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The beneficial role of lutein and zeaxanthin in cataracts

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Abstract

Cataracts remain the leading cause of visual loss and blindness worldwide. Cataract surgery is the most common surgical procedure in several countries and its occurrence is expected to increase substantially due to the ageing of the population and the reduced visual acuity threshold required for considering it. Cataracts are characterised by lens opacity and are caused by the precipitation of proteins induced by oxidative damage. The fact that oxidation of the lens is a contributing cause for cataracts suggests that antioxidants may play a positive role in cataract prevention. Lutein and zeaxanthin, two dietary xanthophylls exclusively deposited in the macula lutea and known for their beneficial role in age-related macular degeneration, are the only carotenoids deposited in the lens and may have an important role in reducing the ROS-induced damage of the lens contributing to cataract development. This paper will review the current science derived from epidemiological and intervention studies addressing the association between lutein and zeaxanthin intake, their serum level, and the possible benefits for primary prevention of age-related cataract. Additional insights into the potential health cost savings from the increased intake of these dietary ingredients originating from a U.S. study are also provided.

Introduction

The incidence of age-related cataracts, responsible for 51% of world blindness (approximately 20 million people in 2010), is expected to rise due to the increase in life expectancy [1], escalating the already large public health expenditures and resulting in billions of dollars in healthcare costs. In developing countries, cataracts are the principal cause of blindness among people over 40 years of age due to improper nutrition and infectious diseases [2].

Cataracts are characterised by lens opacity induced by cumulative or excessive exposure to light, oxygen and metals that generate reactive oxygen species (ROS) leading to peroxidation of membrane lipids and subsequent destruction and precipitation of lens protein crystalline(s). Currently, cataracts are successfully treated by surgical removal of the

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lens, followed by implantation of an artificial lens at the time of surgery. The surgical procedure provides excellent improvement in patient visual acuity and quality of life; however, patients living in developing countries or not covered by health insurance can have limited or delayed access to it. In addition, the costs of cataract extraction represent an important public health burden; thus, strategies to prevent cataracts or delay their progression should be followed [3].

The fact that oxidation of the lens is a major cause for cataracts suggests that antioxidants may play a positive role in cataract prevention. Because most of the enzymatic cofactors and other constituents which contribute to the lens antioxidant defence mechanism originate from diet, it is likely that diet has an important role in reducing the ROS-induced damage of the lens [4]. Evidence has emerged suggesting that healthy lifestyle and proper nutrition may have a beneficial effect on the onset of cataracts [5, 6] and special attention has been paid to two dietary antioxidants in particular: lutein and zeaxanthin.

The purpose of this paper is to provide an overview of the science addressing the beneficial relationship between lutein and zeaxanthin intake and cataracts.

Lutein and zeaxanthin: Focus on prevention

Lutein and zeaxanthin, two dietary xanthophylls exclusively deposited in the macula lutea and key components of the macular pigment, are the only carotenoids deposited in the lens. Here they can be found in all the lens layers although they are more concentrated in the epithelial and cortical layers than the nuclear layer [7].

The rationale for the protective role of lutein and zeaxanthin in both the retina and the lens stems from their ability (1) to filter harmful short-wave blue light, (2) to function as antioxidants and (3) to stabilise membrane integrity. These biological functions are believed to play an important role in helping to reduce light-induced oxidative damage caused by ROS, which contributes to the pathogenesis of age-related macular degeneration (AMD) and cataracts [8].

Studies conducted in patients with AMD or healthy subjects show that macular pigment optical density (MPOD), which provides an indication of lutein and zeaxanthin in the macula and is measured with non-invasive technologies, can be augmented with increased intake of lutein and zeaxanthin. The scientific literature also suggests that in individual 50+ years old, there is an inverse relationship between MPOD and lens opacity quantified in terms of lens optical density (LOD) [9, 10]. Since increased LOD provides an indication of lens senescence, which is strongly related to cataracts [9], the fact that high MPOD is associated with decreased LOD suggests that lutein and zeaxanthin in the eye may retard lens ageing [9, 10].

The protective role of these two carotenoids and the underlying mechanism of action is supported by (1) their exclusive presence in the lens and (2) observations from *in vitro* studies indicating that pretreatment of human lens epithelial (HLE) cells with lutein and zeaxanthin: (i) induces their accumulation in the lens, (ii) decreases UVB-induced lipid peroxidation and stress signalling activation [4] and (iii) reduces H_2O_2-mediated damage of lens protein, lipid and DNA [11].

An *in vivo* intervention study conducted in quails confirmed that lens carotenoids can be increased by dietary intake of zeaxanthin [12]. Additionally, a study performed in streptozotocin-induced diabetic rats showed that lutein supplementation was effective in preventing the development and progression of cataracts and an increase in lipid peroxidation [13].

Epidemiological studies provide much of the scientific data on lutein and zeaxanthin and indicate the possible protective effect of dietary intake of lutein and zeaxanthin and/or their serum levels against cataract incidence, mainly nuclear cataracts, or risk of cataract extraction [14–29], although some publications report a null or negative effect [14, 28–31]. A summary of some of the papers addressing

Study	Cohort	Age	Lutein (L) and/or zeaxanthin (Z) daily intake (µg)		Key outcome
			Lowest	Highest	
Brown et al., 1999 [15]	36,344 men	45–75 years	1.300	6.871	• Risk of cataract extraction was 19% lower in the group with the highest quintile of consumption of L and Z when compared to the lowest quintile of intake (RR: 0.81, 95% CI: 0.65–1.01; *p* for trend=0.03). • As cataracts develop over many years, frequent consumption of foods high in carotenoids early in life or for long periods may be associated with a lower risk of senile cataract extractions.
Chasan Taber et al., 1999 [16]	77,466 women	45–71 years	1.172	11.685	• Subjects with the highest quintile of intake of L and Z had a 22% decreased risk of cataract extraction compared with those in the lowest quintile (RR: 0.78; 95% CI: 0.63–0.95; *p* for trend=0.04).
Lyle et al., 1999 [23]	1,354	43–84 years	298	1.245	• Subjects in the highest quintile of L intake in the distant past were half as likely to have an incident cataract as persons in the lowest quintile of intake (95% CI 0.3–0.8; *p* for trend=0.002). • High intake of L at baseline was associated with a non-significant OR of 0.6 (95% CI 0.4–1.1; *p* for trend=0.09). • Lutein was the only carotenoid out of five examined that was associated with nuclear cataracts. • Consumption of spinach and other dark leafy greens (concentrated source of lutein) was inversely associated with nuclear cataracts for persons with the highest intakes (OR: 0.6; 95% CI: 0.4–0.9; *p* for trend=0.02).
Jaques et al., 2001 [18]	478 women	53–73 years	–	5.600	• The prevalence of nuclear opacification was significantly lower in the upper four L/Z quintiles of intake categories relative to the lowest quintile category (*p* for trend=0.03), although the association did not remain statistically significant after adjustment for other nutrients.
Rodriguez-Rodriguez et al., 2006 [19]	177	>65 years	<256 (5th %)	>3290 (95th %)	• Subjects whose daily L intake was >3290 µg were less likely to have cataracts (OR=0.086; CI: 0.007–1.084; $p<0.05$) than those whose consumption was <256 µg. • In men, high intakes of Z seemed to have a protective effect (OR=0.96; CI: 0.91–0.99; $p<0.05$).
Vu et al., 2006 [20]	2,322	>40 years	472	1037	• Inverse association between high dietary LZ intake and prevalence of nuclear cataracts. The odds ratio (95% CI) for those in the top quintile of energy-adjusted LZ intake was 0.64 (CI: 0.40–1.03; *p* for trend=0.018). • In the analysis with LZ as continuous variable, the odds ratio for every 1 mg increase in energy-adjusted daily LZ intake was 0.60 (0.40–0.90) for nuclear cataracts. • Cortical and posterior subcapsular cataracts were not significantly associated with LZ intake.
Christen et al., 2008 [44]	35,551 women	>45 years	1.177	6.716	• Women in the highest quintiles of lutein/zeaxanthin per day (corresponding to more than 6 mg/day) had 18% lower risk of cataracts compared to women with median lutein/zeaxanthin intake approximating 1 mg per day (RR: 0.82; 95% CI: 0.71–0.95; *p* for trend =0.04). • A borderline significant inverse association between higher intake of green leafy vegetables such as spinach and risk of cataracts was also observed.
Moeller et al., 2008 [22]	1802 women	50–79 years	600	3.300	• Women in the highest quintiles of dietary lutein and zeaxanthin intake had a 32% lower prevalence of nuclear cataract (OD: 0.68; 95% CI: 048–0.97; $p=0.04$) and 37% lower prevalence of nuclear sclerosis score ≥0.4 (OD: 0.63; CI: 0.43–0.94; $p=0.04$ for trend) compared with those with low levels.

Table 1 Published observational studies addressing the relationship between dietary consumption of lutein (L)/zeaxanthin (Z) and cataracts

the positive relationship between cataract incidence or extraction and high lutein and zeaxanthin in the diet or serum is presented in Tables 1 and 2.

Three recently published meta-analyses examining the association between dietary or blood lutein and zeaxanthin and age-related cataract and referring to the studies listed in Tables 1 and 2 support the efficacy of these carotenoids in reducing the risk of this eye condition, in particular nuclear cataracts [32–34]. More specifically, the dose-response analysis published by Ma et al. in 2013 showed a statistically significant 3% decrease in nuclear cataract risk for each 300 µg increase in daily dietary lutein and zeaxanthin intake [33].

Only two human intervention studies [35, 36] have been conducted up to the present date to explore

Study	Cohort	Age	Serum level (μmol/l)		Key outcome
			Lutein	Zeaxanthin	
Lyle et al., 1999 [17]	325	50–86 years	Lutein+zeaxanthin combined Low: <0.18 High: ≥0.38		• Serum lutein/zeaxanthin were not significantly associated with 5 y incidence of severe nuclear cataract, however a marginal inverse association with lutein (OR: 0.3; 95% CI: 0.1–1.2; p=0.13 for linear trend) was suggested for people ≥65 y of age.
Gale et al., 2001 [14]	372 men and women	66–75 years	Low: 0.14 High: >0.20	Low: 0.03 High: >0.05	• Risk of posterior subcapsular cataract was lowest in those with higher concentrations of lutein (OR: 0.5; 95% CI: 0.2–1.0, p for trend: 0.012). • No statistical significant association was found between lutein or zeaxanthin serum levels and risk of nuclear or cortical cataracts.
Delcourt et al., 2006 [24]	644	>60 years	Low: 0.17 High: ≥0.38	Low: 0.04 High: ≥0.09	• Highest tertiles of plasma zeaxanthin were significantly associated with 75% reduced risk of nuclear cataract (OR: 0.23; 95% CI: 0.08–0.68; p for trend 0.003) and 43% reduced risk for any cataract (OR: 0.53; 95% CI: 0.31–0.89; p for trend 0.01). • No association with plasma lutein levels was observed, while a statistically significant 66% reduction of risk for nuclear cataract was found with high plasma dehydrolutein. • No statistically significant association with cortical or posterior subcapsular cataract was found for any of the carotenoids.
Dherani et al., 2008 [25]	1112	>50 years	Low: <0.0762 High: ≥0.1137	Low: <0.0155 High: ≥0.0214	• Highest tertiles of plasma zeaxanthin or lutein were associated with decreased odds of cataract (OR: 0.66; 95% CI: 0.45–0.96; p=0.03 for zeaxanthin and OR: 0.73; 95% CI: 0.43–1.02; p=0.06 for lutein). • Inverse associations were found between cataract and blood antioxidants in an antioxidant-depleted study sample.
Moeller et al., 2008 [22]	1802 women	50–79 years	Lutein+zeaxanthin combined Low: 0.15 High: 0.5		• Women in the highest quintile category of serum levels of lutein and zeaxanthin were 32% less likely to have nuclear cataract (OD: 0.68; 95% CI, 0.47–0.98; p for trend=0.01) compared with those in the lowest quintile category. • A 21% reduction on nuclear sclerosis (score ≥4) was also observed, although it did not reach statistical significance in the multivariable adjusted analysis.
Karppi et al., 2012 [26]	1689	61–80 years	Low: <0.2 High: >0.27	Low: <0.030 High: >0.041	• Subjects in the highest tertile of plasma concentrations of lutein had 42% lower risks of nuclear cataract compared with those in the lowest tertile (relative risk (RR)=0.58; 95% CI 0.35–0.98; p=0.041). • Subjects in the highest tertile of plasma concentrations of zeaxanthin had 41% lower risks of nuclear cataract compared with those in the lowest tertile (RR=0.59; 95% CI 0.35–0.99; p=0.046).
Ravindran et al., 2011 [27]	5638 people	>60 years	Q1: 0.125 Q4: 0.460	Q1: 0.021 Q2: 0.066	• Lutein and zeaxanthin were significantly inversely associated with cataract, but the associations were weaker and not consistently observed by type of cataract.

Table 2 Published observational studies addressing the relationship between the L/Z serum/plasma concentrations and cataracts

the cause–effect relationship between lutein and zeaxanthin supplementation and benefits for cataracts, providing additional support for the positive findings collected from observational studies and addressing the importance of supplementation, especially when the dietary intake of these carotenoids is low. The Age-Related Eye Disease Study 2 (AREDS2), a large intervention trial primarily conducted to evaluate the effect of nutritional intervention with lutein and zeaxanthin on reduction in the risk of progression to advanced AMD [37, 38], also assessed the effect of these carotenoids on cataracts or progression to cataract surgery. Although the results of the primary analysis comparing the progression of cataract with or without lutein and zeaxanthin supplementation resulted in a non-significant hazard ratio of 0.96 (95% CI 0.84–1.10), in subjects in the lowest quintiles of lutein and zeaxanthin dietary intake, supplementation with 10 mg lutein and 2 mg zeaxanthin for 5 years resulted in a 30% reduction of any cataract and 32% reduction of cataract surgery when compared to no lutein and zeaxanthin supplementation [36]. It should be noted that the AREDS2 study popula-

Study	Cohort	Age	Lutein/zeaxanthin dose	Period of supplementation	Key outcome
The AREDS2 research group, 2013 [36]	3159	50–85 years	10 mg L+2 mg Z (daily)	5 years	• Subjects in the lowest quintile of lutein and zeaxanthin intake benefit from the addition of lutein/zeaxanthin from the AREDS supplement: When comparing L+Z vs. no L+Z, in these subjects a significant reduction in risk of progression to cataract surgery, any cataract or any severe cataract of 32%, 30% and 36%, respectively ($p<0.05$) was observed. • No overall effect of lutein/zeaxanthin supplementation was observed in the study. The hazard ratios for progression to cataract surgery for patients receiving the carotenoids was 0.96 (95% CI: 0.84–1.10; $p=0.54$).
Olmedilla et al., 2003 [35]	15	55–73 years	12 mg of all-trans lutein (3 times a week)	2 years	• Supplementation with lutein increased serum concentrations, whereas no changes were observed in the placebo group. • Lutein supplementation significantly improved visual acuity in cataract patients. • Glare sensitivity at low, medium and high thresholds also improved in the lutein group compared to the baseline values. • Cataract progression was not observed in 80% of the patients in the lutein group compared to just 20% of subjects in the placebo group.

Table 3 Interventional studies addressing the effect of supplementation with L and Z on visual function and cataract progression in cataract patients

tion was well nourished compared to the general U.S. adult population, with above-average intake of dietary nutrients, including much higher intake and mean serum levels of lutein and zeaxanthin. The intake of the lowest quintile is more representative of what is typical in the adult population, therefore the outcomes of the subgroup analysis may be what is more relevant. In the study published by Olmedilla in 2003, 2-year supplementation of cataract patients with lutein resulted in improvements in visual function (visual acuity and glare) [35]. A summary of these two human intervention studies is shown in Table 3.

These observed beneficial effects are important in light of a possible reduction of medical expenditures associated with the condition. A report issued in 2013 by Frost and Sullivan and commissioned by the Council for Responsible Nutrition (CRN) Foundation [39] provided insights into the potential net savings that could be achieved in four different diseases, including age-related eye diseases (AMD and cataract), by using dietary supplements as a preventive health-care measure to reduce the rate of medical events in the U.S. high-risk population over 55 years. By reviewing published studies directly assessing the direct causal relationship between intake of lutein and zeaxanthin and the relative risk of the disease events, the report showed that the relative risk reductions for AMD and cataract associated with the use of lutein and zeaxanthin were 23% and 15.3%, respectively, overall offering a potential net health-care cost savings (after accounting for the cost of lutein and zeaxanthin supplements) between 2013 and 2020 of nearly $1 billion/year.

Conclusion

Lutein and zeaxanthin are the only dietary carotenoids deposited in the macula lutea and are well known for their ability to act as antioxidants and as a filter of blue light. Lutein and zeaxanthin are also the only dietary carotenoids deposited in the lens. The selective uptake of these carotenoids in this structure combined with their biological function support their potential beneficial role also in age-related cataracts, thus expanding the positive effect observed in patients with AMD and in healthy subjects. The science originating from observational studies suggests that adequate dietary intake or serum lutein and zeaxanthin may help to reduce the risk of cataract incidence as well as the need for cataract extraction. The results of intervention stud-

ies further support the importance of an adequate intake of lutein and zeaxanthin and reinforce the benefits of supplementation with these carotenoids when proper dietary intake is not achieved, as occurs in the modern diet [40–43].

Conflict of interest

Samanta Maci and Rafaela Pontes are employees of Kemin Human Nutrition and Health.

Human and Animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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