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REVIEW

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Nano-Nutraceuticals for age-related macular degeneration: Innovations in ocular delivery systems

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of vision loss among older adults, severely impacting quality of life. It manifests in two forms: dry AMD, characterized by the accumulation of drusen, and wet AMD, involving abnormal blood vessel growth under the retina. Current treatments, particularly anti-VEGF therapies for wet AMD, are limited by cost, procedural discomfort, and associated risks, while no FDA-approved therapies exist for dry AMD. Nutraceuticals such as lutein, zeaxanthin, curcumin, resveratrol, and omega-3 fatty acids offer potential in mitigating oxidative stress and inflammation, key factors in AMD pathogenesis. Despite promising preclinical data, their clinical utility is hampered by poor solubility, instability, and low bioavailability in ocular tissues. Nanotechnology offers innovative solutions to these challenges through the development of nanocarrier systems like liposomes, nanoparticles, and emulsions. These systems enhance the delivery, stability, and targeted release of bioactive compounds, improving therapeutic outcomes while minimizing systemic side effects. This review explores the pathophysiology of AMD, the role of nutraceuticals in retinal health, barriers to effective ocular drug delivery, and recent advances in nanotechnology that address these limitations. The integration of nano-nutraceuticals represents a promising strategy for the prevention and management of AMD.

KEYWORDS

Retinal Degeneration; Liposomes; Curcumin; Dietary Supplements; Retinal Degeneration; Resveratrol

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Introduction

AMD overview

Age-related macular degeneration (AMD) is a complex, chronic, and progressive eye disease that significantly impairs central vision, ultimately impacting the quality of life and independence of older adults. It affects the macula, the middle section of the retina that's crucial for clear, direct vision you need to read and drive. The condition shows up in two main types: dry (atrophic) AMD, which gets worse as drusen (clumps of fat and protein) build up, and wet (neovascular) AMD, which is more severe and happens when unusual blood vessels grow under the retina, causing quick vision loss [1]. With the aging global population, the socioeconomic and public health burden of AMD is expected to intensify.

Current therapeutic limitations

While anti-vascular endothelial growth factor (anti-VEGF) therapies have revolutionized the treatment of wet AMD, they are not without limitations. These include high treatment costs, frequent intravitreal injections, and associated risks such as infections, retinal detachment, and patient non-compliance due to procedural discomfort [1,2]. In contrast, there are no FDA-approved therapies for dry AMD, leaving a significant gap in preventative and early-stage interventions. Current treatments primarily aim to slow disease progression rather than reverse damage or restore vision.

Role of nutraceuticals

Nutraceuticals, defined as food-derived compounds with health benefits, have garnered attention for their role in retinal health. Compounds such as lutein, zeaxanthin, omega-3 fatty acids, curcumin, and resveratrol offer protective effects against the oxidative stress and chronic inflammation central to AMD pathogenesis. These agents are found in various fruits, vegetables, and marine sources and have shown promise in modulating molecular pathways involved in retinal degeneration [3]. However, despite encouraging in vitro and animal model data, translating these benefits into clinical success remains challenging due to limitations in bioavailability and targeted delivery.

Advantages of nanotechnology

Nanotechnology introduces a transformative dimension to the administration of nutraceuticals by engineering nanoscale delivery systems that can traverse ocular barriers and release therapeutic agents in a controlled and site-specific manner. By encapsulating bioactives within liposomes, nanoparticles, or emulsions, nanocarriers can improve solubility, protect compounds from enzymatic degradation, and enhance permeability through ocular tissues [4]. This technological advancement not only boosts therapeutic efficacy but also reduces dosage frequency and systemic side effects, thereby improving patient adherence and clinical outcomes.

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Pathophysiology of AMD

Oxidative stress and inflammation

The retina is highly vulnerable to oxidative stress because it consumes a lot of oxygen, light exposure, and abundant polyunsaturated fatty acids. Reactive oxygen species (ROS) accumulation triggers lipid peroxidation and DNA damage, contributing to retinal pigment epithelium (RPE) dysfunction [5]. Chronic inflammation exacerbates this damage, creating a cycle that drives AMD progression.

Drusen formation

Drusen are extracellular deposits of lipids and proteins that build space between the retinal pigment epithelium (RPE) and Bruch's membrane. Their presence is a hallmark of early AMD and contributes to RPE atrophy and photoreceptor degeneration.

Neovascularization

In wet AMD, hypoxia and inflammation stimulate VEGF expression, promoting the growth of fragile, leaky blood vessels beneath the retina. These vessels lead to hemorrhage, fluid accumulation, and rapid vision loss [6].

Genetic and environmental factors

Polymorphisms in genes such as CFH, ARMS2, and HTRA1 have been associated with increased AMD risk. Environmental factors—including smoking, poor diet, and UV exposure—also significantly contribute to disease development [7].

Nutraceuticals in AMD Management

Key nutraceuticals

Lutein and Zeaxanthin: These xanthophyll carotenoids are highly concentrated in the macula, where they perform dual protective functions. Firstly, they serve as optical filters, selectively absorbing harmful high-energy blue light, thereby preventing photochemical damage to photoreceptor cells [8,9]. Secondly, their potent antioxidant capacity helps neutralize reactive oxygen species (ROS) generated by light exposure and metabolic activity in the retina. By reducing oxidative stress, these compounds help preserve photoreceptor and retinal pigment epithelial (RPE) cell function, delaying AMD onset and progression. Furthermore, lutein and zeaxanthin have been shown to improve macular pigment optical density (MPOD), a critical factor in visual performance and protection (Figure 1).

Omega-3 Fatty Acids: Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are long-chain omega-3 polyunsaturated fatty acids integral to retinal structure and function. DHA is a major structural component of photoreceptor membranes, ensuring fluidity and optimal signal transduction, while EPA serves as a precursor for anti-inflammatory eicosanoids. Together, these fatty acids modulate inflammatory responses, reduce angiogenesis, and enhance neuronal survival in retinal tissues. Clinical studies indicate that higher dietary intake of omega-3s correlates with a reduced risk of AMD development, especially in individuals with low baseline fish consumption [10].

Curcumin and Resveratrol: These natural polyphenolic compounds exert multifaceted protective effects on retinal health. Curcumin, derived from turmeric, and resveratrol, found in grapes and berries, both exhibit strong anti-inflammatory and antioxidant properties. They inhibit nuclear factor kappa B (NF-κB) signaling and downregulate pro-inflammatory cytokines, thereby mitigating chronic inflammation implicated in AMD [11,12]. Additionally, they protect against oxidative damage to RPE cells and may inhibit pathological angiogenesis through suppression of vascular endothelial growth factor (VEGF). Preclinical studies suggest these compounds support mitochondrial integrity and autophagy, processes vital for retinal cell homeostasis and longevity.

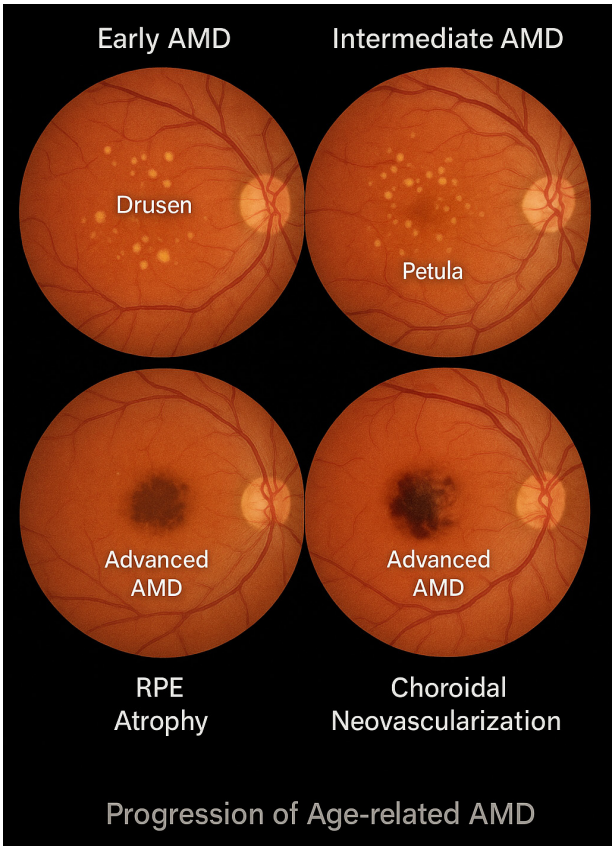

Figure 1. AMD progresses through distinct stages, from early drusen accumulation to advanced geographic atrophy or neovascularization.

Clinical evidence

The Age-Related Eye Disease Study (AREDS) and its follow-up, AREDS2, are landmark investigations that have shaped current clinical guidelines for nutritional intervention in AMD. AREDS established the efficacy of high-dose antioxidant vitamins and minerals in reducing the risk of progression to advanced AMD in individuals with intermediate disease. AREDS2 refined this formulation by replacing beta-carotene with lutein and zeaxanthin and evaluating the addition of omega-3 fatty acids [13,14]. The revised supplement showed a modest yet statistically significant reduction in the progression to late-stage AMD, particularly in subgroups not receiving beta-carotene. These studies underscored the importance of targeted nutritional strategies in managing AMD and laid the

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foundation for integrating nutraceuticals into standard care protocols.

Bioavailability challenges

Despite their therapeutic potential, many nutraceuticals suffer from poor bioavailability, which severely limits their clinical efficacy. These compounds often exhibit low aqueous solubility, making them poorly absorbed in the gastrointestinal tract. Moreover, they are susceptible to enzymatic degradation and first-pass metabolism, which further diminishes their systemic availability. Even when absorbed, achieving therapeutic concentrations in ocular tissues is challenging due to anatomical barriers such as the blood-retinal barrier. Consequently, high oral doses are required, which may increase the risk of systemic side effects without guaranteeing sufficient retinal accumulation [15]. These limitations necessitate the development of advanced delivery systems to enhance ocular bioavailability and therapeutic outcomes.

Ocular Barriers to Drug Delivery

Anatomical barriers

The eye's intricate anatomy serves as a formidable defense against external agents, including therapeutic drugs (Figure 2).

Corneal Epithelium: The corneal epithelium, with its tight intercellular junctions, acts as a primary shield, restricting the permeability of topically applied agents to deeper ocular structures. This barrier function, while protective, severely limits drug penetration into the anterior chamber. More critically for posterior eye diseases like AMD [16].

Blood-Retinal Barrier (BRB): It acts analogously to the blood-brain barrier, tightly regulating the movement of substances from systemic circulation into retinal tissues. The BRB's selective permeability hinders the delivery of systemically administered drugs, posing a major obstacle in targeting the retina therapeutically [17].

Physiological barriers

Beyond structural defenses, dynamic physiological mechanisms further complicate drug delivery to the eye.

Tear Film and Blinking: The tear film, essential for ocular surface health, rapidly dilutes and removes topically applied drugs through reflex blinking and nasolacrimal drainage, often within minutes of administration [18]. Additionally, metabolic enzymes present in the tear film, cornea, and other ocular tissues can degrade active pharmaceutical ingredients before they reach their intended targets.

Enzymatic Degradation: These enzymatic processes significantly reduce drug half-life and effectiveness, making it difficult to maintain therapeutic concentrations. Collectively, these anatomical and physiological barriers necessitate the development of innovative, targeted delivery strategies, such as nanocarriers, to optimize drug bioavailability and clinical efficacy in AMD treatment [19].

Implications: Overcoming these barriers is critical for delivering therapeutic levels of bioactives to the posterior segment of the eye. Innovative drug delivery systems are required to enhance residence time and penetration.

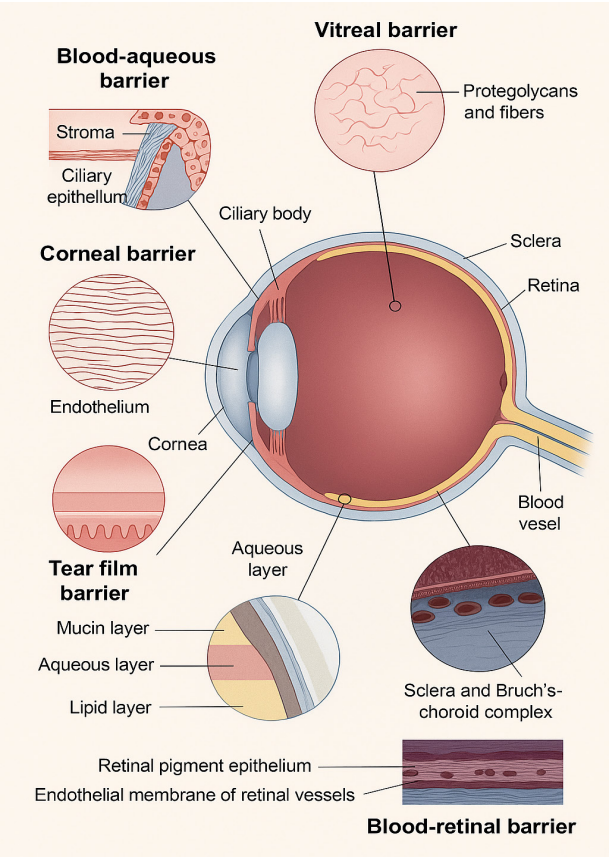

Figure 2. Ocular barriers affecting drug delivery.

Nanocarrier Systems for Ocular Delivery

Types of nanocarriers

Liposomes

Phospholipid-based vesicles capable of encapsulating both water-soluble and fat-soluble drugs. Their biocompatibility and ability to merge with ocular cell membranes enhance corneal penetration and promote sustained drug release in ocular tissues.

Solid Lipid Nanoparticles (SLNs)

Composed of solid lipids, these nanocarriers offer high physical stability and protect encapsulated drugs from degradation. They provide controlled release, improving drug residence time in ocular tissues [20,21].

Nanostructured Lipid Carriers (NLCs)

These are second-generation lipid nanoparticles combining solid and liquid lipids. They enhance drug loading, reduce expulsion during storage, and enable modified release profiles for better therapeutic control [21].

Polymeric Nanoparticles

Made from biodegradable polymers such as PLGA, these carriers provide prolonged drug release and can be surface-modified for targeted retinal delivery. They minimize systemic toxicity and improve therapeutic index [22].

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Dendrimers

Highly branched synthetic polymers with numerous functional end groups that allow precise drug conjugation. They enhance solubility, bioavailability, and enable multi-drug loading for synergistic therapy.

Nanoemulsions

Thermodynamically stable dispersions of oil and water, nanoemulsions significantly improve the solubility of hydrophobic drugs [23]. Their small droplet size ensures better permeation through ocular barriers and enhanced bioavailability (Figure 3).

Advantages

Nanocarrier-based drug delivery systems offer several significant advantages that directly address the limitations of conventional ocular therapies. By enhancing drug penetration through ocular barriers such as the corneal epithelium and blood-retinal barrier, these systems enable therapeutic agents to reach target retinal tissues more effectively [24]. Their capacity for prolonged retention within ocular compartments ensures a sustained release of bioactive compounds, which maintains therapeutic concentrations over extended periods and minimizes the need for frequent re-administration (Table 1).

Furthermore, these systems allow for controlled and site-specific drug release, thereby reducing systemic absorption and adverse effects. This targeted delivery minimizes drug wastage and increases treatment efficiency. The reduced dosing frequency not only enhances pharmacological outcomes but also significantly improves patient compliance, especially important in chronic conditions like AMD that require long-term management [25]. Collectively, these advantages position nanocarriers as a transformative strategy in ocular drug delivery, optimizing both efficacy and patient-centric care.

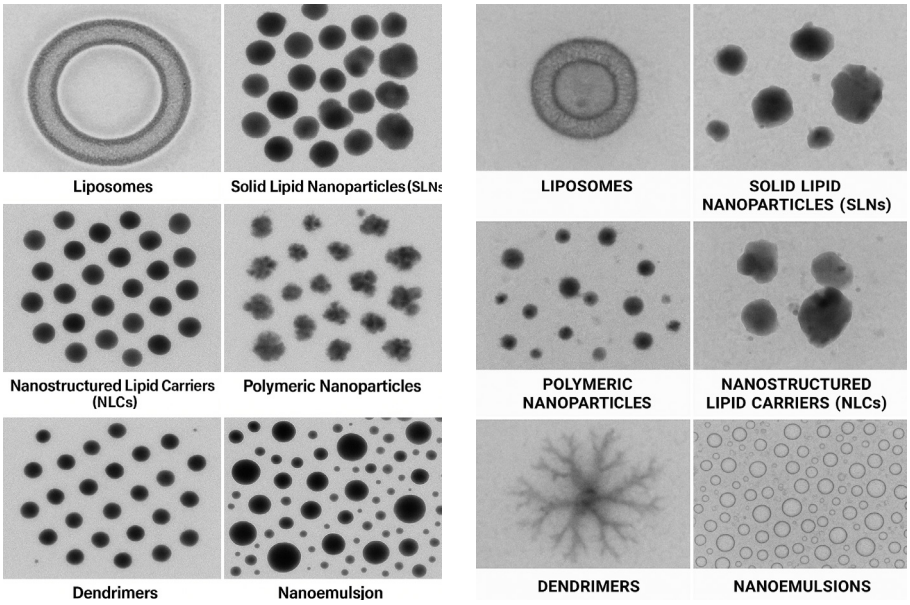

Figure 3. Structural comparison of various nanocarriers.

Table 1. Summary of various nano-nutraceutical formulations, properties, and advantages.

Formulation Type	Key Properties	Advantages
Nanoemulsions	Small droplet size, high surface area	Enhanced solubility and absorption of lipophilic compounds
Solid Lipid Nanoparticles (SLNs)	Solid core, lipid-based matrix	Improved stability, controlled release
Nanostructured Lipid Carriers (NLCs)	Combination of solid and liquid lipids	Higher drug loading, reduced drug expulsion
Polymeric Nanoparticles	Biodegradable polymers (e.g., PLGA, chitosan)	Targeted delivery, sustained release
Liposomes	Phospholipid bilayer vesicles	Biocompatible, protects bioactives from degradation
Nanosuspensions	Pure drug particles in suspension form	Enhanced dissolution rate, suitable for poorly soluble compounds
Dendrimers	Branched, tree-like structure	High payload capacity, precise targeting
Metallic Nanoparticles (e.g., gold, silver)	Surface modifiable, size-tunable	Antioxidant, antimicrobial activity, improved delivery
Nanoencapsulation	Encapsulation in nanocarriers (e.g., cyclodextrins)	Protection from environmental degradation, improved taste masking

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Clinical and Preclinical Studies

Preclinical evidence

Preclinical studies conducted in animal models, such as rodents and rabbits, provide foundational insights into the potential benefits of nano-nutraceuticals for AMD. These studies have consistently demonstrated enhanced ocular bioavailability and targeted delivery of nano-encapsulated compounds to the retina, overcoming traditional anatomical and physiological barriers [26]. Consequently, there is a measurable reduction in biochemical markers of oxidative stress and inflammation, key drivers of AMD pathogenesis. However, the translational relevance of these findings remains uncertain due to interspecies differences in ocular anatomy and metabolism, and the limited duration of most studies which may not fully capture long-term effects or toxicity (Table 2).

Clinical trials

Despite encouraging preclinical data, the clinical evaluation of nano-nutraceuticals in AMD patients remains in its infancy, with a scarcity of large-scale, randomized controlled trials. Preliminary pilot studies, such as those investigating curcumin nanoparticles, have suggested safety and some efficacy signals, including decreased retinal inflammation without significant adverse effects. Nonetheless, these early-phase trials often involve small cohorts and short follow-ups, limiting their statistical power and the ability to generalize findings [27]. More rigorous and extensive clinical validation is necessary before nano-nutraceuticals can be confidently integrated into standard AMD treatment protocols.

Outcome measures

Assessment of therapeutic success in nano-nutraceutical interventions hinges on objective ophthalmologic parameters. Improvements in best-corrected visual acuity (BCVA) serve as the primary functional indicator of visual improvement. Additionally, reductions in central retinal thickness measured via optical coherence tomography (OCT) reflect the resolution of retinal edema and neovascular activity. Biomarkers of oxidative stress in ocular fluids or systemic circulation provide biochemical evidence of therapeutic effect. However, the heterogeneity in study designs, measurement techniques, and endpoint definitions across trials complicates cross-study comparisons and meta-analyses [28].

Table 2. Summary of key preclinical and clinical studies on nano-nutraceuticals in AMD management.

Study Type	Nano-Nutraceutical	Model / Subjects	Key Findings
Preclinical	Lutein-loaded liposomes	Animal model (rat/mouse)	Enhanced retinal uptake and protection against oxidative stress
Preclinical	Zeaxanthin-loaded nanoparticles	Oxidative stress-induced models	Reduced photoreceptor damage and improved retinal function
Preclinical	Curcumin-loaded PLGA nanoparticles	Light-induced retinal degeneration	Inhibition of inflammatory markers and retinal cell apoptosis
Clinical	Nano-formulated Omega-3 fatty acids	AMD patients	Improved visual acuity and reduced drusen formation
Clinical	Nanocarotenoid formulation (Lutein + Zeaxanthin)	Human subjects with early AMD	Slowed progression of AMD, increased macular pigment density
Preclinical	Resveratrol nanoparticles	Retinal pigment epithelium models	Protection against oxidative damage, enhanced cell survival
Clinical	Liposomal antioxidant complex	AMD patient group	Reduced inflammation and oxidative biomarkers

Safety, Regulatory, and Ethical Considerations

Safety profiles

The introduction of nanocarriers into ocular tissues raises critical safety concerns. Nanoparticles can induce cytotoxic effects through mechanisms such as oxidative damage, membrane disruption, or inflammation. Immunogenicity is another risk, as foreign nanomaterials might trigger undesirable immune responses, leading to tissue damage or chronic inflammation [29]. Long-term safety data are particularly sparse, making it difficult to ascertain potential cumulative or delayed adverse effects on delicate retinal cells. Therefore, biocompatibility, biodegradability, and thorough toxicological evaluation are indispensable prerequisites for clinical translation.

Regulatory landscape

Regulatory approval for nanomedicine formulations remains a challenging and evolving process. Agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) enforce stringent requirements encompassing quality control, manufacturing reproducibility, pharmacokinetics, and in vivo efficacy. Nanocarriers, by their complex nature, pose unique characterization challenges, such as batch-to-batch consistency and stability, that complicate regulatory review [30]. Additionally, guidelines for ocular nanomedicines are still being refined, necessitating robust preclinical and clinical data to satisfy safety and efficacy criteria.

Ethical aspects

The deployment of nano-nutraceutical therapies raises several ethical considerations. Informed consent must encompass clear communication regarding the novel nature of nanotechnology-based treatments, potential unknown risks, and benefits. Accessibility and affordability are critical to avoid widening existing healthcare disparities; high costs associated with advanced nanomedicines may restrict access to privileged

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populations, contradicting principles of equity and justice. Ethical frameworks should also address the implications of long-term nanoparticle retention in ocular tissues and the environmental impact of nanomaterial production and disposal [31].

Challenges in Nano-Nutraceutical Therapy for AMD

Research gaps

To establish the true clinical value of nano-nutraceuticals, extensive long-term studies involving large and diverse patient populations are essential. These trials must rigorously assess both effectiveness and safety over extended periods to overcome current evidence limitations.

Technological innovations

Advancements in nanotechnology may enable the development of smart, stimuli-responsive nanocarriers that release therapeutic agents precisely when triggered by changes in the ocular environment, such as variations in pH, temperature, or light, enhancing treatment specificity and minimizing side effects.

Clinical integration

For nano-nutraceuticals to become a routine part of AMD management, seamless cooperation is required among scientists, healthcare providers, regulatory agencies, and pharmaceutical companies. This collaboration will drive the creation of affordable, scalable formulations that can be efficiently produced and widely distributed.

Conclusions

Nano-nutraceuticals represent a groundbreaking advancement in the management of age-related macular degeneration (AMD), addressing the critical limitations inherent in traditional nutraceutical delivery. Conventional formulations of key compounds such as lutein, zeaxanthin, omega-3 fatty acids, curcumin, and resveratrol face significant hurdles—namely poor solubility, rapid degradation, limited bioavailability, and inadequate retinal targeting due to the eye's complex anatomical and physiological barriers. Nanotechnology-based delivery systems, including liposomes, solid lipid nanoparticles, and polymeric carriers, overcome these obstacles by protecting bioactives from enzymatic degradation, enhancing ocular penetration, and enabling controlled, sustained release. This improved delivery not only maximizes therapeutic concentrations in retinal tissues but also reduces dosing frequency and systemic side effects, potentially improving patient adherence, a major issue in AMD treatment. Preclinical studies in animal models provide promising evidence of reduced oxidative stress and inflammation with nano-nutraceuticals, although clinical trials remain preliminary and limited in scope. Therefore, while nanotechnology holds substantial promise, translating these innovations into effective, safe, and widely accessible therapies demands rigorous, large-scale clinical validation, along with addressing regulatory, ethical, and manufacturing challenges.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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