


Effectiveness of Lutein and Zeaxanthin Supplementation on the Progression of Geographic Atrophy and Visual Acuity in Age-Related Macular Degeneration: A Systematic Review Based on Clinical Trials

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ABSTRACT

Introduction: Geographic atrophy (GA) is an advanced form of dry age-related macular degeneration (AMD) that can cause severe central vision loss if its progression extends to the foveal area. Currently, therapeutic options for GA remain limited, with safety profiles requiring further evaluation. Lutein and zeaxanthin, as the main components of the Age-Related Eye Disease Study (AREDS2) formula, have become the focus of current research. Both are antioxidants concentrated in the macula, which exert protective effects on retinal structures and reduce oxidative stress. This systematic review aims to evaluate the effectiveness of oral lutein and zeaxanthin supplementation on GA progression and visual acuity in AMD patients. **Methods:** Literature searches were conducted across four biomedical databases based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. A total of four studies met the inclusion criteria and were analyzed qualitatively. **Results:** The analysis showed that oral supplementation of lutein (10 mg/day) and zeaxanthin (2 mg/day) may reduce the progression of non-central GA and stabilize or improve visual acuity in patients with AMD. Lutein at doses of 10 mg and 20 mg demonstrated similar effectiveness in improving visual acuity through an increase in macular pigment optical density (MPOD). **Conclusion:** Based on the findings of this systematic review, oral supplementation with lutein (10 mg/day) and zeaxanthin (2 mg/day), as incorporated in the AREDS2 formulation, appears to slow the progression of non-central GA and preserve foveal integrity (foveal sparing). Further long-term studies are required to confirm the clinical benefits and long-term safety.

Keywords: Age-related macular degeneration, geographic atrophy, lutein, zeaxanthin.

ABSTRAK

Pendahuluan: Atrofi geografis (GA) merupakan bentuk lanjut degenerasi makula terkait usia (AMD) tipe kering yang dapat menyebabkan penurunan penglihatan sentral berat jika progresivitasnya meluas hingga ke area fovea. Saat ini, pilihan modalitas terapi GA masih terbatas dengan profil keamanan yang perlu evaluasi lebih lanjut. *Lutein* dan *zeaxanthin* sebagai komponen utama formula Age-Related Eye Disease Study (AREDS2) menjadi fokus penelitian saat ini. Keduanya merupakan antioksidan yang terkonsentrasi di makula, yang memiliki efek protektif terhadap struktur retina dan mengurangi stres oksidatif. Tinjauan sistematis ini bertujuan untuk mengevaluasi efektivitas suplementasi oral *lutein* dan *zeaxanthin* terhadap progresivitas GA dan ketajaman penglihatan pasien AMD. **Metode:** Pencarian literatur dilakukan pada 4 *database* biomedis berdasarkan protokol *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). Sebanyak 4 studi memenuhi kriteria inklusi dan dianalisis secara kualitatif. **Hasil:** Analisis menunjukkan bahwa suplementasi oral *lutein* (10 mg/hari) dan *zeaxanthin* (2 mg/hari) dapat mengurangi progresivitas GA non-sentral dan menstabilkan atau memperbaiki ketajaman penglihatan pasien AMD. *Lutein* dosis 10 mg dan 20 mg memiliki efektivitas serupa dalam memperbaiki ketajaman penglihatan melalui peningkatan nilai densitas optik pigmen makula (MPOD). **Simpulan:** Berdasarkan temuan tinjauan sistematis ini, suplementasi oral dengan *lutein* (10 mg/hari) dan *zeaxanthin* (2 mg/hari), sebagaimana terkandung dalam formulasi AREDS2, tampaknya dapat memperlambat perkembangan GA non-sentral dan menjaga integritas fovea (*foveal sparing*). Studi jangka panjang lebih lanjut diperlukan untuk mengonfirmasi manfaat klinis dan keamanan jangka panjang. **Komang Diah Kurnia Kesumaputri, Ni Made Dwipayani, I Made Dwi Surya Wibawa, Putu Anindya Agrasidi, Felicia. Efektivitas Suplementasi Lutein dan Zeaxanthin terhadap Progresivitas Atrofi Geografis dan Ketajaman Penglihatan pada Degenerasi Makula Terkait Usia: Tinjauan Sistematis Berbasis Uji Klinik.**

Kata Kunci: Degenerasi makula terkait usia, atrofi geografis, *lutein*, *zeaxanthin*.

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INTRODUCTION

Age-related macular degeneration (AMD) is a neurodegenerative disease characterized by the accumulation of deposits beneath the retina, leading to degeneration of the macula, retinal pigment epithelium (RPE), and choroid, as well as the development of abnormal neovascularization in the retina.[1] This condition is characterized by reduced central vision, visual distortion, and may progress to the formation of central scotoma.[2] AMD is classified into two types based on its clinical manifestation and progression, namely dry (non-exudative) AMD and wet (exudative) AMD. Approximately 90% of all AMD cases are classified as dry AMD, which is characterized by the presence of drusen in the early stages and geographic atrophy (GA) in the advanced stages.[3]

In 2020, the global prevalence of AMD was estimated at 189 million individuals, of whom approximately 1.85 million were affected by blindness. AMD is one of the leading causes of irreversible blindness worldwide among individuals aged over 55 years. In Indonesia, AMD ranks as the third most common cause of blindness.[4,5] The burden of AMD in Indonesia it is expected to increase in line with rising life expectancy, however, its exact prevalence remains uncertain.[6]

The incidence of geographic atrophy (GA) increases fourfold every decade among individuals aged 50 to 80 years.[7] GA affects the outer retinal layers, leading to progressive loss of retinal pigment epithelium (RPE) cells, photoreceptors, and a reduction in choriocapillaris vascular density. The progression of GA varies depending on the size and location of the atrophic lesions, as well as foveal involvement.[7-10] When GA extends to involve the fovea, it may result in severe impairment of central visual acuity.[11]

Oxidative stress plays a crucial role in the pathogenesis of AMD, particularly in the progression of GA. The retina is highly susceptible and highly exposed to oxidative stress due to its high oxygen consumption and substantial energy demand required to convert light into neural signals. Lutein and zeaxanthin are carotenoids present in the macula that function as antioxidants. Several studies[12–14] have reported that the concentrations of these carotenoids in the macula are lower in patients with AMD.

The Age-Related Eye Disease Study (AREDS) demonstrated that oral supplementation with high-dose antioxidants and zinc can reduce the progression of advanced AMD. However, β-carotene, included as an antioxidant in the original AREDS formulation, has been associated with an increased risk of lung cancer, particularly in individuals with a history of smoking. Therefore, in the subsequent AREDS2 study, β-carotene was replaced with lutein and zeaxanthin, which have a more favorable safety profile.[15]

This systematic review evaluates the effectiveness of oral lutein and zeaxanthin supplementation on the progression of geographic atrophy and visual acuity in patients with AMD, based on evidence from multiple clinical trials.

METHODS

This study is a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] guidelines, and registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42025108888).[17] Literature search was performed in PubMed, ScienceDirect, Google Scholar, and MedRxiv between May 1 and May 20 2025, using Medical Subject Headings (MeSH) terms and Boolean operators as follows: ("Age-related macular degeneration" OR "macular degeneration") AND (lutein) AND (zeaxanthin) AND ("geographic atrophy").

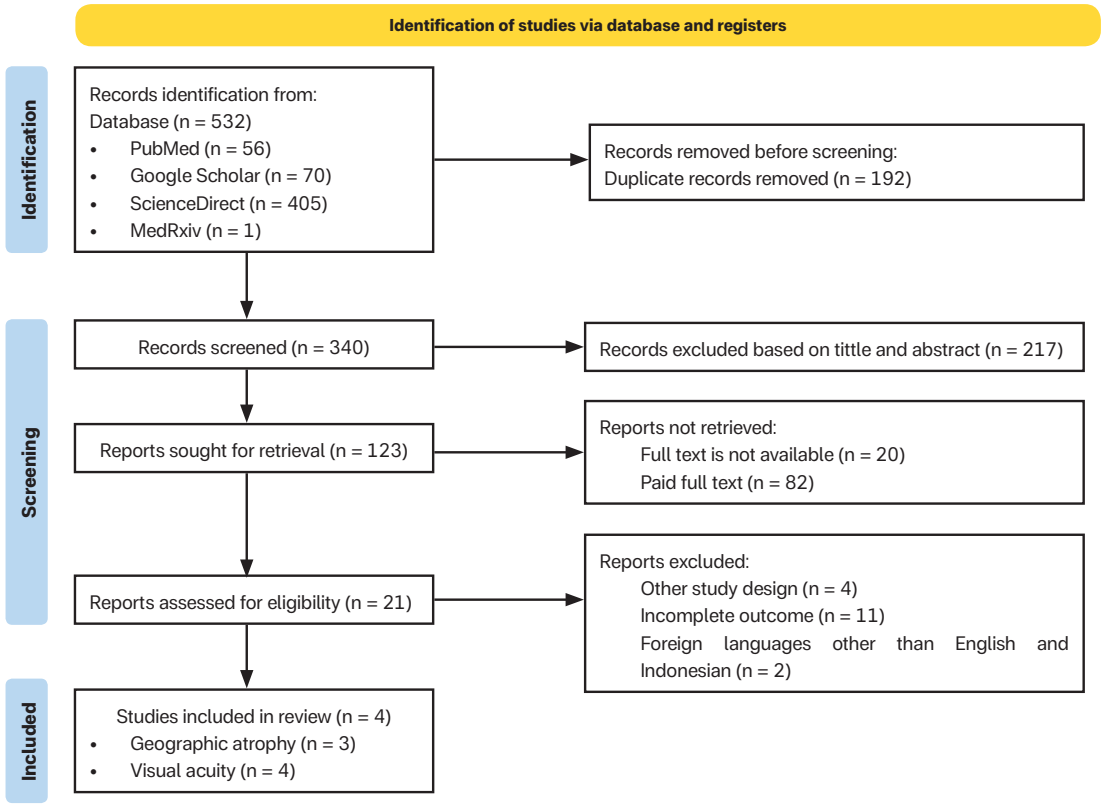
The inclusion criteria were as follows: (a) Participants: patients with advanced macular degeneration presenting with geographic atrophy (GA); (b) Studies assessing the effectiveness of oral lutein and zeaxanthin supplementation in the macular degeneration; (c) Outcomes: reporting at least one efficacy outcome of lutein and zeaxanthin supplementation, including GA progression and visual acuity; (d) Study design: interventional studies or clinical trials; and (e) Language: English or Indonesian. The exclusion criteria were as follows: (a) Studies with review, observational, or case report designs; (b) Full-text articles not accessible or requiring paid access; and (c) Participants with other intraocular conditions that could confound the intervention outcomes, including macular disorders other than AMD and intraocular diseases causing irreversible visual impairment, such as amblyopia, glaucoma, and anterior ischemic optic neuropathy.

Risk of bias was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) across five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of outcomes; and (5) bias in the selection of reported results.[18] Study characteristics including author, year of publication, study design, sample size, intervention regimen, control regimen, and outcomes, were systematically extracted and are summarized in the **Table**. A qualitative analysis was conducted to synthesize the evidence on the effectiveness of lutein and zeaxanthin supplementation on geographic atrophy progression and visual acuity in patients with age-related macular degeneration.

RESULTS

Following a systematic literature search across four biomedical databases, 532 studies were identified based on the search terms used. After duplicate screening, 340 studies remained, which were subsequently filtered based on the relevance of their titles and abstracts. A total of 123 studies with relevant titles and abstracts were further assessed for full-text availability and accessibility, yielding 21 studies. These studies were read in their entirety and comprehensively evaluated, resulting in 4 studies with a randomized controlled trial (RCT) design that met the predefined inclusion and exclusion criteria. The study selection procedure followed the PRISMA guidelines, as reported in the **Scheme.**

Each included study was subsequently assessed for risk of bias using RoB 2.[18] Based on the bias analysis, two studies were rated as having some concerns, while the remaining two studies demonstrated a low risk of bias. Regarding the studies with some concerns, both had less than 95% of the total sample remaining at the end of the analysis, attributable to participants lost to follow-up or withdrawal (dropout). The risk of bias assessment for each individual study, along with a summary across each domain, is presented in the **Figure.**



Scheme. PRISMA flowchart of the study selection process.

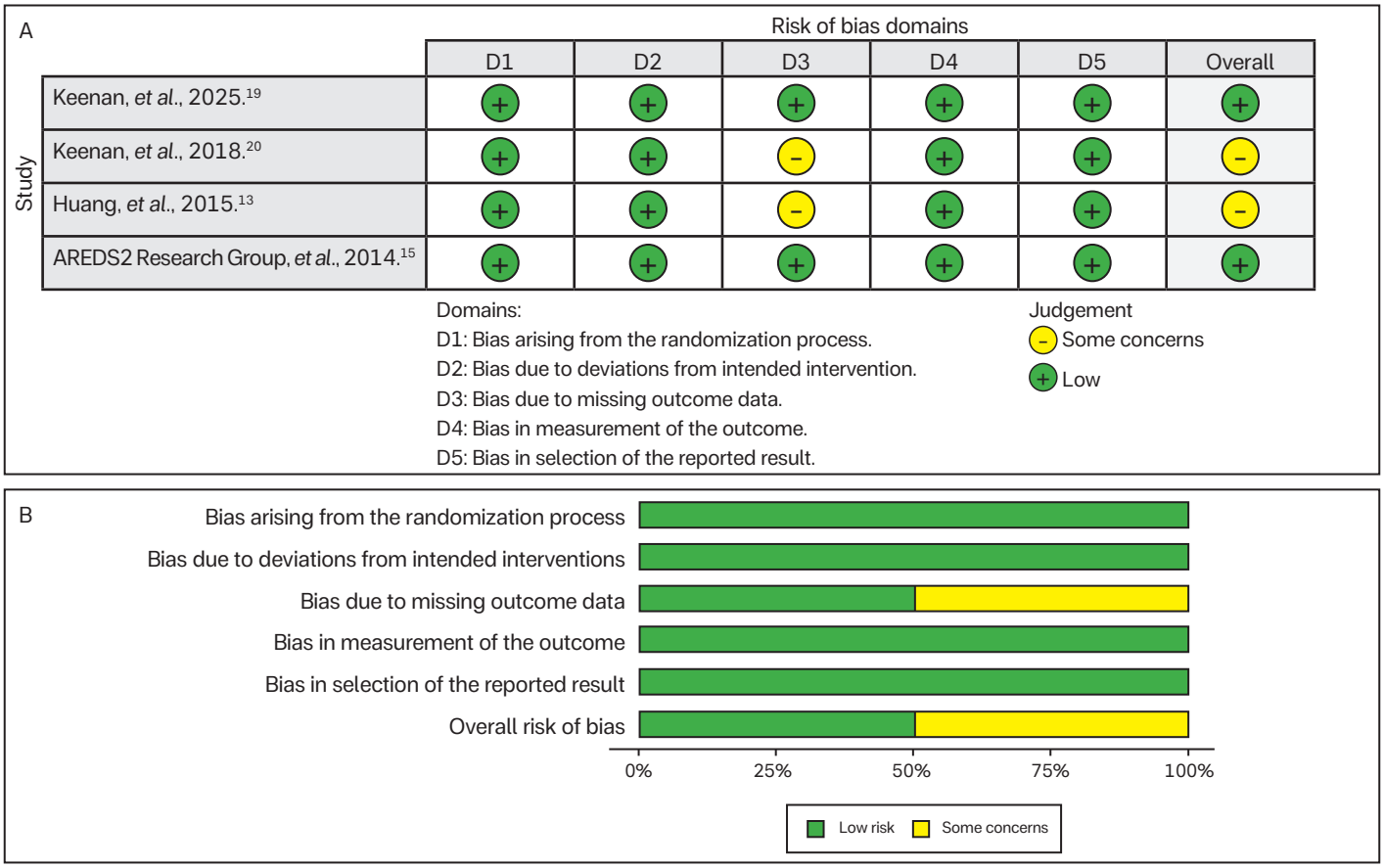


Figure. Risk-of-bias assessment using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

Of the four included RCT studies, all reported outcomes related to the effectiveness of lutein and zeaxanthin therapy on visual acuity, while two studies additionally reported outcomes related to GA progression. The total sample size across all studies reached 9,781 patients. Each study applied varying age inclusion criteria, with the majority enrolling participants aged >50 to 85 years. Regarding intervention regimens, three studies employed the same regimen consisting of lutein 10 mg combined with zeaxanthin 2 mg, while one study used different doses of lutein (10 mg and 20 mg) and zeaxanthin (10 mg). Three studies reported outcomes related to geographic atrophy, and three studies reported outcomes related to visual acuity. The characteristics of each included study are systematically presented in the **Table .**

Table. Characteristics and research results related to the effectiveness of lutein and zeaxanthin on the progression of geographic atrophy and visual acuity in age-related macular degeneration patients.

Author	Year	Study Design	Sample Size	Intervention Regimen	Control Regimen	Baseline Visual Acuity	Research Outcomes
Keenan, *et al.*[19]	2025	RCT	3,640 participants aged 55–80	A combination of 10 mg of lutein and 2 mg of zeaxanthin.	There were 3 control regimens: (1) 350 mg of DHA and 650 mg of EPA; (2) 10 mg of lutein and 2 mg of zeaxanthin, plus 350 mg of DHA and 650 mg of EPA; (3) placebo.	76.8±10.5	– The progression of GA toward the macular center was significantly slower (p = 0.017) in the intervention group (L/Z) compared to the control group (without L/Z), with expansion rates of 84.5 µm/year (95% CI 72.4–96.6 µm/year) and 105.3 µm/year (95% CI 93.2–117.3 µm/year), respectively. – BCVA scores did not differ significantly (p = 0.058) between the intervention group (L/Z) and the control group (without L/Z), but the decline in visual acuity occurred more slowly in the intervention group.
Keenan, *et al.*[20]	2018	RCT	1,826 participants aged 50–85	A combination of 10 mg of lutein and 2 mg of zeaxanthin.	There were 3 control regimens: (1) 350 mg of DHA and 650 mg of EPA; (2) 10 mg of lutein and 2 mg of zeaxanthin, plus 350 mg of DHA and 650 mg of EPA; (3) placebo.	67.5±20.2	– There was no significant difference in the rate of geographic atrophy progression between the intervention group (L/Z) and the control group (without L/Z), with a p-value of 0.33, in both patients with central and non-central geographic atrophy.
Huang, *et al.*[13]	2015	RCT	112 samples from individuals aged over 50	There were 3 intervention regimens: (1) 10 mg of lutein; (2) 20 mg of lutein; (3) 10 mg of lutein and 10 mg of zeaxanthin for 2 years.	Placebo for 2 years.	- Placebo group: 0.34±0.19 - 10 mg lutein group: 0.31±0.21 - 20 mg lutein group: 0.31±0.21	– Lutein/zeaxanthin supplements can increase their concentrations in serum and the macula and improve visual acuity in patients with AMD – Doses of 10 mg and 20 mg of lutein were equally effective after a 2-year intervention period.

Author	Year	Study Design	Sample Size	Intervention Regimen	Control Regimen	Baseline Visual Acuity	Research Outcomes
AREDS2 Research Group, *et al.*[15]	2014	RCT	4,203 participants aged 50–85	A combination of 10 mg of lutein and 2 mg of zeaxanthin.	There were 3 control regimens: (1) 350 mg of DHA and 650 mg of EPA; (2) 10 mg of lutein and 2 mg of zeaxanthin, plus 350 mg of DHA and 650 mg of EPA; (3) placebo.	N/A	– There was no significant difference in visual acuity between patients receiving the intervention regimen (L/Z) and the control regimen (without L/Z), whether in patients who experienced a decline in visual acuity of ≥ 10, ≥ 15, or ≥ 30 letters from baseline. – No significant therapeutic effect was observed on the progression of central GA in patients receiving the intervention regimen (L/Z).

Abbreviations: AMD: age-related macular degeneration; AREDS: age-related eye disease study; ARMS: age-related maculopathy susceptibility 2; CHF: complement factor H; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; RCT: randomized-controlled trial; N/A: Not available; L/Z: Lutein/zeaxanthin.

DISCUSSION

Supplementation of Lutein/Zeaxanthin in AREDS2

The Age-Related Eye Disease Study (AREDS) was a long-term, multicenter, prospective study involving 4,757 participants aged 55 to 80 years, designed by the National Eye Institute (NEI) to evaluate the effects of zinc and specific antioxidant vitamins on the progression of advanced AMD in an elderly population.[21] The AREDS formulation was developed based on recommendations from nutritionists, ophthalmologists, and biochemists who reviewed basic science evidence, clinical trial data, and epidemiological findings. In 2001, the AREDS formulation was published and established as the standard of care for AMD patients. It comprised β-carotene (15 mg [25,000 IU]/day) as a carotenoid with systemic antioxidant properties, vitamin C (500 mg/day), vitamin E (400 IU/day), zinc oxide (80 mg/day), and cupric oxide (2 mg/day).[22] High-dose β-carotene supplementation has been reported to increase the risk of lung cancer in smokers. Further analysis from one clinical study demonstrated that male smokers carried a higher risk regardless of the tar or nicotine content of cigarettes.[23] Consequently, β-carotene was replaced with more appropriate carotenoids for the AREDS2 formulation, namely lutein and zeaxanthin.[23,24] Lutein and zeaxanthin are dipolar carotenoids with terminal dihydroxylation found in various dietary sources, including spinach, broccoli, peas, parsley, corn, and egg yolk.[25,26] Beyond their presence in animal and plant-based foods, lutein and zeaxanthin also constitute the primary carotenoids of the macular pigment in the retina, collectively referred to as macular xanthophylls. The concentrations of lutein and zeaxanthin differ between the central and peripheral retina. Zeaxanthin is present at approximately twice the concentration in the fovea, whereas lutein predominates in the parafoveal region. Both lutein and zeaxanthin are also found in the ocular lens.[27,28]

The AREDS2 formulation consists of lutein (10 mg/day), zeaxanthin (2 mg/day), vitamin C (500 mg/day), vitamin E (400 IU/day), zinc oxide (25 mg/day), and cupric oxide (2 mg/day).[28] Compared to the original AREDS formulation, the key modifications include the substitution of β-carotene with lutein and zeaxanthin, as well as a reduction in the daily zinc dose. The daily zinc dose in the original AREDS formulation was 80 mg; however, the tolerable upper intake level of zinc is 40 mg/day. Several studies have reported that high-dose zinc supplementation is associated with genitourinary complications and anemia.[22,29]

The AREDS2 study reported that participants receiving lutein/zeaxanthin supplementation demonstrated a significant reduction in the rate of progression to advanced AMD ($p<0.05$) compared to those who did not receive lutein/zeaxanthin supplementation. Patients receiving the AREDS2 supplement also experienced stabilization and improvement in best-corrected visual acuity (BCVA), with no reported adverse effects. As a result, the AREDS2 formulation is currently regarded as the standard of care for reducing the progression of AMD.[28]

ROLE OF LUTEIN/ZEAXANTHIN IN AGE-RELATED MACULAR DEGENERATION

Effectiveness of Lutein/Zeaxanthin in Geographic Atrophy Progression

AMD is a neurodegenerative disease characterized by the accumulation of deposits beneath the retina, leading to degeneration of the macula, retinal pigment epithelium (RPE) layer, and choroid, as well as the abnormal growth of retinal blood vessels.[1] The disease is clinically manifested by reduced central vision, visual distortion, and the potential development of a central scotoma.[2] AMD is classified into two subtypes based on its manifestation and progression: dry (non-exudative) AMD and wet (exudative) AMD. Approximately 90% of all AMD cases are of the dry subtype, characterized by the presence of drusen in the early stages and geographic atrophy (GA) in the advanced stage.[3]

Geographic atrophy (GA) represents the end stage of dry AMD, defined as a rounded or oval area of atrophy measuring 175 µm or greater in diameter.[11] GA affects the outer retinal layers, resulting in the progressive loss

of RPE cells, photoreceptor cells, and reduced vascular density in the choriocapillaris.[7-10]

The pathophysiology of GA is complex and is thought to involve chronic inflammation driven by excessive activation of the complement system, leading to the loss of photoreceptors, RPE, and the underlying choroidal capillaries. The loss of these structures manifest as sharply demarcated atrophic lesions, which are the hallmark of GA. With advancing age, the accumulation of oxidative damage promotes the formation of drusen (extracellular deposits) and lipofuscin (intracellular deposits).[30]

Drusen are composed of several key components, including cellular debris, lipids, lipoproteins, and amyloid deposits. Oxidative byproducts of lipofuscin, such as A2E and malondialdehyde (MDA) can generate reactive oxygen species (ROS) upon light exposure, trigger immune responses, and induce deoxyribonucleic acid (DNA) damage and apoptosis in RPE cells.[31] The accumulation and oxidative effects of lipofuscin, together with drusen deposits, they contribute to the activation of inflammatory pathways, including the complement system, which when dysregulated by genetic mutations or polymorphisms such as the complement factor H (CFH), C3, or complement factor I (CFI), can lead to progressive retinal cell death, the defining feature of GA.[31]

Lutein and zeaxanthin can prevent the formation of ROS in retinal cell membranes, thereby reducing oxidative damage.[32] One in vivo study demonstrated that lutein and zeaxanthin supplementation enhanced antioxidant capacity and preserved the expression of key retinal proteins, including rhodopsin (Rho), rod arrestin (Sag), G protein subunit alpha transducin 1 (Gnat1), neural cell adhesion molecule (NCAM), growth-associated protein 43 (GAP43), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), insulin-like growth factor 1 (IGF1), nuclear factor erythroid 2–related factor 2 (Nrf2), and heme oxygenase-1 (HO-1).[33] These protective mechanisms may attenuate chronic inflammation in the retina cells, thereby inhibiting the progression of GA. The effectiveness of lutein and zeaxanthin on GA progression in AMD has been evaluated in several clinical trials.[15,19,20] The RCT by Keenan, *et al*., (2025) demonstrated that GA progression toward the central macula was significantly slower (p = 0.017) in the intervention group (receiving lutein and zeaxanthin supplementation) compared to the control group (without lutein and zeaxanthin supplementation), with rates of expansion of 84.5 µm/year (95% CI: 72.4–96.6 µm/year) and 105.3 µm/year (95% CI: 93.2–117.3 µm/year), respectively.[19] In the study by Keenan, *et al*., (2018), the rate of geographic atrophy area expansion in patients with central and non-central GA receiving lutein and zeaxanthin therapy was not significantly different (p = 0.33) compared to the control group (without lutein and zeaxanthin).[20] In another RCT evaluating the effectiveness of lutein and zeaxanthin on central GA progression, no significant therapeutic effect was observed in patients receiving the intervention regimen (L/Z).[15]

From a theoretical standpoint, both carotenoids are selectively distributed within the retina, with the highest concentrations found in the central macula, particularly the foveal region. This distribution is considered consistent with the finding that lutein and zeaxanthin supplementation is more effective in slowing the progression of non-central GA, which are lesions located in the peripheral macular area.[19]

The findings from Keenan, *et al*., (2025) also suggest that the combination of lutein/zeaxanthin with vitamins C and E in the AREDS2 formulation may potentiate the phenomenon of foveal sparing, a condition in which the foveal area tends to remain intact despite surrounding retinal degeneration. This finding is of particular clinical significance, as the fovea is the center of high-acuity vision.[19] Several studies have reported that although soft drusen frequently appear in the central macula, GA progression is approximately four times slower in the fovea compared to other retinal regions.[20,34-36] This suggests the existence of a natural protective mechanism, which may be further augmented by carotenoid supplementation.

Effectiveness of Lutein/Zeaxanthin in Visual Acuity

Visual acuity in AMD patients is closely related to GA progression. The rate of GA progression varies according to the size and location of the atrophy and foveal involvement.[7-10] When GA extends to the fovea, severe central visual acuity loss may occur.[11] Lutein and zeaxanthin are potent antioxidants that play a critical role in protecting and maintaining the structural integrity of the retina, including photoreceptors and RPE cells, which are directly associated with visual acuity. The mechanism by which lutein and zeaxanthin improve visual acuity extends beyond their protective effects against oxidative damage, but also involves the enhancement of macular pigment optical density (MPOD). An increase in MPOD values can improve overall visual function, including visual acuity, contrast sensitivity, and visual performance under extreme lighting conditions, such as glare reduction.[37]

The effectiveness of lutein and zeaxanthin supplementation on visual acuity has been evaluated in several clinical trials.[13,19] The RCT by Keenan, *et al*., (2025) reported that BCVA values were not significantly different (p = 0.058) between the intervention group (receiving lutein and zeaxanthin supplementation) and the control group (without lutein and zeaxanthin supplementation), however, the rate of visual acuity decline was slower in the intervention group.[19] The study by Huang, *et al*., (2015), which further evaluated the differential effectiveness of lutein supplementation at varying doses on MPOD values, reported that lutein at doses of 10 mg and 20 mg showed equivalent efficacy after a 2-year intervention period.[13] MPOD values were reported to increase significantly during the intervention period (p < 0.001). Based on these findings, a lutein dose of 10 mg is recommended as the preferred regimen for long-term AMD therapy.[13]

CONCLUSION

Based on the findings of this systematic review, oral supplementation with lutein (10 mg/day) and zeaxanthin (2 mg/day), as incorporated in the AREDS2 formulation, appears to slow the progression of non-central GA and preserve foveal integrity (foveal sparing) by protecting RPE cells from photo-oxidative damage and modulating retinal inflammation process. In doing so,

lutein and zeaxanthin may also help stabilize and improve visual acuity in AMD patients by maintaining retinal structural integrity and increasing MPOD values. While these findings suggest a meaningful therapeutic benefit, future studies should explore the role of lifestyle factors alongside AREDS2 therapy, as a combined approach that may further improve outcomes in AMD management.

REFERENCES

1. Seddon JM, Sobrin L, Davoudi S. Epidemiology and risk factors for age-related macular degeneration. Ryan's retina. 3rd ed. Elsevier; 2023.
2. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet. 2018;392(10153):1147–59. doi: 10.1016/S0140-6736(18)31550-2.
3. Sethi S. A review of age-related macular degeneration and current concepts in management. TNOA J Ophthalmic Sci Res. 2024;62(4):387–96. doi: 10.4103/tjosr.tjosr_74_23.
4. Vision Loss Expert Group of the Global Burden of Disease Study; GBD 2019 Blindness and Vision Impairment Collaborators. Global estimates on the number of people blind or visually impaired by age-related macular degeneration: a meta-analysis from 2000 to 2020. Eye (Lond). 2024;38(11):2070–82. doi: 10.1038/s41433-024-03050-z.
5. Apte RS. Age-related macular degeneration. N Engl J Med. 2021;385(6):539–47. doi: 10.1056/NEJMcp2102061.
6. Kementerian Kesehatan Republik Indonesia. Infodatin: pusat data dan informasi Kementerian Kesehatan RI - situasi gangguan penglihatan. Jakarta: Kementerian Kesehatan Republik Indonesia; 2018.
7. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. Geographic atrophy: mechanism of disease, pathophysiology, and role of the complement system. J Manag Care Spec Pharm. 2023;29(5-a Suppl):S2–S11. doi: 10.18553/jmcp.2023.29.5-a.s2.
8. Bagheri S, Lains I, Silverman RF, Kim I, Eliott D, Silva R, et al. Percentage of foveal vs total macular geographic atrophy as a predictor of visual acuity in age-related macular degeneration. J Vitreoretin Dis. 2019;3(5):278–82. doi: 10.1177/2474126419859454.
9. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. Retina. 2017;37(5):819–35. doi: 10.1097/IAE.0000000000001392.
10. Fleckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C, et al. The progression of geographic atrophy secondary to age-related macular degeneration. Ophthalmology. 2018;125(3):369–90. doi: 10.1016/j.ophtha.2017.08.038.
11. Sacconi R, Corbelli E, Querques L, Bandello F, Querques G. A review of current and future management of geographic atrophy. Ophthalmol Ther. 2017;6(1):69–77. doi: 10.1007/s40123-017-0086-6.
12. Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, et al. Lutein, zeaxanthin, and mesozeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. Prog Retin Eye Res. 2016;50:34–66. doi: 10.1016/j.preteyeres.2015.10.003.
13. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. Biomed Res Int. 2015;2015:564738. doi: 10.1155/2015/564738.
14. Bone RA, Davey PG, Roman BO, Evans DW. Efficacy of commercially available nutritional supplements: analysis of serum uptake, macular pigment optical density and visual functional response. Nutrients 2020;12(5):1321. doi: 10.3390/nu12051321.
15. Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report no. 3. JAMA Ophthalmol. 2014;132(2):142–49. doi: 10.1001/jamaophthalmol.2013.7376.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
17. National Institute for Health Research. PROSPERO: International Prospective Register of Systematic Reviews [Internet]. York (UK): University of York, Centre for Reviews and Dissemination; 2011. Available from: https://www.crd.york.ac.uk/prospero/.
18. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898.
19. Keenan TDL, Agron E, Keane PA, Domalpally A, Chew EY; Age-Related Eye Disease Study Research Group. Oral antioxidant and lutein/zeaxanthin supplements slow geographic atrophy progression to the fovea in age-related macular degeneration. Ophthalmology. 2025;132(1):14–29. doi: 10.1016/j.ophtha.2024.07.014.

20. Keenan TD, Agron E, Domalpally A, Clemons TE, van Asten F, Wong WT, et al. Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. Ophthalmology. 2018;125(12):191–28. doi: 10.1016/j.ophtha.2018.05.028.

21. Wright C, Mazzucco AE, Becker SM, Sieving PA, Tumminia SJ. NEI-supported age-related macular degeneration research: past, present, and future. Transl Vis Sci Technol. 2020;9(7):49. doi: 10.1167/tvst.9.7.49.

22. Gorusupudi A, Nelson K, Bernstein PS. The Age-Related Eye Disease 2 Study: micronutrients in the treatment of macular degeneration. Adv Nutr. 2017;8(1):40–53. doi: 10.3945/an.116.013177.

23. Middha P, Weinstein SJ, Mannisto S, Albanes D, Mondul AM. β-carotene supplementation and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: the role of tar and nicotine. Nicotine Tob Res. 2019;21(8):1045–50. doi: 10.1093/ntr/nty115.

24. Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA. Intakes of lutein, zeaxanthin, and other carotenoids and age-related macular degeneration during 2 decades of prospective follow-up. JAMA Ophthalmol. 2015;133(12):1415–24. doi: 10.1001/jamaophthalmol.2015.3590.

25. Cho YK, Park DH, Jeon IC. Medication trends for age-related macular degeneration. Int J Mol Sci. 2021;22(21):11837. doi: 10.3390/ijms222111837.

26. 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. doi: 10.3390/nu14040827.

27. Pasenkiewicz-Gierula M, Hryc J, Markiewicz M. Dynamic and energetic aspects of carotenoids in-and-around model lipid membranes revealed in molecular modelling. Int J Mol Sci. 2024;25(15):8217. doi: 10.3390/ijms25158217.

28. Maurizio BP, Maria RM, Andrea B, Alessandro A, Francesco R. Micronutrients and benefits of supplementation for reducing the risk of progression of age-related macular degeneration – an update. Eur Ophthalmic Rev. 2018;12(1):39–44. doi: 10.17925/EOR.2018.12.1.39.

29. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2017;7(7):CD000254. doi: 10.1002/14651858.CD000254.pub4.

30. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system. J Manag Care Spec Pharm. 2023;29(5-a Suppl):S2–S11. doi: 10.18553/jmcp.2023.29.5-a.s2.

31. Romero-Vazquez S, Llorens V, Soler-Boronat A, Figueras-Roca M, Adan A, Molins B. Interlink between inflammation and oxidative stress in age-related macular degeneration: Role of complement factor H. Biomedicines. 2021;9(7):763. doi: 10.3390/biomedicines9070763.

32. Narimatsu T, Negishi K, Miyake S, Hirasawa M, Osada H, Kurihara T, et al. Blue light-induced inflammatory marker expression in the retinal pigment epithelium-choroid of mice and the protective effect of a yellow intraocular lens material in vivo. Exp Eye Res. 2015;132:48–51. doi: 10.1016/j.exer.2015.01.003.

33. Sahin K, Gencoglu H, Akdemir F, Orhan C, Tuzcu M, Sahin N, et al. Lutein and zeaxanthin isomers may attenuate photo-oxidative retinal damage via modulation of G protein-coupled receptors and growth factors in rats. Biochem Biophys Res Commun. 2019;516(1):163–70. doi: 10.1016/j.bbrc.2019.06.032.

34. Saßmannshausen M, Behning C, Weinz J, Goerdt L, Terheyden JH, Chang P, et al. Characteristics and spatial distribution of structural features in age-related macular degeneration: a MACUSTAR study report. Ophthalmol Retina. 2023;7(5):420–30. doi: 10.1016/j.oret.2022.12.007.

35. Pollreisz A, Reiter GS, Bogunovic H, Baumann L, Jakob A, Schlanitz FG, et al. Topographic distribution and progression of soft drusen volume in age-related macular degeneration implicate neurobiology of fovea. Invest Ophthalmol Vis Sci. 2021;62(2):26. doi: 10.1167/iovs.62.2.26.

36. Hwang CK, Agron E, Domalpally A, Cukras CA, Wong WT, Chew EY, et al. Progression of geographic atrophy with subsequent exudative neovascular disease in age-related macular degeneration: AREDS2 report 24. Ophthalmol Retina. 2021;5(2):108–117. doi: 10.1016/j.oret.2020.10.008.

37. Wilson LM, Tharmarajah S, Jia Y, Semba RD, Schaumberg DA, Robinson KA. The effect of lutein/zeaxanthin intake on human macular pigment optical density: A systematic review and meta-analysis. Adv Nutr. 2021;12(6):2244–54. doi: 10.1093/advances/nmab071.