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THE EFFICACY OF CAROTENOID SUPPLEMENTS IN REDUCING THE RISK OF OCULAR DISEASES: BIOCHEMICAL CORRELATIONS AND IMPACT ON HEALTH POLICIES

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CONTEXT CONTEXT: *Degenerative ocular diseases, such as age-related macular degeneration and senile cataract, affect millions of individuals worldwide. In the absence of effective curative pharmacological interventions at early stages, preventive approaches acquire strategic relevance in medical practice. Within this context, ocular-tropic carotenoids – lutein, zeaxanthin, and meso-zeaxanthin – have been identified as key biomolecules in retinal protection, acting through synergistic antioxidant, anti-inflammatory, and blue light filtering mechanisms.*

METHODS: *A systematic and critical review of the specialised literature was performed, exploring publications from the past 10 years indexed in major databases: PubMed, ScienceDirect, MDPI, and NCBI. Included were randomised clinical trials, meta-analyses, and fundamental biochemical investigations evaluating the effects of carotenoid supplementation on macular pigment optical density (MPOD). Concurrently, data from international public health guidelines were integrated to enable a transdisciplinary approach.*

RESULTS: *Nutritional supplementation with lutein and zeaxanthin was associated with significant increases in MPOD and improvements in visual function parameters. Findings from the AREDS and AREDS2 studies demonstrated a reduction in the risk of progression from intermediate to advanced stages by approximately 25%. At the molecular level, carotenoids reduce oxidative stress, modulate inflammatory pathways (including inhibition of NF-κB and IL-6), and contribute to retinal function stability. From a public health perspective, these interventions exhibit a favourable cost-effectiveness profile and can be incorporated into primary and secondary prevention strategies, particularly in the geriatric population with increased nutritional vulnerability.*

CONCLUSION: *In an epidemiological context marked by a rising incidence of degenerative ocular diseases, carotenoids emerge as agents with scientifically documented potential and demonstrated efficacy both clinically and biochemically. Their integration into public health strategies may contribute to reducing the visual and economic burden associated with chronic ocular diseases against the backdrop of demographic ageing.*

Keywords: carotenoids, macular degeneration, oxidative stress

INTRODUCTION

Carotenoids, a group of natural lipophilic pigments, are compounds exhibiting antioxidant, anti-inflammatory, antiproliferative, and antiangiogenic properties, thereby protecting against cellular damage and chronaic diseases associated with oxidative stress. They are present in fruits and vegetables such as carrots, tomatoes, corn, bell pepper, pineapple, as well as in leafy greens like lettuce, spinach, peas, and broccoli [1]. Remarkably, among over 1100 carotenoids found in nature, only lutein, zeaxanthin, and meso-zeaxanthin are specifically concentrated in the *macula lutea*, sharing a common molecular formula $C_{40}H_{56}O_2$, collectively referred to as the macular pigment [2, 3].

The retina is an extension of the brain and is one of the tissues with the highest oxygen consumption in the human body, making it highly sensitive to various stimuli. The retinal pigment epithelium is a tissue layer with intense metabolic activity, residing in a pro-oxidant stressful environment. The formation of free radicals in the retina is favoured by its structural characteristics, including high oxygen levels and dense blood supply, elevated concentrations of polyunsaturated fatty acids, and exposure to visible and ultraviolet (UV) light radiation [4, 5].

The accumulation of damage and oxidative stress in the macular area can lead to degeneration of retinal tissues and the manifestation of specific signs of age-related macular degeneration (AMD), such as decreased central visual acuity and image distortion [6].

In 2020, AMD accounted for 1.85 million cases of blindness and an additional 6.23 million cases of moderate to severe visual impairment globally, reflecting a total burden of over 8 million individuals with significant visual impairment [7].

Thus, at a time when the use of electronic devices and exposure to blue light are increasing – exacerbated during and after the COVID-19 pandemic – as well as within the context of population ageing both nationally and globally, understanding the role of carotenoids becomes essential. These compounds have risen to the status of biochemical defenders of our vision. As they cannot be synthesised by the human body, their intake through diet or dietary supplements represents an indispensable means of supporting ocular health.

The aim of this study is to critically and thoroughly examine the efficacy of carotenoid-based dietary supplements – particularly lutein, zeaxanthin, and beta-carotene – in reducing the risk and slowing the progression of degenerative ocular diseases, correlating clinical and epidemiological evidence with the biochemical mechanisms involved in retinal protection. Furthermore, the analysis seeks to evaluate how this data can underpin strategic recommendations in public health policies, with an emphasis on ophthalmic prevention in vulnerable populations.

METHODS

A systematic and critical review of the specialised literature was conducted. Within this review, the most recent findings and relevant studies in the field were examined and integrated, offering a comprehensive perspective on the potential of carotenoids in ocular protection.

A total of 18 scientific articles published within the past 10 years were critically assessed, using the following internationally recognised databases: PubMed, ScienceDirect, MDPI, and NCBI. This ensured a solid foundation for the analysis and interpretation of the results.

The following keywords were used to identify relevant articles: carotenoids, macular degeneration, oxidative stress.

The review included articles presenting clinical studies, meta-analyses, and systematic reviews that directly addressed the biochemical aspects and the role of carotenoids in reducing the risk and slowing the progression of degenerative ocular conditions.

RESULTS

Following the integrative analysis of the specialised literature and data obtained from clinical studies, a compelling profile of the efficacy of carotenoids – particularly lutein, zeaxanthin, and meso-zeaxanthin – in protecting retinal tissue and reducing the risk of progression of degenerative ocular conditions has been outlined.

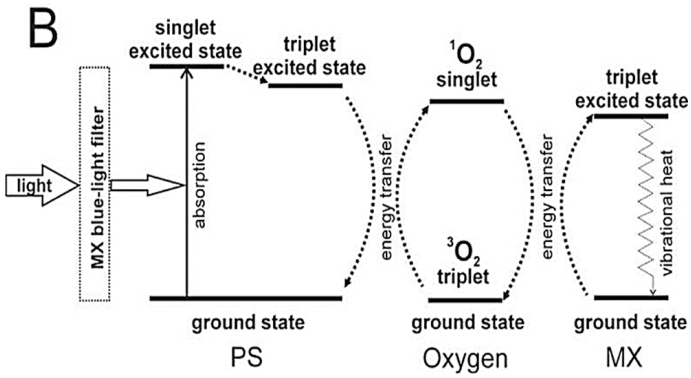
The functions of macular carotenoids are determined by their physical and chemical properties, functional groups, and molecular configuration. Their antioxidant properties are essential for preserving the structural integrity of the retina, especially given its heightened vulnerability due to constant light exposure, the high concentration of chromophores in photoreceptor cells, the significant content of docosahexaenoic acid (DHA) in polyunsaturated lipids, and the intense activity of mitochondria. These factors contribute to the retina's increased susceptibility to oxidative stress. Therefore, preventing oxidative damage is crucial for maintaining long-term visual function [8].

The physical antioxidant actions of carotenoids include blue light filtering, physical quenching of excited triplet states of photosensitisers, and singlet oxygen ($^1O_2$). Their chemical actions include reactions with singlet oxygen, interception of reactive oxygen species, and lipid chain-breaking activity [9].

The human eye possesses complex mechanisms to distribute and absorb radiation among its various structures. For instance, UV radiation with wavelengths shorter than 295 nm is filtered by the cornea, preventing the most energetic wavelengths (UV-C and part of UV-B) from reaching the lens. In adults, the lens absorbs UV-B and all UV-A (295–400 nm), allowing only visible light (>400 nm) to reach the retina. Consequently, depending on the concentration of macular pigment, it functions as a filter that absorbs 40–90% of incident short-wavelength blue light, acting as a protective shield for the retina [2, 10].

The retina contains numerous triplet photosensitisers which, when activated, have the potential to cause damage to visual cells. The triplet excited state of these photosensitisers has a relatively long lifetime, significantly increasing the likelihood of collisions with other molecules, including molecular oxygen. During these collisions, energy is transferred to molecular oxygen, generating singlet oxygen – a highly reactive and toxic species. This type II photosensitisation process is illustrated in figure 1B. It involves energy transfer from the excited state of oxygen to a xanthophyll molecule, which returns the oxygen to its ground state, while the macular carotenoid molecule releases the excess energy as heat, thus maintaining its structural integrity for reuse. Therefore, physical quenching is significantly more effective than chemical quenching [9].(Figure 1)

Figure 1. Antioxidant action of macular carotenoids: blue light filtration and physical quenching of singlet oxygen – (B)



Note: MX – macular carotenoids, PS – photosensitisers. Source: Widomska J, Subczynski WK. Mechanisms enhancing the protective functions of macular xanthophylls in the retina during oxidative stress. Exp Eye Res. 2019 Jan;178:238-246.

Research suggests that a combination of lutein, zeaxanthin, and meso-zeaxanthin in equal proportions may be more effective at neutralising singlet oxygen than each carotenoid individually. This is explained by the formation of specific aggregates between the three carotenoids, which enhance their quenching capacity. Furthermore, Ma L et al. demonstrated that supplements containing meso-zeaxanthin have a greater impact on increasing the MPOD compared to those without this carotenoid [11].

Another retinal protective mechanism involves lipid chain degradation. The interaction between carotenoid molecules and lipid-derived radicals can effectively prevent lipid peroxidation. Free radicals are scavenged through electron transfer (1 and 2), adduct formation (3), and hydrogen atom transfer (4) [1, 9].

$Car+R\bullet+ \rightarrow Car\bullet++R$ (1)
$Car+e- \rightarrow Car\bullet-$ (2)
$Car+ROO\bullet \rightarrow [Car-ROO]\bullet+ROO\bullet \rightarrow ROO-Car-ROO$ (3)
$Car[H]+R\bullet \rightarrow Car\bullet+RH$ (4) [1].

A better understanding of these roles can directly contribute to the development of effective prevention and treatment strategies for various ocular conditions, such as AMD and senile cataract, significantly impacting people's quality of life.

AMD is one of the leading causes of irreversible blindness among elderly adults in developed countries.

It affects approximately one in eight individuals over the age of 60. Recent epidemiological estimates indicate that globally around 200 million people are currently affected by AMD, with projections suggesting a significant increase in prevalence, reaching approximately 300 million cases by 2040. The risk of developing the condition increases with age and appears to be higher among men than women, although this varies by country [12, 13].

In a meta-analysis conducted by Liwen Feng et al., published in 2019, the researchers evaluated the effects of lutein supplementation on MPOD in randomised controlled trials including patients with AMD. Analysing nine studies involving a total of 920 participants (855 with AMD), they concluded that lutein supplementation at doses of 10 or 20 mg per day (for more than six months) was associated with significant improvements in MPOD, visual acuity, and contrast sensitivity. The results suggested that higher doses of lutein over longer treatment periods might accelerate and amplify the beneficial effects [14].

Given the significant impact of this disease on quality of life, researchers at the National Eye Institute (NEI), part of the US National Institutes of Health (NIH), initiated two large and rigorous studies: AREDS (Age-Related Eye Disease Study) and AREDS2. Their aim was to determine whether certain dietary supplements could slow the progression of AMD and potentially prevent or delay the onset of cataracts [15].

The AREDS study included 4,757 participants aged between 55 and 80 years, with cataracts, AMD, or both. AMD outcomes were based on 3,640 participants who had early or more advanced stages of the disease. Cataract outcomes were based on 4,629 participants with cataracts in one or both eyes [15].

The researchers followed the participants for approximately five years, analysing the effects of a specific formula outlined in table 1.

Table 1. Nutritional formulations tested in the AREDS and AREDS2 studies

Nutrienți	Formula AREDS*	Formula AREDS2
Vitamina C	500 mg	500 mg
Vitamina E	400 UI	400 UI
Beta-caroten	15 mg	-
Cupru (oxid de cupru)**	2 mg	2 mg
Luteină	-	10 mg
Zeaxantină	-	2 mg
Zinc	80 mg	80 mg

Note: *Not recommended for current or former smokers; **added to avoid zinc-related copper deficiency; mg = milligrams; IU = international units.* *Source:* National Eye Institute. About AREDS and AREDS2. 2024 Dec 3. https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/about-areds-and-areds2

The results were encouraging, at least regarding AMD. In patients with intermediate disease or advanced AMD in one eye, supplementation reduced the risk of progression to advanced stages by approximately 25% over five years. However, supplementation had no significant effect on cataracts. Despite its promise, the formula was not without risks. Notably, beta-carotene was associated with an increased risk of lung cancer among current and former smokers. Additionally, the high zinc dose raised concerns about digestive tolerance [15].

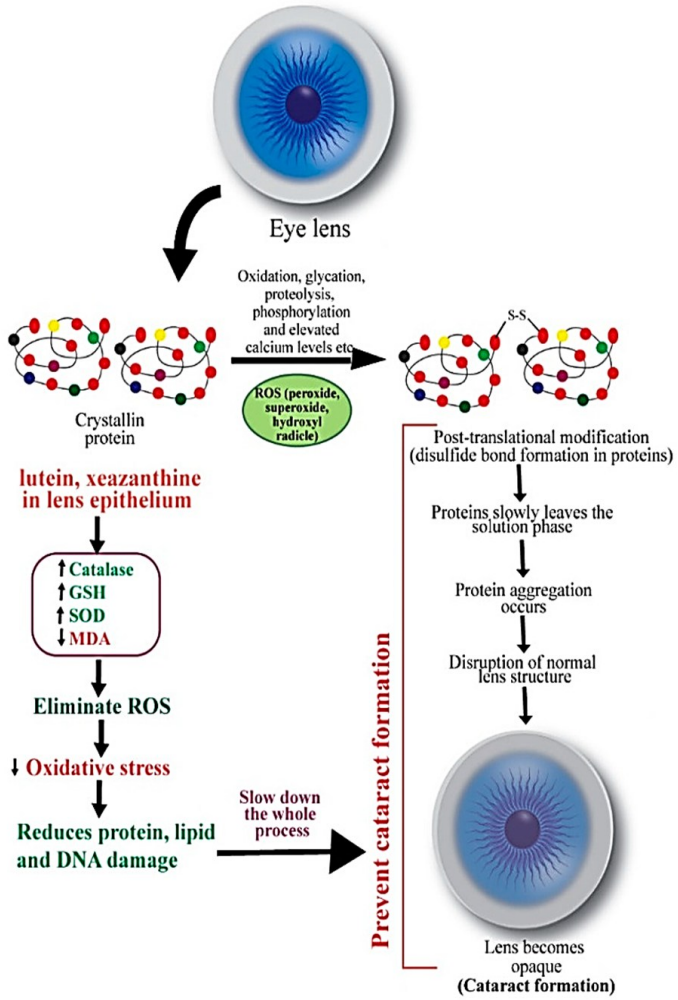
These limitations prompted a second study, AREDS2, which included 4,203 participants aged 50 to 85. AREDS2 enrolled only individuals with intermediate AMD in both eyes, or intermediate AMD in one eye and advanced AMD in the other. It excluded those without AMD or with early AMD, as AREDS data showed no benefit for these groups. The primary goal of this new study was to improve the original formula by removing beta-carotene and replacing it with two carotenoids – lutein and zeaxanthin – considered safer and more effective. Additionally, the effect of omega-3 fatty acids (EPA and DHA), hypothesised to benefit eye health, was tested. AREDS2 also evaluated whether maintaining a high zinc dose was necessary or if a lower dose would be sufficient. After five years of observation, conclusions were clear: replacing beta-carotene with lutein and zeaxanthin did not compromise treatment efficacy but improved safety, especially for smokers. The addition of omega-3 fatty acids had no significant impact on AMD progression. Furthermore, the lower zinc dose was as effective as the original, reducing adverse effects. Based on these results, the optimised formula currently recommended as AREDS2 contains: vitamin C (500 mg), vitamin E (400 IU), zinc (25 or 80 mg depending on tolerance), copper (2 mg), lutein (10 mg), and zeaxanthin (2 mg). The formula no longer includes beta-carotene, making it safe for smokers as well [15].

Cataracts, like AMD, are an increasing health concern causing vision loss due to oxidation of the lens structures. Laboratory studies have shown that lutein can prevent cataract formation in bovine lens cells by inhibiting lens cell proliferation and migration. Some observational studies found a significant association between high blood lutein levels and a lower risk of cataract development. In contrast, other studies report no correlation between lutein intake and cataracts. These discrepancies may be due to study limitations and different cataract types [16].

Figure 2 schematically illustrates lens opacification in cataracts and how xanthophylls may slow its onset and progression. Due to processes such as oxidation, glycation, proteolysis, phosphorylation, and increased calcium levels, reactive oxygen species – including peroxides, superoxides, and hydroxyl radicals – rise. These radicals induce post-translational modifications in lens proteins, characterised by disulfide bond formation, leading to protein aggregation, structural damage, and ultimately lens opacification. On the other hand, figure 2 also shows the protective role of lutein and zeaxanthin in the lens epithelium. They enhance the activity of antioxidant enzymes (catalase, glutathione, superoxide dismutase) and reduce lipid peroxidation, with malondialdehyde as a marker of oxidative stress.

Consequently, these processes reduce oxidative stress, preventing damage to proteins, lipids, and DNA, thereby delaying or preventing cataract onset and progression [17, 18].

Figure 2. Schematic diagram showing the mechanisms of action of macular carotenoids in cataract prevention



Note: GSH – glutathione; SOD – superoxide dismutase; MDA – malondialdehyde.
Source: Johra FT, Bepari AK, Bristy AT, Reza HM. A Mechanistic Review of β-Carotene, Lutein, and Zeaxanthin in Eye Health and Disease. Antioxidants (Basel). 2020 Oct 26;9(11):1046.

DISCUSSION

The relevance of this research topic lies in the identification and understanding of the functions of carotenoids, highlighted by their dual properties. The protective effects of lutein and zeaxanthin are supported by a multitude of well-documented biochemical mechanisms: the selective filtering of phototoxic blue light, reduction of oxidative stress at the retinal pigment epithelium, and decrease of chronic subclinical inflammation involved in the pathogenesis of AMD. Moreover, the selective accumulation of these carotenoids in the foveal region is directly proportional to visual performance, suggesting that dietary supplementation is crucial when dietary intake is insufficient, especially among the elderly or those with limited access to a balanced diet.

The AREDS2 clinical trial serves as a model for assessing nutritional intake in AMD, demonstrating that replacing beta-carotene with lutein and zeaxanthin not only maintains the efficacy of the original antioxidant formula, but also offers a superior safety profile, particularly for smokers, in whom beta-carotene was previously associated with an increased risk of lung cancer. Subgroup analyses confirmed the benefit of supplementation in intermediate and advanced stages of AMD, with a significant reduction in progression risk, though without curative therapeutic effects. Nutritional formulas based on AREDS and AREDS2 results are widely used in developed countries, particularly in the United States and Western Europe, where they are integrated into ophthalmological practice and recommended for patients with intermediate or advanced AMD. However, in many regions worldwide – including Central and Eastern Europe, as well as countries with limited medical resources and access to specialised supplements – the use of these formulas remains low, reflecting an urgent need to raise awareness and adapt public health policies to extend the benefits of these preventive interventions.

CONCLUSION

The efficacy of carotenoids in reducing the risk of degenerative ocular diseases represents a biochemically grounded intervention, clinically supported and epidemiologically justified. Results from pivotal studies such as AREDS2 demonstrate a statistically significant reduction in the progression of intermediate and advanced AMD among individuals receiving adequate supplementation, especially when combined with zinc and antioxidant vitamins. These findings require a reassessment of current ophthalmic prevention paradigms, justifying the inclusion of carotenoid supplements in public health policies – not merely as an adjunct intervention, but as an essential element in strategies to reduce the burden of age-related ocular diseases.

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