


AREDS2 as a Retinal Geroprotective Strategy: A Literature Review Through a Geroscience Lens

Bhirau Wilaksono[1], Enno Elfandari[2], Rayhani Ichsan[3], Dhini Alfiandari[4], Nurul Mufidah Damry[4], Andi Makkawaru Chairul[5], Nurul Mutiah Aminuddin[3], Novi Safitri Nurdin[6], Aida Ayu Chandrawati[6], Nurussyariah Hammado[7]

[1]Center of Excellence for Healthy Longevity and Physical Fitness, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[2]Department of Forensic and Medicolegal, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[3]Department of Anatomy, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[4]Department of Histology, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[5]Department of Physiology, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[6]Department of Biochemistry, Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia,
[7]Faculty of Medicine, Universitas Negeri Makassar, Makassar, Indonesia

ABSTRACT

Introduction: Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss among the elderly population. The Age-Related Eye Disease Study 2 (AREDS2) supplementation was developed as an evidence-based nutraceutical strategy to slow the progression of AMD. This review aims to evaluate the clinical evidence and potential application of AREDS2 as a geroprotective retinal intervention within the framework of precision geromedicine. **Methods:** A narrative review of recent AREDS and AREDS2 studies was conducted, integrating concepts from geroscience related to retinal aging. **Results**: The AREDS2 formulation, which replaced beta-carotene with lutein and zeaxanthin, demonstrated an 18% reduction in AMD progression risk without increasing lung cancer risk among smokers. AREDS2 components target key aging pathways, including oxidative stress, mitochondrial dysfunction, chronic inflammation, and dysregulated autophagy. In addition, potential modulation of mTOR and AMPK signaling suggests a role in extending retinal healthspan. **Conclusion**: AREDS2 represents a promising nutraceutical approach as a retinal gerotherapy within the paradigm of precision geromedicine. Its clinical implications include preventing AMD progression, optimizing visual function in older adults, and enabling integration into precision-based ophthalmologic practice. Further research is warranted to validate the molecular mechanisms and assess the cross-population effectiveness, thereby strengthening its role in broader age-related ocular health interventions.

Keywords: Age-related macular degeneration, AMD, AREDS2, geroscience, precision geromedicine, retinal geroprotection.

ABSTRAK

Pendahuluan: Degenerasi makula terkait usia (*age-related macular degeneration*/AMD) merupakan salah satu penyebab utama kehilangan penglihatan permanen pada populasi lanjut usia. Suplementasi Age-Related Eye Disease Study 2 (AREDS2) dikembangkan sebagai strategi nutraseutikal berbasis bukti untuk memperlambat progresivitas AMD. Artikel ini menelaah bukti klinis serta potensi penerapan AREDS2 sebagai intervensi geroprotektif pada retina dalam kerangka *precision geromedicine*. **Metode:** Tinjauan naratif terhadap berbagai penelitian terbaru mengenai AREDS dan AREDS2 dilakukan dengan mengintegrasikan konsep-konsep gerosains yang berkaitan dengan proses penuaan retina. **Hasil:** Formulasi AREDS2, yang menggantikan *beta-carotene* dengan *lutein* dan *zeaxanthin*, terbukti menurunkan risiko progresivitas AMD sebesar 18% tanpa meningkatkan risiko kanker paru pada perokok. Komponen AREDS2 menargetkan berbagai jalur utama yang berperan dalam proses penuaan, termasuk stres oksidatif, disfungsi mitokondria, inflamasi kronis, serta disregulasi autofagi. Selain itu, potensi modulasi jalur pensinyalan mTOR dan AMPK menunjukkan bahwa AREDS2 dapat berperan dalam memperpanjang *healthspan* retina. **Simpulan:** AREDS2 merupakan pendekatan nutraseutikal yang menjanjikan sebagai terapi geroprotektif retina dalam paradigma *precision geromedicine*. Implikasi klinisnya meliputi pencegahan progresivitas AMD, optimalisasi fungsi penglihatan pada populasi lanjut usia, serta peluang integrasi ke dalam praktik oftalmologi berbasis presisi. Penelitian lebih lanjut masih diperlukan untuk memvalidasi mekanisme molekuler yang mendasarinya serta mengevaluasi efektivitasnya pada berbagai populasi, sehingga dapat memperkuat peran AREDS2 dalam intervensi kesehatan mata terkait penuaan secara lebih luas. **Bhirau Wilaksono, Enno Elfandari, Rayhani Ichsan, Dhini Alfiandari, Nurul Mufidah Damry, Andi Makkawaru Chairul, Nurul Mutiah Aminuddin, Novi Safitri Nurdin, Aida Ayu Chandrawati, Nurussyariah Hammado. AREDS2 sebagai Strategi Geroproteksi Retina: Tinjauan Pustaka dari Perspektif Gerosains.**

Kata Kunci: *Age-related macular degeneration*, AMD, AREDS2, gerosains, *precision geromedicine*, geroproteksi retina.

https://doi.org/10.55175/cdk.v53i08.2130

Alamat Korespondensi *bhirau@gmail.com*

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive degenerative disease affecting the macula, the central region of the retina responsible for central vision and color perception. AMD represents a leading cause of irreversible visual loss in individuals aged over 50 years, with its prevalence rising in parallel with the growth of the global older adult population.[1] In the United States, more than 11 million individuals are living with AMD, a figure projected to double by 2050.[2] AMD ranks as the leading cause of non-cataract blindness among older adults in numerous countries.[3]

Based on clinical staging, advanced AMD is classified into two principal subtypes: the dry type, characterized by geographic atrophy of the retinal pigment epithelium (RPE) and photoreceptors; and the wet (neovascular) type, characterized by abnormal choroidal neovascularisation that may lead to subretinal hemorrhage and fibrosis.[3,4]

The pathogenesis of AMD is multifactorial and complex, involving the interplay of oxidative stress, chronic inflammation, mitochondrial dysfunction, impaired autophagy, complement system dysregulation, and genetic predisposition. Chronic inflammation plays a pivotal role in the aging retinal microenvironment; dysregulation of the alternative complement pathway, together with mutations in complement factor H (CFH), C3, and C2/BF genes, collectively increases susceptibility to retinal damage.[5] The accumulation of reactive oxygen species (ROS) and the decline in endogenous antioxidant capacity, including superoxide dismutase (SOD), accelerate retinal cell damage.[6] Furthermore, dysregulation of lipid metabolism, together with the accumulation of cholesterol esters and lipid oxidation products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) within retinal tissue, exacerbates degenerative changes.[7] Activation of the NF-□B inflammatory pathway and the NLRP3 inflammasome further amplifies the local inflammatory response. The aging process also induces epigenetic alterations, including DNA methylation and histone modifications, which influence the expression of retinal protective genes. The role of microRNAs, particularly miR-34a and miR-146a, in regulating inflammation and retinal cell senescence is increasingly recognized.[7]

In addressing AMD as an increasingly prevalent public health concern in the aging population, the Age-Related Eye Disease Study (AREDS) represented a landmark contribution. AREDS evaluated the efficacy of supplementation with vitamin C, vitamin E, beta-carotene, zinc, and copper in slowing AMD progression.[8] However, evidence of an elevated risk of lung cancer associated with beta-carotene supplementation in smokers prompted the development of the modified Age-Related Eye Disease Study 2 (AREDS2) formula, in which beta-carotene was replaced by lutein and zeaxanthin, two macular carotenoids that function as blue light filters and potent antioxidants, with the addition of omega-3 fatty acids (*docosahexaenoic acid* [DHA]/ *eicosapentaenoic acid* [EPA]), which support retinal mitochondrial function. The AREDS2 study demonstrated an 18% reduction in the risk of progression to advanced AMD, with an improved safety profile, particularly among active smokers.[9] The mechanisms of action underlying the AREDS2 formula extend beyond antioxidant activity to encompass anti-inflammatory and anti-angiogenic effects, as well as modulation of molecular aging pathways including the mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuin-1 (SIRT1). Current understanding within the field of geroscience positions AMD as a disease amenable to modification through interventions targeting the fundamental processes of biological aging. The geroscience framework conceptually links biological aging to the progressive increase in susceptibility to chronic degenerative disease, offering a novel paradigm for AMD prevention through geroprotective nutraceuticals such as the AREDS2 formulation.[10]

A key challenge in the application of AREDS2 in contemporary clinical practice lies in individual genetic variation that influences the response to supplementation, including polymorphisms in the CFH and ARMS2 (Age-Related Maculopathy Susceptibility 2) gene.[11] The precision geromedicine approach enables personalization of supplementation strategies based on individual genetic risk profiles and metabolic status, representing the future direction of geriatric ophthalmology in extending retinal healthspan across the aging trajectory. This review aims to evaluate the AREDS2 formulation as a retinal geroprotective strategy through a geroscience lens.

MAIN REVIEW

Formulation and Geroprotective Mechanisms of AREDS2

The AREDS2 formulation represents an advancement over the original AREDS formula, replacing beta-carotene with lutein and zeaxanthin, two macular carotenoids that function as antioxidants and blue-light filters, while incorporating omega-3 fatty acids (DHA/EPA) to further enhance retinal protection in older adult populations.[12] Its core composition comprises vitamin C (500 mg), vitamin E (400 IU), lutein (10 mg), zeaxanthin (2 mg), zinc (25 mg), copper (2 mg), and omega-3 fatty acids. These components act synergistically to target the principal pathways of retinal aging: oxidative stress, chronic inflammation, mitochondrial dysfunction, and impaired autophagy.[7] Lutein and zeaxanthin serve as blue light filters and reactive oxygen species (ROS) scavengers, while simultaneously modulating the expression of protective genes through activation of nuclear factor erythroid 2-related factor 2 (NRF2) and suppression of the NLRP3 inflammasome.[13,14] Vitamins C and E function as primary antioxidants, protecting retinal cell membranes from lipid peroxidative damage, while zinc and copper support endogenous antioxidant defense as cofactors of superoxide dismutase (SOD), and maintain DNA integrity and the metabolic function of the retinal pigment epithelium (RPE).[7,15]

Beyond its antioxidant and anti-inflammatory roles, the AREDS2 formulation also exhibits caloric restriction mimetic properties through modulation of molecular aging signaling pathways, specifically, inhibition of mTOR and activation of AMPK, which collectively support mitochondrial function and autophagy while enhancing retinal cell resilience against oxidative stress.[16,17] Additionally, certain components of the formulation, such as zinc, confer benefits that extend beyond the retina, including immunomodulatory effects, neuroprotection against neurodegeneration, and support for cardiovascular and dermatological health **(Figure 1)**.[18]

*Created by Bhirau Wilaksono.

Figure 1. Vitamin C (500 mg) and vitamin E (400 IU): potent antioxidants that inhibit oxidative stress. Zinc (25 mg) and copper (2 mg): support antioxidant enzymes and retinal cell integrity. Lutein (10 mg) and zeaxanthin (2 mg): enhance macular pigment density, absorb blue light, and protect against oxidative damage.

The clinical superiority of the AREDS2 formulation is supported by evidence demonstrating that this supplementation regimen reduces the risk of AMD progression by up to 18% without increasing the risk of lung cancer in active smokers. The efficacy of AREDS2 is further influenced by individual genetic variation, notably polymorphisms in CFH and ARMS2, thereby making precision nutraceutical intervention, personalized to individual genetic and metabolic risk profiles, a promising approach within the framework of modern geromedicine.[19]

By targeting oxidative stress, chronic inflammation, vascular dysfunction, and dysregulation of molecular aging pathways, AREDS2 can be categorized as a retinal geroprotective intervention of direct relevance to contemporary geriatric ophthalmology. Furthermore, these multifaceted mechanisms position AREDS2 as more than a conventional supplement; it represents a nutraceutical capable of modulating aging processes to actively support retinal healthspan **(Table)**.[20,21]

AREDS2 as a Retinal Gerotherapy

Gerotherapy is a branch of geroscience that aims to target the biological mechanisms of aging to extend healthspan, including preserving retinal function, which is particularly vulnerable to age-related degenerative processes.[22–24]

AMD, as the principal manifestation of retinal aging, is characterized by the accumulation of drusen, oxidative stress, mitochondrial dysfunction, impaired autophagy, and low-grade chronic inflammation (inflammaging) **(Figure 2)**.[27]

Table. Mechanisms of action of AREDS2 components in protecting the retina against AMD.

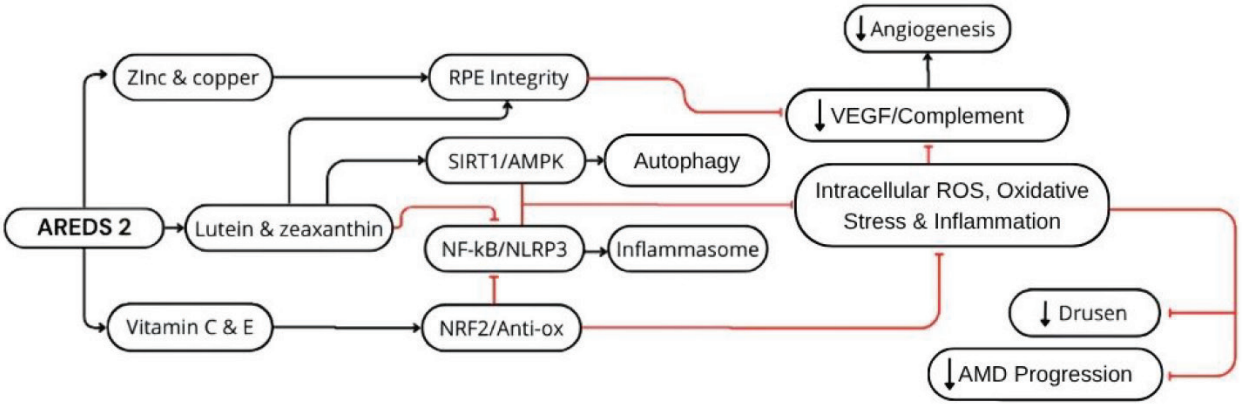
Mechanism	Reference
Vitamin C (500 mg) and vitamin E (400 IU) are potent antioxidants that neutralise free radicals and protect retinal cells from oxidative damage.	Wong, *et al*.[25]
Zinc (25 mg) and copper (2 mg) support antioxidant enzyme activity and retinal cell integrity. Acting as cofactors for superoxide dismutase (SOD) and related antioxidant enzymes, zinc and copper enhance endogenous antioxidant defense, thereby protecting retinal cells from oxidative damage.	Wong, *et al*.[25]
Lutein and zeaxanthin exert anti-inflammatory properties, attenuating chronic inflammation within the macula and thereby promoting overall retinal health.	Wang, *et al*.[26]
The components of the AREDS2 formulation collectively modulate angiogenesis, inhibiting abnormal blood vessel growth in neovascular AMD and supporting overall retinal vascular health.	Parmar, *et al*.[19]

The AREDS2 formulation was developed as a safer and more efficacious successor to AREDS1 for use in older adult populations, replacing beta-carotene with lutein and zeaxanthin, with certain formulations also incorporating omega-3 fatty acids (DHA/EPA).[28] Lutein and zeaxanthin accumulate within the macula, where they serve as blue light filters and potent antioxidants, reducing ROS levels, stabilizing photoreceptor membranes, and attenuating oxidative stress within retinal tissue.[29,30] Omega-3 fatty acids support mitophagy, suppress the expression of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and inhibit the mTOR pathway mechanisms that are collectively relevant to slowing retinal cell aging.[29]

Vitamins C and E, zinc, and copper within the AREDS2 formulation strengthen endogenous retinal antioxidant defense, maintain redox balance, and preserve DNA stability. Zinc additionally reinforces the function of the retinal pigment epithelium (RPE) as an immunological barrier of the retina and suppresses microglial inflammation. By simultaneously targeting oxidative stress pathways, chronic inflammation, mitochondrial dysfunction, and impaired autophagy, this formulation meets the defining criteria for retinal gerotherapy.[17,31]

In vitro studies and animal models have demonstrated that AREDS2 components, notably lutein and zeaxanthin, can upregulate SIRT1 expression, suppress the NF-κB inflammatory pathway, and maintain proteostasis and retinal cell survival. This approach is consistent with the principles of caloric restriction mimetics, which modulate the mTOR/AMPK axis to support retinal metabolic homeostasis.[29,30,32]

The precision geromedicine dimension of AREDS2 is of particular clinical significance, as the response to supplementation may vary according to individual genetic profiles, notably polymorphisms in CFH and ARMS2, which influence both AMD risk and therapeutic response. Post-hoc analyses have indicated that individuals carrying high-risk genotypes derive greater protective benefit from this formulation, although prospective validation remains warranted.[33]



*Created by Bhirau Wilaksono.

Figure 2. Mechanisms of action of the principal AREDS2 components, illustrating how vitamin C and E, lutein and zeaxanthin, and zinc and copper act through key molecular targets to inhibit AMD progression. Vitamin C and E activate NRF2 to attenuate oxidative stress; lutein and zeaxanthin suppress the NF-κB/NLRP3 inflammasome pathway while simultaneously reducing ROS; SIRT1/AMPK activation enhances autophagy; and zinc and copper restore RPE integrity, collectively reducing ROS burden and inflammatory tone, inhibiting VEGF expression and complement activation, decreasing drusen accumulation, and slowing AMD progression. **Abbreviations:** AREDS2: Age-Related Eye Disease Study 2; RPE: Retinal pigment epithelium; SIRT1: Sirtuin-1; AMPK: AMP-activated protein kinase; NF-κB: Nuclear factor Kappa B; NLRP3: NLR family pyrin domain containing 3; NRF2: Nuclear factor erythroid 2-related factor 2; VEGF: Vascular endothelial growth factor; ROS: Reactive oxygen species.

Taken together, AREDS2 functions not only as a preventive supplement against AMD but also as a credible candidate within the category of retinal gerotherapy, an intervention that targets aging pathways to extend retinal healthspan. This emerging paradigm supports the integration of precision nutraceuticals into modern geriatric ophthalmology as a relatively low-cost, well-tolerated, and evidence-based approach.

Clinical Efficacy of AREDS2 as a Retinal Geroprotective Intervention

The AREDS2 study provides robust evidence that nutraceutical supplementation can slow AMD progression. By replacing beta-carotene with lutein and zeaxanthin, two macular carotenoids with antioxidant and photoprotective properties, and incorporating omega-3 fatty acids, the AREDS2 formulation reduces the risk of progression to advanced AMD by approximately 18%, particularly among individuals with low baseline dietary intake of lutein and zeaxanthin. Furthermore, the substitution of beta-carotene eliminates the associated risk of lung cancer, thereby improving the safety profile of AREDS2 for current and former smokers.[9]

Beyond its direct clinical effects, the micronutrients in AREDS2, including zinc, vitamin C, vitamin E, vitamin D3, and B-complex vitamins, are known to participate in epigenetic modifications, including regulation of DNA methylation and one-carbon metabolism, indicating that this intervention also modulates retinal aging processes at the molecular level.[23,34] Lutein and zeaxanthin not only accumulate selectively within the macula but also stabilize cell membranes, inhibit lipid peroxidation, filter high-energy blue light, induce the protective NRF2 pathway, and suppress the NLRP3 inflammasome.[30] Vitamins C and E protect the extracellular space and retinal membranes from ROS, while zinc and copper support endogenous antioxidant function and maintain DNA stability and RPE metabolism.[23] The addition of omega-3 fatty acids further contributes to the modulation of core aging pathways through AMPK activation and mTOR inhibition, supporting autophagy, reducing pro-inflammatory protein synthesis, and improving mitochondrial function.

In vitro studies and murine AMD models have demonstrated that AREDS2 components can reduce levels of vascular endothelial growth factor (VEGF) and tumor necrosis factor-alpha (TNF-α), two key mediators of pathological angiogenesis, while promoting RPE cell regeneration and enhancing retinal resilience against oxidative stress.[34,35] Evaluation of patients using optical coherence tomography (OCT) and fundus autofluorescence has confirmed a slowing of RPE and photoreceptor layer thinning in AREDS2 users, indicating structural retinal protection that supports the preservation of visual function in older adults.[36]

From a geroscience perspective, AREDS2 may be categorized as a caloric restriction mimetic based on the influence of its components on the mTOR and AMPK pathways. This approach extends retinal healthspan not only by slowing macular degeneration but by targeting retinal aging processes at their core molecular level. Inter-individual variability in response, attributable to genetic factors including polymorphisms such as CFH Y402H and ARMS2 A69S, further underscores the relevance of precision geromedicine in this context. Post hoc analyses have indicated that subgroups carrying high-risk genotypes show more pronounced slowing of AMD progression with AREDS2, although broader prospective validation remains necessary.[37]

AREDS2 represents one of the most compelling early examples of clinically validated nutraceutical-based gerotherapy. The formulation can be augmented by adding complementary geroprotective agents, such as resveratrol, mild senolytic compounds, or mitophagic peptides, to further strengthen mechanistically targeted interventions against retinal biological aging.

CONCLUSION

AREDS2 represents an evidence-based nutraceutical strategy that effectively slows AMD progression by acting through mechanisms of antioxidant protection, anti-inflammatory action, and modulation of key cellular aging pathways, including mTOR and AMPK. The formulation further supports the personalization of therapeutic approaches based on individual genetic profiles, metabolic status, and risk factors, in alignment with the precision geromedicine paradigm. As a retinal geroprotective intervention, AREDS2 has the potential not only to strengthen retinal tissue resilience against oxidative stress and chronic inflammation but also to extend retinal healthspan, thereby supporting long-term visual health in older adult populations. Although clinical trials have demonstrated significant benefits, further research is required to validate efficacy across diverse populations, identify reliable biomarkers of therapeutic response, and explore potential synergies with healthy lifestyle approaches and other anti-aging therapies. With appropriately directed development, AREDS2 has the potential to become an integral component of preventive and promotive geriatric ophthalmology strategies grounded in the healthy aging framework.

REFERENCES

1. Kashi AK, Souied E, Fares S, Borrelli E, Capuano V, Jung C, et al. The spectrum of central choriocapillaris abnormalities on swept-source optical coherence tomography angiography in the fellow eye of unilateral exudative age-related macular degeneration patients: from flow deficits to subclinical non-exudative neovascularization. J Clin Med. 2021;10(12):2658. doi: 10.3390/JCM10122658.
2. Rein DB, Wittenborn JS, Zhang X, Honeycutt AA, Lesesne SB, Saaddine J. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Arch Ophthalmol. 2009;127(4):533–40. doi: 10.1001/ARCHOPHTHALMOL.2009.58.
3. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye and vision (London, England) 2016;3:34. https://doi.org/10.1186/s40662-016-0063-5.
4. Vyawahare H, Shinde,P. Age-related macular degeneration: epidemiology, pathophysiology, diagnosis, and treatment. Cureus 2022;14(9):e29583. https://doi.org/10.7759/cureus.29583.
5. Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduction Targeted Ther. 2022;7(1):1–40. https://doi.org/10.1038/s41392-022-01251-0.
6. Iakovou E, Kourti M. A comprehensive overview of the complex role of oxidative stress in aging, the contributing environmental stressors and emerging antioxidant therapeutic interventions. Front Aging Neurosci. 2022;14:827900. https://doi.org/10.3389/fnagi.2022.827900.
7. Upadhyay M, Bonilha V. Analysis of oxidative stress-mediated degeneration in retina and RPE using sodium iodate (NaIO3) model. Free Radic Biol Med. 2018;128:S128. doi: 10.1016/J.FREERADBIOMED.2018.10.318.
8. Prea SM Chan, EC, Dusting GJ, Vingrys AJ, Bui BV, Liu GS, et al. Gene therapy with endogenous inhibitors of angiogenesis for neovascular age-related macular degeneration: beyond anti-VEGF therapy. J Ophthalmol. 2015;1:201726. https://doi.org/10.1155/2015/201726.
9. Langford-Smith A, Keenan TDL, Clark SJ, Bishop PN, Day AJ. The role of complement in age-related macular degeneration: Heparan sulphate, a ZIP code for complement factor H?. J Innate Immun. 2014;6(4):407–16. doi: 10.1159/000356513.
10. Suzumura A, Terao R, Kaneko H. Protective effects and molecular signaling of n-3 fatty acids on oxidative stress and inflammation in retinal diseases. Antioxidants. 2020;9(10):920. doi: 10.3390/ANTIOX9100920.
11. Awh CC, Lane AM, Hawken S, Zanke B, Kim IK. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology. 2013;120(11):2317–23. doi: 10.1016/J.OPHTHA.2013.07.039.
12. Wang L, Chen Y, Sternberg P, Cai J. Essential roles of the PI3 kinase/akt pathway in regulating Nrf2-dependent antioxidant functions in the RPE. Invest Ophthalmol Vis Sci. 2008;49(4):1671–8. doi: 10.1167/IOVS.07-1099.
13. Wang D, Chen Y, Li J, Wu E, Tang T, Singla RK, et al. Natural products for the treatment of age-related macular degeneration. Phytomedicine. 2024;130:155522. https://doi.org/10.1016/j.phymed.2024.155522.
14. Iakovou E, Kourti M. A comprehensive overview of the complex role of oxidative stress in aging, the contributing environmental stressors and emerging antioxidant therapeutic interventions. Front Aging Neurosc. 2022;14:827900. https://doi.org/10.3389/fnagi.2022.827900.
15. Reinisalo M, Karlund A, Koskela A, Kaarniranta K, Karjalainen RO. Polyphenol stilbenes: molecular mechanisms of defence against oxidative stress and aging-related diseases. Oxidative Med Cell Longevity. 2015;2015:340520. https://doi.org/10.1155/2015/340520.
16. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. Nutrients 2017;9(12):1286. https://doi.org/10.3390/nu9121286.
17. Basyal D, Lee S, Kim HJ. Antioxidants and mechanistic insights for managing dry age-related macular degeneration. Antioxidants (Basel). 2024;13(5):568. https://doi.org/10.3390/antiox13050568.

18. Marino N, Putignano G, Cappilli S, Chersoni E, Santuccione A, Calabrese G, et al. Towards AI-driven longevity research: a overview. Front Aging. 2023;4:1057204. https://doi.org/10.3389/fragi.2023.1057204.

19. Shanaida M, Mykhailenko O, Lysiuk R, Hudz N, Balwierz R, Shulhai A, et al. Carotenoids for antiaging: nutraceutical, pharmaceutical, and cosmeceutical applications. Pharmaceuticals 2025;18(3):403. https://doi.org/10.3390/ph18030403.

20. Parmar UPS, Surico PL, Mori T, Singh RB, Cutrupi F, Premkishore P, et al. Antioxidants in age-related macular degeneration: lights and shadows. Antioxidants (Basel). 2025;14(2):152. https://doi.org/10.3390/antiox14020152.

21. Alugoju P, Krishna Swamy VKD, Anthikapalli NVA, Tencomnao T. Health benefits of astaxanthin against age-related diseases of multiple organs: a comprehensive review. Crit Rev Food Sci Nutr. 2023;63(31):10709–74. doi:10.1080/10408398.2022.2084600.

22. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186(2):243–78. doi: 10.1016/J.CELL.2022.11.001.

23. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709–13. doi: 10.1016/J.CELL.2014.10.039.

24. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019;571(7764):183–92. doi: 10.1038/S41586-019-1365-2.

25. Sivaprasad S, Chong N V. The complement system and age-related macular degeneration. Eye. 2006;20(8):867–72. doi: 10.1038/SJ.EYE.6702176.

26. Wong KH, Nam HY, Lew SY, Naidu M, David P, Kamalden TA, et al. Discovering the potential of natural antioxidants in age-related macular degeneration: a review. Pharmaceuticals (Basel). 2022 Jan 14;15(1):101. doi: 10.3390/ph15010101.

27. Buonfiglio F, Korb CA, Stoffelns B, Pfeiffer N, Gericke A. Recent advances in our understanding of age-related macular degeneration: mitochondrial dysfunction, redox signaling, and the complement system. Aging Dis. 2024;16(3):1535–75. doi: 10.14336/AD.2024.0124.

28. Chew EY, Clemons T, SanGiovanni JP, Danis R, Domalpally A, McBee W, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report no 1). Ophthalmology. 2012;119(11):2282–9. doi: 10.1016/J.OPHTHA.2012.05.027.

29. Suzumura A, Terao R, Kaneko H. Protective effects and molecular signaling of n-3 fatty acids on oxidative stress and inflammation in retinal diseases. Antioxidants (Basel). 2020;9(10):920. doi: 10.3390/ANTIOX9100920.

30. Mrowicka M, Mrowicki J, Kucharska,E, Majsterek I. Lutein and zeaxanthin and their roles in age-related macular degeneration-neurodegenerative disease. Nutrients 2022;14(4):827. https://doi.org/10.3390/nu14040827.

31. Wong KH, Nam HY, Lew SY, Naidu M, David P, Kamalden TA, et al. Discovering the potential of natural antioxidants in age-related macular degeneration: a review. Pharmaceuticals (Basel, Switzerland) 2022;15(1):01. https://doi.org/10.3390/ph15010101.

32. Fingar DC, Blenis J. Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. Oncogene. 2004;23(18):3151–71. doi:10.1038/SJ.ONC.1207542.

33. Lambert NG, ElShelmani H, Singh MK, Mansergh FC, Wride MA, Padilla M, et al. Risk factors and biomarkers of age-related macular degeneration. Prog Retin Eye Res. 2016;54:64–102. doi: 10.1016/J.PRETEYERES.2016.04.003.

34. Bian Q, Gao S, Zhou J, Qin J, Taylor A, Johnson EJ, et al. Lutein and zeaxanthin supplementation reduces photooxidative damage and modulates the expression of inflammation-related genes in retinal pigment epithelial cells. Free Radic Biol Med. 2012;53(6):1298–307. doi: 10.1016/J.FREERADBIOMED.2012.06.024.

35. Tuo J, Ross RJ, Herzlich AA, Shen D, Ding X, Zhou M, et al. A high omega-3 fatty acid diet reduces retinal lesions in a murine model of macular degeneration. Am J Pathol. 2009;175(2):799–807. doi: 10.2353/AJPATH.2009.090089.

36. Detaram DH, Mitchell P, Russell J, Burlutsky G, Liew G, Gopinath B. Dietary zinc intake is associated with macular fluid in neovascular age-related macular degeneration. Clin Exp Ophthalmol. 2020;48(1):61–8. doi: 10.1111/CEO.13644.

37. Gemenetzi M, Lotery AJ. Complement pathway biomarkers and age-related macular degeneration. Eye (Lond). 2016;30(1):1–14. doi: 10.1038/EYE.2015.203.