," "astaxanthin," "resveratrol," "flavonoids," "apocarotenoids," "crocetin," "norbixin," "oxidative stress," "retinal protection," and "clinical trials."

Inclusion criteria encompassed: (1) original research studies (randomized controlled trials, observational studies, preclinical investigations); (2) systematic reviews and meta-analyses; (3) studies published in English; and (4) studies focusing on nutritional interventions for AMD prevention or management. Exclusion criteria included: (1) case reports and small case series ($n < 10$); (2) studies not specifically focused on AMD; and (3) publications without peer review.

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially relevant articles. Data extraction was performed using a standardized form capturing study characteristics, methodology, intervention details, outcomes, and key findings. The quality of included studies was assessed using appropriate tools including Cochrane Risk of Bias tool for randomized trials and Newcastle-Ottawa Scale for observational studies. The collected evidence was synthesized narratively, with findings organized by supplement type and mechanism of action.

2 Limitations of Current AREDS2 Formulation

The AREDS2 formulation, while beneficial, exhibits several significant limitations that necessitate the development of improved supplemental approaches. Understanding these constraints provides the rationale for exploring next-generation supplements that can address the multifactorial pathology of AMD more comprehensively.

2.1 Efficacy Gaps in AMD Protection

The AREDS2 formula shows intermediate efficacy mainly in diminishing progression from intermediate to advanced AMD, but it neither prevents disease onset in early stages nor arrests progression entirely. Contemporary evidence indicates that although the formulation decreases the risk of progression to advanced AMD by approximately 25%, a considerable residual risk remains unmitigated by supplementation [5, 4]. Moreover, recent research suggests that the AREDS2 formulation may exert variable effects on different subtypes of advanced AMD. A 2024 investigation by Keenan et al. demonstrated that AREDS2 supplements delayed the progression of non-central geographic atrophy toward the macular center by 55%, despite exhibiting no substantial effect on overall area enlargement [12]. This implies that protective effects may be spatially specific and most effective in the central macula, where lutein and zeaxanthin are most densely concentrated.

2.2 Safety Concerns

The initial AREDS formulation contained β-carotene, which was linked to an elevated risk of lung cancer in current and former smokers [4]. Although AREDS2 substituted β-carotene with lutein and zeaxanthin, other reservations persist. The elevated zinc content (80 mg) in AREDS2 has been connected to genitourinary complications, including hospitalizations for urinary tract problems, and potential copper deficiency necessitating supplementation [4, 13]. Furthermore, the ideal zinc dosage remains debated, with AREDS2 identifying no significant efficacy difference between 80 mg and 25 mg doses [4]. The formulation also does not accommodate the specific requirements of diverse populations with differing genetic risk profiles for AMD, especially those with polymorphisms in complement factor H and other genes associated with inflammation [14, 15].

2.3 Incomplete Pathological Targeting

While the AREDS2 formulation counteracts oxidative stress via antioxidant vitamins and carotenoids, it affords limited defense against other crucial pathological mechanisms in AMD, notably chronic inflammation and mitochondrial dysfunction [8, 16]. The retinal pigment epithelium (RPE) is especially susceptible to mitochondrial dysfunction owing to its high metabolic activity and oxygen consumption, yet the current formulation does not specifically target mitochondrial health [16, 17]. Additionally, the formula does not confront the buildup of toxic metabolites like A2E (a constituent of lipofuscin) that contributes to RPE impairment in AMD [18]. The inflammatory aspect of AMD, particularly complement system activation, is also not addressed by the existing formulation, denoting a significant therapeutic void [14, 15].

3 Emerging Carotenoids: Astaxanthin and Beyond

3.1 Astaxanthin: Superior Antioxidant Properties

Astaxanthin (3,3'-dihydroxy-β,β-carotene-4,4'-dione) is a powerful xanthophyll carotenoid that displays significantly strengthened antioxidant capabilities relative to lutein and zeaxanthin. Its unique molecular structure, characterized by extended conjugation with 13 double bonds and polar end groups, permits it to integrate into biological membranes more efficiently than other carotenoids [19]. This configuration allows astaxanthin to offer superior protection against oxidative stress by neutralizing free radicals both on the membrane surface and within its hydrophobic core [19, 20]. Biochemically, astaxanthin has been shown to possess 10-100 times greater antioxidant potency than vitamin E, β-carotene, and lutein in various experimental systems [19].

The mechanistic benefits of astaxanthin are especially pertinent to retinal protection. In contrast to other carotenoids that are mainly concentrated in the macula, astaxanthin disperses throughout the retinal layers, potentially offering more extensive protection [20]. Its chemical structure enables it to efficiently quench singlet oxygen and neutralize reactive oxygen species (ROS) produced by photooxidative stress, which is particularly relevant to light-induced retinal damage [19, 16]. Furthermore, astaxanthin has been demonstrated to upregulate intrinsic antioxidant systems via activation of the Nrf2 pathway, boosting the expression of enzymes such as heme oxygenase-1 [19, 21].

3.2 Mitochondrial Protection and Anti-inflammatory Effects

Beyond its direct antioxidant activity, astaxanthin confers significant benefits for mitochondrial function and inflammation reduction—key elements in AMD pathogenesis. In experimental models, astaxanthin diminished mitochondrial reactive oxygen species (mtROS) production by 50% following the induction of oxidative stress [22]. It also assisted in maintaining redox balance by preserving the GSH/GSSG ratio (a crucial indicator of cellular oxidative status) and averted the decline in cellular ATP after oxidative insult [22, 21]. These mitochondrial protective effects are particularly applicable to retinal pigment epithelial cells, which have substantial energy requirements and are especially prone to mitochondrial impairment [16, 17].

The anti-inflammatory properties of astaxanthin are mediated through multiple pathways. It inhibits the activation of NF-κB, a primary regulator of inflammation, and diminishes the expression of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 [19]. In models of airway epithelium relevant to oxidative stress responses, astaxanthin pretreatment averted the rise in p21 mRNA expression that typically follows oxidative challenge, indicating protection against stress-induced senescence [22]. These anti-inflammatory effects are especially valuable for tackling the chronic inflammatory dimension of AMD that is not sufficiently targeted by the current AREDS2 formulation [14, 15].

3.3 Clinical Evidence for Ocular Protection

Although human studies specifically focused on AMD remain limited, emerging clinical evidence buttresses the ocular protective effects of astaxanthin. A clinical study in the Journal of Cell Signaling showed that astaxanthin exerted protective effects on primary human nasal epithelial cells against oxidative stress by reducing mtROS production and preserving redox homeostasis [22]. While not directly examined in retinal tissue, these mechanisms are highly applicable to AMD pathophysiology [8, 16].

A comprehensive review of astaxanthin's biological activities noted that doses of 4-18 mg daily have been safely used in human studies for periods up to 12 weeks, with no major adverse effects beyond occasional increased bowel movements and red stool discoloration [19]. The favorable safety profile of astaxanthin, coupled with its potent antioxidant and anti-inflammatory properties, renders it a promising candidate for next-generation AMD supplements. However, large-scale clinical trials specifically assessing its efficacy in AMD prevention and progression are necessary to establish optimal dosing and confirm clinical benefits [6, 19].

4 Polyphenols and Resveratrol: Multifunctional Protection

4.1 Resveratrol: Activation of Cellular Defense Mechanisms

Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenol compound found in grapes, berries, and red wine that activates multiple cellular defense pathways relevant to AMD protection [10, 23]. Its primary mechanism involves enhancing SIRT1 deacetylase activity, a key regulator of cellular stress response and longevity [23, 24]. SIRT1 activation leads to deacetylation of various transcription factors and cofactors, resulting in reduced inflammation, enhanced mitochondrial biogenesis, and increased resistance to oxidative stress. In experimental models, resveratrol pretreatment reduced mtROS production by 50% following oxidative stress induction and helped maintain cellular redox status [22].

Additionally, resveratrol has been shown to activate the Nrf2 pathway, leading to increased expression of antioxidant enzymes including glutathione synthetase [25]. In cigarette smoke-induced oxidative stress models using human type II alveolar epithelial cells, resveratrol activated Nrf2 and induced glutathione synthesis [25]. These mechanisms are highly relevant to AMD, as oxidative stress and reduced antioxidant capacity are central to its pathogenesis [8, 16]. Furthermore, resveratrol demonstrates anti-angiogenic properties through inhibition of VEGF expression and signaling, potentially offering protection against the neovascular form of AMD [23, 26].

4.2 Flavonoids: Diverse Protective Mechanisms

Flavonoids constitute a broad category of polyphenolic compounds with diverse mechanisms pertinent to AMD protection. These compounds are found in various fruits, vegetables, tea, and cocoa, and display potent antioxidant, anti-inflammatory, and vascular protective effects [10, 27]. Specific flavonoids including quercetin, epigallocatechin gallate (EGCG), and anthocyanins have demonstrated particular potential for retinal protection through multiple mechanisms. They mitigate oxidative stress through direct free radical scavenging and indirect augmentation of endogenous antioxidant systems, curb inflammation via modulation of NF-κB and other inflammatory pathways, and stabilize mitochondrial function by preventing permeability transition pore opening and enhancing electron transport chain efficiency [10, 28].

The vascular protective effects of flavonoids are especially relevant for AMD, as choroidal blood flow abnormalities and endothelial dysfunction contribute to disease pathogenesis. Flavonoids improve endothelial function by increasing nitric oxide bioavailability, reducing endothelial inflammation, and protecting against vascular oxidative stress [10, 29]. These effects may help preserve choroidal blood flow and reduce the hypoxic drive for neovascularization in AMD. Additionally, certain flavonoids have been shown to inhibit complement activation, which is particularly significant given the established genetic connection between complement factor H polymorphisms and AMD risk [14, 27].

4.3 Clinical Evidence and Formulation Considerations

While human studies specifically examining flavonoids in AMD are limited, epidemiological evidence suggests that higher dietary intake of flavonoid-rich foods correlates with a reduced risk of AMD progression [10, 30]. The challenge with many polyphenols, including resveratrol and certain flavonoids, is their poor bioavailability due to extensive metabolism and rapid elimination. Innovative delivery systems including phospholipid complexes, nanoparticles, and sustained-release formulations are under investigation to enhance their ocular bioavailability [31, 32].

Combination approaches that incorporate multiple polyphenols with complementary mechanisms may offer synergistic benefits for AMD protection. For instance, combining resveratrol (SIRT1 activation) with flavonoids that activate Nrf2 or inhibit complement may furnish more comprehensive protection against the multiple pathological processes involved in AMD [10, 27]. However, well-designed clinical trials are required to establish optimal dosing, confirm efficacy, and identify potential interactions with other AMD supplements [6, 10].

5 Apocarotenoids and Other Innovative Compounds

5.1 Crocetin and Norbixin: Enhanced Retinal Protection

Apocarotenoids represent a promising class of compounds derived from carotenoid metabolism that demonstrate enhanced bioavailability and tissue distribution compared to their parent compounds. Crocetin (a dicarboxylic acid carotenoid derived from saffron) and norbixin (an apocarotenoid from annatto seeds) have shown particularly encouraging results for retinal protection [33, 34]. These compounds exhibit superior antioxidant properties compared to lutein and zeaxanthin, with demonstrated capacity to protect RPE cells more effectively against apoptosis subsequent to blue light exposure in the presence of A2E (a component of

lipofuscin) [33, 34]. This specific mechanism is highly relevant to AMD, as A2E accumulation and light-induced damage contribute significantly to RPE dysfunction and cell death [18, 35].

The structural advantages of apocarotenoids include smaller molecular size and increased water solubility compared to traditional carotenoids, potentially improving their tissue distribution and bioavailability [33, 36]. Crocetin has been shown to cross the blood-brain barrier effectively, suggesting analogous potential for retinal penetration. Mechanistic studies indicate that crocetin and norbixin not only provide direct antioxidant protection but also modulate gene expression involved in antioxidant defense, inflammation, and cellular stress response [33, 34]. These pleiotropic effects render them particularly attractive for addressing the multifactorial pathology of AMD [6, 33].

5.2 Omega-3 Fatty Acids: Re-evaluation of Evidence

The AREDS2 study concluded that the addition of omega-3 fatty acids (DHA 350 mg + EPA 650 mg) to the AREDS formulation conferred no additional benefit for reducing AMD progression risk [4]. However, more recent evidence implies that omega-3 fatty acids may still contribute to AMD protection through mechanisms not fully captured in the original trial design. Omega-3 fatty acids incorporate into retinal membranes, enhancing fluidity and supporting visual transduction processes. They also generate specialized pro-resolving mediators (SPMs) that actively resolve inflammation rather than simply suppressing it [37, 38].

This pro-resolving activity may be particularly important for addressing the chronic inflammatory component of AMD [15, 38]. Emerging evidence suggests that the timing and ratio of EPA to DHA may considerably influence their effectiveness in AMD protection [39]. Additionally, genetic factors may modulate response to omega-3 supplementation, with some data indicating greater benefit in individuals with specific genetic polymorphisms related to inflammation and omega-3 metabolism [40]. These insights propose that a more personalized approach to omega-3 supplementation, rather than complete exclusion from AMD formulas, may be justified [6, 39].

5.3 Combination Therapies and Synergistic Effects

The future of AMD supplementation likely resides in rational combinations of compounds with complementary mechanisms that target multiple pathways in AMD pathogenesis. For example, combining astaxanthin (potent antioxidant and mitochondrial protector) with resveratrol (SIRT1 activator and Nrf2 inducer) and crocetin (A2E protector and enhanced bioavailable antioxidant) may provide more comprehensive protection than any single compound [6, 11]. Evidence from preclinical models supports synergistic interactions between different classes of antioxidants, where combined effects surpass the sum of individual benefits [41, 42].

The challenge in formulating combination supplements involves optimizing doses to maximize benefits while minimizing potential interactions and ensuring safety. Additionally, biomarker-based approaches may help identify which patients are most likely to benefit from specific combinations based on their genetic profile, disease characteristics, and biochemical markers of oxidative stress and inflammation [14, 43]. Well-designed clinical trials assessing these targeted combination approaches are necessary to advance the field beyond the current one-size-fits-all AREDS2 formulation [6, 11].

6 Clinical Translation and Future Directions

6.1 Formulation Challenges and Bioavailability

The development of effective next-generation AMD supplements confronts significant formulation challenges related to the chemical properties of many promising compounds. Many carotenoids and polyphenols possess poor water solubility, low stability, and limited bioavailability, which curtails their therapeutic potential [19, 31]. Innovative delivery systems including phospholipid complexes, nanoemulsions, liposomes, and cyclodextrin inclusion complexes are being explored to enhance absorption, stability, and tissue delivery of these compounds [31, 32]. For instance, astaxanthin in phospholipid complexes has demonstrated significantly enhanced bioavailability compared to standard preparations in experimental models [19, 44].

The blood-retinal barrier presents an additional challenge for delivering therapeutic concentrations of supplements to retinal tissues. Strategies to enhance retinal delivery include targeting specific transport systems, prodrug approaches, and sustained-release formulations that maintain therapeutic levels over extended periods [31, 45]. Additionally, the potential for interactions between components in combination supplements must be carefully evaluated, as some compounds may compete for absorption or metabolism when co-administered [11]. Addressing these formulation challenges is crucial for realizing the full potential of next-generation AMD supplements [6, 31].

6.2 Personalization of Supplementation Strategies

The limited efficacy of the current universal AREDS2 formulation for all AMD patients underscores the need for personalized approaches based on genetic risk factors, disease characteristics, and nutritional status [14, 43]. Genetic testing for AMD risk variants (particularly in complement factor H, ARMS2, and HTRA1 genes) may help identify patients who would derive the most benefit from specific supplemental components [14, 46]. For example, individuals with high genetic risk for inflammation-driven AMD might benefit more from supplements with enhanced anti-inflammatory components such as astaxanthin or resveratrol [14, 15].

Nutritional status assessment may also guide supplementation strategies, as patients with deficient or suboptimal levels of specific nutrients may obtain greater benefit from targeted supplementation [7, 47]. Biomarker-based approaches using measures of oxidative stress (e.g., isoprostanes), inflammation (e.g., CRP, cytokine profiles), and mitochondrial function could help identify patients most likely to respond to specific antioxidant and anti-inflammatory supplements [43]. This personalized approach represents a significant advance over current practice and could substantially improve the efficacy of nutritional supplementation for AMD [6, 43].

6.3 Design of Future Clinical Trials

Well-designed clinical trials are essential to validate the efficacy of next-generation AMD supplements and establish evidence-based recommendations. Future trials should incorporate several key design elements including: (1) adequate sample size to detect clinically meaningful effects on AMD progression; (2) appropriate patient stratification based on genetic risk factors, disease stage, and nutritional status; (3) standardized outcome measures including both structural (e.g., imaging biomarkers) and functional (e.g., visual function, dark adaptation) endpoints; (4) sufficient duration to detect effects on disease progression; and (5) comprehensive safety assessment [6, 48].

Composite endpoints that capture both anatomic progression (e.g., GA growth rate, drusen volume change) and functional outcomes (e.g., low luminance visual acuity, reading speed) may provide a more comprehensive assessment of efficacy than single endpoints [12, 49]. Additionally, trials should incorporate imaging biomarkers that can detect treatment effects earlier than traditional endpoints, potentially reducing required study duration and sample size [50]. The integration of emerging technologies such as artificial intelligence-based image analysis and wearable devices for continuous functional assessment may further enhance the sensitivity of future trials to detect meaningful treatment effects [51].

7 Discussion

The findings of this comprehensive review indicate that next-generation nutritional supplements for AMD show significant promise in addressing the limitations of the current AREDS2 formulation. The emerging compounds discussed—including astaxanthin, resveratrol, flavonoids, and apocarotenoids—exhibit enhanced mechanistic capabilities targeting the multifactorial pathogenesis of AMD, particularly in addressing oxidative stress, inflammation, mitochondrial dysfunction, and toxic metabolite accumulation.

The superior antioxidant potency of astaxanthin (10-100 times greater than lutein and other carotenoids) positions it as a particularly promising candidate for next-generation formulations [19]. Its unique ability to span cellular membranes and distribute throughout retinal layers, rather than being concentrated primarily in the macula, suggests potential for more comprehensive retinal protection compared to current AREDS2 carotenoids [19, 20]. Similarly, the multifunctional properties of resveratrol—activating SIRT1, enhancing Nrf2-mediated antioxidant defenses, and inhibiting VEGF signaling—address multiple AMD pathways simultaneously, potentially offering broader protection than single-mechanism compounds [23, 24].

The apocarotenoids crocetin and norbixin present particularly innovative approaches to AMD supplementation, with their enhanced bioavailability and specific protective effects against A2E-mediated phototoxicity addressing a key gap in current AREDS2 protection [33, 34]. Their water solubility and ability to cross biological barriers efficiently suggest potential for improved tissue delivery compared to traditional fat-soluble carotenoids [33, 36].

The concept of combination therapy emerges as a central theme from this analysis, with evidence suggesting that rational combinations of compounds with complementary mechanisms may provide synergistic benefits exceeding those of individual components [11, 41]. This approach aligns with the understanding of AMD as a multifactorial disease requiring multi-targeted interventions. However, the development of such

combinations requires careful consideration of potential interactions, optimal dosing ratios, and formulation challenges to ensure stability and bioavailability of all components [11, 31].

The move toward personalized supplementation strategies represents another significant advancement beyond the current one-size-fits-all approach [14, 43]. The recognition that genetic factors, nutritional status, and disease characteristics influence individual response to specific supplements suggests that future AMD management should incorporate biomarker-guided, individualized approaches rather than universal recommendations [14, 43, 46].

8 Conclusion and Future Perspectives

The AREDS2 formulation has represented the standard of care for nutritional supplementation in AMD for over a decade, but significant limitations in its efficacy and safety profile have prompted the search for next-generation supplements. Emerging evidence suggests that compounds including astaxanthin, resveratrol, flavonoids, and apocarotenoids such as crocetin and norbixin may offer superior protection against AMD progression through enhanced antioxidant, anti-inflammatory, and mitochondrial protective effects [6, 19, 33]. These compounds target multiple pathways in AMD pathogenesis that are not adequately addressed by the current AREDS2 formulation.

The future of AMD supplementation likely lies in rational combinations of these novel compounds, potentially personalized based on genetic risk factors, disease characteristics, and nutritional status [14, 43]. However, well-designed clinical trials are needed to validate the efficacy of these approaches and establish optimal dosing regimens [6, 48]. Additionally, advances in formulation technology are required to overcome the bioavailability challenges associated with many of these compounds [31, 32].

Despite the promise of these next-generation supplements, it is important to emphasize that nutritional supplementation should be viewed as one component of a comprehensive approach to AMD management that includes lifestyle modifications (e.g., smoking cessation, healthy diet, exercise) and regular ophthalmologic care [7, 52]. The recent approval of pharmaceutical treatments for geographic atrophy (pegcetacoplan and avacincaptad pegol) provides additional options for advanced disease, though their risk-benefit profile remains controversial [53, 54].

In conclusion, the field of nutritional supplementation for AMD is evolving beyond the AREDS2 formulation toward more targeted, effective, and personalized approaches. While further research is needed, the compounds discussed in this review represent promising candidates for the next generation of AMD supplements that may offer improved protection against this sight-threatening disease [6, 11].

Ethical Considerations

This review article did not involve direct human or animal research. All information was obtained from publicly available scientific literature. The authors declare no conflicts of interest related to this work. Proper citations have been provided for all referenced materials to acknowledge the contributions of original researchers.

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