

Supplemental nutrition for retinal health: Evidence based analysis of commercial preparations in India

Ashish Sharma¹, Nilesh Kumar^{1,2}, Nikulaa Parachuri^{1,3}, Baruch D Kuppermann⁴, Francesco Bandello⁵

Purpose: Antioxidants have been lately postulated as supportive and prophylactic supplements for various retinal disorders, especially age-related macular degeneration (AMD). Forty-eight brands of such supplements containing lutein and zeaxanthin are available in India. The aim of the study was to assess the market leaders in supplements for ophthalmology in view of AREDS recommendations. **Methods:** Descriptive review of top-selling supplements for eye health were compared to the contents of the AREDS-recommended levels. **Results:** None of the top 10 selling brands had exact or near similar composition as recommended in the AREDS-2 study, which is the most widely accepted level-1 evidence in AMD prevention. **Conclusion:** Physicians prescribing these antioxidants, especially for the prevention of advanced AMD, should be vigilant and aware of the contents of the prescribed brands.

Key words: AMD, AREDS-2, nutritional supplement

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The role of supplements in maintaining overall health and homeostasis has caught the attention of the general populace, given the rise in sales of such supplements.^[1] This meteoric rise in sales may be attributed to the less stringent advertisement restrictions, availability of such supplements without prescriptions, and promotion materials blaming current lifestyles to lack vital nutrients that must be supplemented for good health.^[2] The rampant use of supplements in the era of COVID-19 and the launch of many immunity boosters also plays to the gullibility of the general population and is an indication of the future growth potential of such a market.^[1]

Parallel to the rise of the pharmacological industry of supplements, many preparations that maintain retinal health and homeostasis have also been marketed. A database search of the monthly index of medical specialties (MIMS) shows 48 brands of supplements containing lutein and zeaxanthin aimed for the eye.^[3] The market cap for ocular antioxidants stood at 131.6 crore INR (approx. 18 million USD) in April 2021.^[4] The idiopathic nature of many retinal diseases, as well as the involvement of micronutrients in the pathogenesis of retinal pathologies such as age-related macular degeneration (AMD), diabetic retinopathy (DR), and other neovascular diseases, make

the retina a lucrative target for such supplements. However, the role of such supplements has been systematically evaluated only for AMD in two landmark trials, age-related eye disease studies (AREDS) and AREDS-2.^[5,6] The use of supplements in other retinal pathologies is either highly derisive or based on anecdotal evidence. This index manuscript aims to assess the formulations of commonly prescribed vitamin supplements in India for macular disorders in light of evidence from AREDS recommendations.

Methods

The descriptive review of the 10 top-selling supplements aimed for eye health was conducted from June 2021 to July 2021. The sales data to form the basis of top-selling brands was acquired from the Intercontinental Medical Statistics (IMS) Health Trend provided by IQVIA Inc., USA, updated and verified for April 2021. The formulation was compared with the recommendations from AREDS-2 (500 mg of vitamin C, 400 IU of vitamin E, 10 mg of lutein, 2 mg of zeaxanthin, 80 mg of zinc, and 2 mg of copper) in terms of the presence and absence of the components as well as their quantities expressed in terms of percentage of the recommended dosage. The AREDS-2 trial was chosen for comparison based on the fact of it is the most widely accepted data on supplements for eye health. It was difficult to get a product monograph from all the

¹Department of Vitreoretina, Lotus Eye Hospital and Institute, Avinashi Road, Coimbatore, Tamil Nadu, India, ²Vitreoretina Division, Madhavi Netralaya, Ara, Bihar, India, ³Department of Vitreoretina, Sankara Eye Hospital, Coimbatore, Tamil Nadu, India, ⁴Gavin Herbert Eye Institute, University of California, Irvine, Irvine, CA, USA, ⁵Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy

Correspondence to: Dr. Ashish Sharma, Lotus Eye Hospital and Institute, Avinashi Road, Civil Aerodrome Post, Peelamedu, Coimbatore, Tamil Nadu - 641 014, India. E-mail: drashish79@hotmail.com

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Table 1: Top 10 selling brands of supplements for eye health, compared to the AREDS-2 recommended levels and indications as per manufacturers' websites and online materials

Brand Name (Company)	Comparison with the AREDS-2 Formulation	Compared with AREDS-2 Doses	Additional components	Indications as per Manufacturer
New I-Site (Sun Pharma)	Absence of Zeaxanthin and Copper	8% of Vitamin C, 2.5% of Vitamin E, 300% of Lutein, 12.5% of Zinc	Beta-carotene, Manganese, Selenium	AMD, Retinitis Pigmentosa
Gloeye (Sun Pharma)	Absence of all the components	0%	Bilberry extract, Pine bark extract	Cataract, AMD, DR
Lutivit (Micro Labs)	Absence of Vitamin C and E and Zeaxanthin	70% of Lutein, 9.3% of Zinc, 50% of copper	Beta-carotene, L-arginine, Lycopene, Methylcobalamine, Manganese, Selenium	Cataract, AMD
Macugold Plus (Ajanta Pharma)	Absence of Vitamin C and E, Zinc, and Copper	100% of Lutein and 30% of Zeaxanthin	Acetylcysteine, Melatonin, and Astaxanthin	AMD and Other macular degeneration
Novoret (Allergan)	Absence of Vitamin C and E	50% of Lutein, 50% of Zeaxanthin, 15% of Zinc, 100% of copper	Astaxanthin, Tocotrienols, Resveratrol	AMD
I-Site Plus (Sun Pharma)	Absence of Vitamin C, E, Zeaxanthin, Zinc, and Copper	32% of Lutein	Astaxanthin, Glutathione	AMD, Cataract, Retinitis Pigmentosa and post-LASIK recovery
Macucheck (Indoco)	Absence of Vitamin C and E	32% of Lutein, 12.8% of Zeaxanthin, 50% of Zinc, and 100% of Copper	Beta-carotene, Manganese, Selenium, Glutathione	AMD
Vitakind-I (Mankind)	Absence of Vitamin C and E	40% of Lutein, 40% of Zeaxanthin, 50% of Zinc, and 100% of copper	Lycopene, Selenium, Methylcobalamine	AMD and Diabetic Retinopathy and Post Cataract
Ocugold Plus (Ajanta Pharma)	Absence of Vitamin C, E, Zinc, and Copper	32% of Lutein and 500% of Zeaxanthin	Lycopene, Astaxanthin, Cholecalciferol	AMD and Diabetic Retinopathy
Retinox (Ajanta Pharma)	Absence of Vitamin C, E, Zinc, and Copper	100% of Lutein and 100% of Zeaxanthin	Astaxanthin, Omega-3 fatty acids	AMD and Diabetic Retinopathy

manufacturers. However, we conducted an online search and reviewed the promotional materials from sales representatives of the companies to compile the indications and claims.

Results

Ten brands of supplements from six pharmaceutical manufacturers were captured from the website of IMS Health Trend of IQVIA Inc on August 2, 2021.^[4] Nine of those 10 brands were having some components similar to AREDS-2, while one brand did not contain any such component. Surprisingly, none of the 10 top-selling ocular supplements were having the exact or near-exact combination to AREDS-2. Vitamins C and E were absent from nine of the 10 brands, and four brands lacked zinc. Three brands were devoid of zeaxanthin, while five brands lacked copper. Lutein was added to all the supplements except for one which did not contain any of the AREDS recommended components. All brands were found to have 2–6 additional components per formulation. The constituents and individual claims or indications for each brand have been tabulated in Table 1.

Discussion

The supplement market has exponentially risen in the last few decades as preventive health measures are gaining attention from the general population.^[1] The supplement market in India is not regulated by the drug controller general of India (DCGI) but by the food safety and standards

association of India (FSSAI).^[7,8] The FSSAI guidelines allow for the marketing of any combination of micronutrients as supplements as long as the formulation does not cross the recommended daily allowance (RDA) for the Indian population as specified by the Indian council of medical research (ICMR).^[9] In the case of the absence of ICMR-specified RDA, Codex Alimentarius-provided RDA should be considered as the maximum limit.^[7] Interestingly, neither lutein nor zeaxanthin's RDA has been specified by both the authorities. RDA specified by ICMR for vitamin C is 80 mg/day compared to the AREDS-2-recommended intake of 500 mg/day. Similarly, the RDA of vitamin E is 10 mg/day (15 IU/day of natural or 22 IU/day of synthetic alpha-tocopherol) compared to 400 IU, 1.7 mg RDA of copper compared to 2 mg, and 17 mg RDA of zinc compared to 80 mg recommended by AREDS-2.^[6,10] The amount of these components [Table 1] in each of the top-selling 10 brands do not breach the RDA levels; only the levels of copper is more or less similar to the AREDS-2 recommended levels, and no other component has crossed even 20% of the recommended levels. The less rigorous regulation on supplements is not inherent to India. US-FDA approval is not required for the marketing of similar formulations in the USA as they are not evaluated for safety and efficacy under the Dietary Supplement Health and Education Act of 1994.^[11]

It makes economic sense for the manufacturers to keep their formulations in this less regulated "supplement" category, which requires only one intervention trial to claim

that the supplement has “shown” benefits for promoting or maintaining health, and only two studies to claim the “proven” benefit.^[2,12] If their formulation breaches the RDA levels, the drug needs to go through all phases of development, which is longer, more expensive, more stringent, and poses a high probability of losing on market realization. Supplements also have less stringent advertisement restrictions compared to any scheduled drug and have more probability to be available as over-the-counter (OTC) medications.^[2]

However, the below-mentioned RDA levels of micronutrients in health supplements have a bright side. The dosage of individual components in the AREDS-2 recommendation is much higher than the RDA and thus has been reported to have various risks and adverse events. Beta-carotene risks the development of lung cancer in smokers,^[13] and is absent in seven out of the top 10 selling brands in India. Beta-carotene was replaced by lutein and zeaxanthin in AREDS-2 recommendations.^[6] A combination of lutein with beta-carotene can result in intestinal malabsorption,^[14] and all three formulations that contained beta-carotene also had lutein ranging from 32% to 300% of AREDS-2-recommended levels. High levels of vitamin E, in tune with the AREDS-2 recommendation, risks the development of prostate cancer in individuals with high selenium levels.^[15] Patients on anticoagulants should also avoid high levels of vitamin E intake.^[16] High levels of zinc intake had a self-reported increased incidence of anemia, though the hematocrit levels remained similar in the AREDS randomized control trials.^[6,17] Zinc, in high volumes, is known to cause anemia but competes with copper for absorption which is present in the AREDS and AREDS-2 recommendations. While the present formulations are not required to undergo strict safety evaluation, it is highly unlikely that these will lead to the adverse events associated with AREDS and AREDS-2 formulations because of the components staying much below the safe RDA levels.

The question to ponder from this analysis is that will this safe formulation help in maintaining the ocular or retinal health when the supplements are not reaching the recommended levels of the only two randomized control trials that have evaluated the efficacy of such nutrients in preventing the development and progression of AMD.

The study is limited by its descriptive nature, where sufficient data to analyze and conclude the efficacy and safety of each formulation is not available. It also considers the fact that the supplements are claimed to benefit in promoting the overall retinal health and for individual indications such as diabetic retinopathy and retinitis pigmentosa among other pathologies., whereas the comparison was done with the AREDS-2 recommendations specific for AMD. The major drawback is the lack of the presence of dedicated web pages on any of the manufacturers’ websites to access referenced materials for verification and reinforcement of the provided indications and claims.

Conclusion

Physicians prescribing these antioxidants, especially for the prevention of advanced AMD, should be vigilant and aware of the content provided by science rather than the marketing-driven content as these formulations seem to

be irrationally popular and fall in the top-selling brands in India.

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Conflicts of interest

Dr Ashish Sharma: CONSULTANT: for Novartis, Allergan, Bayer and Intas.

Baruch D Kuppermann: CLINICAL RESEARCH: Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics; CONSULTANT: Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, Theravance Biopharma.

Dr Francesco Bandello: CONSULTANT: Allergan, Bayer, Boehringer- Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss.

Dr Nilesh Kumar: CONSULTANT: Novartis.

Dr Nikulaa Parachuri: None.

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