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Technical Literature

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Why Dietary Zeaxanthin? - A Scientific Summary

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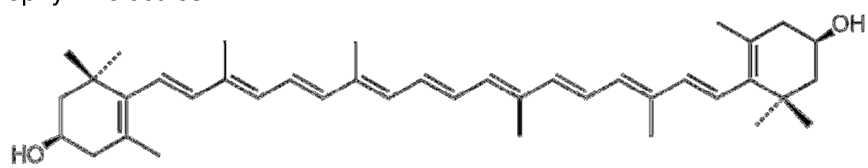
KEY CONCLUSIONS

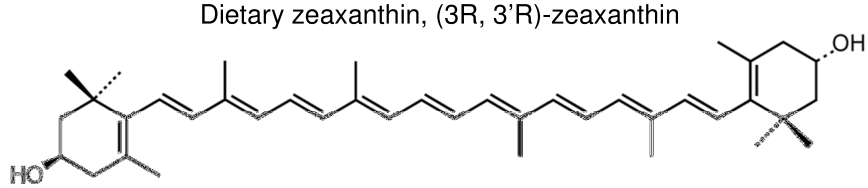
- *Zeaxanthin is a component of the macular pigment along with lutein that is derived from dietary sources.*
- *Epidemiological studies have shown that a diet high in lutein and zeaxanthin or high levels in the serum is correlated with a reduced risk of age-related macular degeneration and cataracts.*
- *Supplementation with zeaxanthin results in increased levels in the serum and the macula, resulting in improved visual function.*
- *Studies suggest consumption of at least 2 mg zeaxanthin daily for eye health benefits, which is much more than what is obtained from the average US diet*

INTRODUCTION

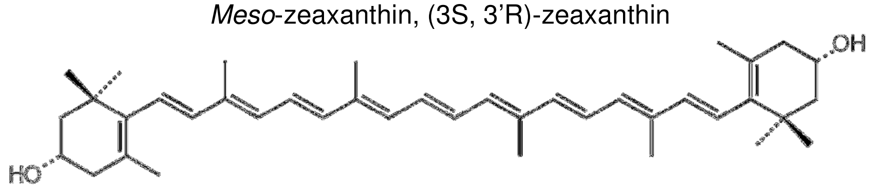
Zeaxanthin is a naturally occurring xanthophyll carotenoid common in foods such as corn, eggs and peppers. It is also known as (3R, 3'R)-zeaxanthin or dietary zeaxanthin. Zeaxanthin has two chiral centers and thus other stereoisomers, namely (3S, 3'S) - and (3S, 3'R)-zeaxanthin (*meso*-zeaxanthin), exist. *Meso*-zeaxanthin is not found in nature except in the macula of humans and primates, and (3S, 3'S)-zeaxanthin is rarely found in nature and is not reportedly present in the human or primate eye (Figure 1).(*1*) In addition to these all-*trans* (also referred to as *all-E*) isomers, there are a broad range of *cis*-isomers of zeaxanthin which may occur as a result of the 18-carbon alternating double bond structure of this group of xanthophyll molecules.



Dietary zeaxanthin, (3R, 3'R)-zeaxanthin



Meso-zeaxanthin, (3S, 3'R)-zeaxanthin



(3S, 3'S)-zeaxanthin

Figure 1. Molecular structures of three zeaxanthin stereoisomers

Dietary zeaxanthin (Z) is found at its highest concentrations in the human body in the fovea of the central macula of the eye.(*2*) It is found in approximately equal proportions to both lutein (L) and *meso*-zeaxanthin (MZ).(*3, 4*) Dietary zeaxanthin is also found in lower quantities in the peripheral retina where the ratio of L:Z:MZ is 2:1:0.5.(*5*) In the fovea, dietary zeaxanthin is believed to act as both an antioxidant to reduce oxidative stress and damage caused by blue light as well as a blue light filter.(*6-10*)

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DIETARY SOURCES OF ZEAXANTHIN FROM PLANTS

Dietary zeaxanthin is found naturally in a wide variety of fruits and vegetables common in the typical US diet as shown in Table 1.(*1, 11-14*) An evaluation of The National Health and Nutrition Examination Survey (NHANES), the USDA/NCC carotenoid database (1998) and the per-capita food consumption from USDA statistic reports (1999) suggests that the lutein:zeaxanthin ratio in the US diet is 5:1.(*15, 16*) The 5:1 ratio of lutein:zeaxanthin in the diet is supported by studies evaluating zeaxanthin levels in the serum, where the same 5:1 ratio is observed.(*17, 18*) Additionally, zeaxanthin is found in high concentration in the goji or wolfberry (*Lycium barbarum/Lycium chinense*) which is more common in the Chinese diet.(*13*) Commercial sources of natural zeaxanthin are derived from marigold flowers (*Tagetes erecta*) and paprika peppers (*Capsicum annuum*).

Table 1. Common Dietary Sources of Zeaxanthin

Food	Serving size	Zeaxanthin Content (µg/serving)
Goji berry	1 oz (28 g)	43,835
Pepper, orange (raw, chopped)	1/2 cup (74.5 g)	1,240
Corn (drained, sweet, yellow, canned, whole kernel)	1/2 cup (132 g)	697
Squash, butternut (raw, cubed)	1/2 cup (70 g)	196
Egg (yolk and white, cooked)	1 egg (50 g)	108
Spinach (raw)	1 cup (30 g)	99
Corn tortilla	1 tortilla (24 g)	37
Orange juice	1 cup (248 g)	64
Carrots (raw, sliced)	1 cup (122 g)	28
Peaches (canned, drained)	1/2 cup (61 g)	5

Despite zeaxanthin being available in common foods, on average the US population consumes much less than the 2 mg zeaxanthin per day recent scientific evidence supports as beneficial.(*19-21*) On average, adults in the US only consume 0.12 mg of zeaxanthin daily. These data make it quite evident that Americans are not regularly consuming sufficient levels of zeaxanthin to gain eye health benefits. The scientific literature supports 10 mg of lutein/day for eye health and function benefits. Based on the 5:1 ratio of lutein:zeaxanthin found in the diet, studies are testing and showing eye health benefits of zeaxanthin at levels of at least 2 mg of zeaxanthin/day in combination with 10 mg lutein/day.

In nature, zeaxanthin exists in a "free" un-esterified form or as an ester. Citrus fruits and peppers are commons sources of zeaxanthin esters whereas free zeaxanthin is found in eggs, corn, spinach and other green vegetables. Based on per capita consumption data from the USDA (*22, 23*), the overwhelming majority of zeaxanthin is consumed in the free form (Figure 2). To absorb zeaxanthin from esterified zeaxanthin, it must first be de-esterified by the body - an enzymatic process that varies among individuals and can affect absorption.(*24*)

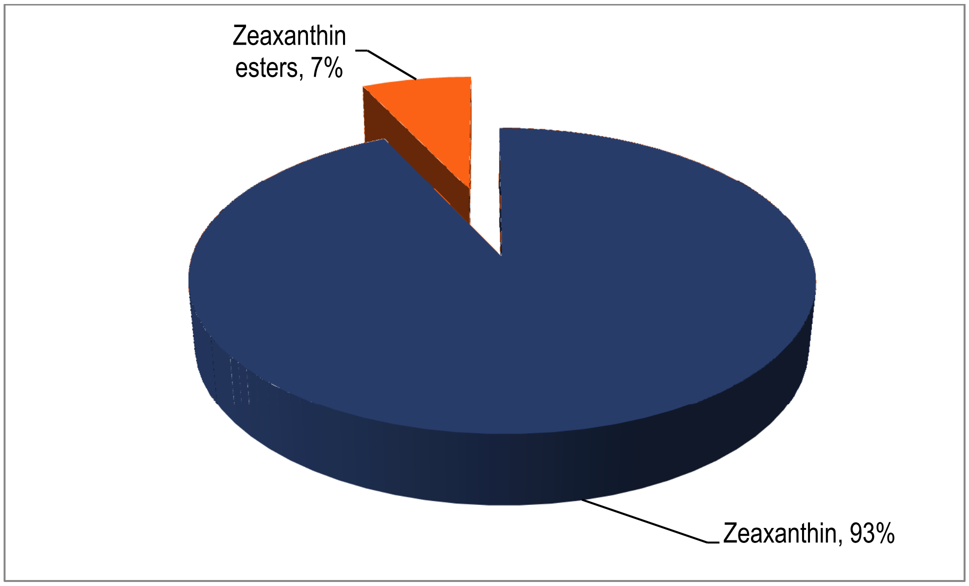

Figure 2. Graph illustrating the relative amounts of free vs. esterified lutein and zeaxanthin in the US diet.

Dietary zeaxanthin should not be confused with *meso*-zeaxanthin or "zeaxanthin isomers" which can contain a mixture of dietary zeaxanthin and its stereoisomers, 3R, 3'S, and 3S, 3'S. These compounds are semi-synthetic(*25*) and not found naturally in the human diet.(*26*) The science investigating the benefits of *meso*-zeaxanthin is limited and lacks the diet-based evidence supporting a role in eye health that dietary zeaxanthin possesses.(*27*)

INTERVENTION STUDIES

There is a growing body of evidence from intervention trials that supports the benefits of supplementation with zeaxanthin and lutein at a 1:5 ratio to mimic dietary sources, and some evidence at even higher inclusion levels of zeaxanthin, either by itself, or in combination with lutein. This body of evidence supports formulating eye supplements to include zeaxanthin at considerably higher levels that those that typically accompany lutein sourced from marigolds.

There are a number of studies that have supplemented both healthy subjects and those with AMD with zeaxanthin derived from a variety of sources. These studies evaluated the impact of zeaxanthin supplementation on serum zeaxanthin levels, MPOD, visual function, antioxidant capacity, and progression to advanced AMD. Table 2 lists the published human clinical trials that had a zeaxanthin only treatment arm or a 10 mg lutein and 2 mg zeaxanthin treatment arm, as this is the dose of lutein and zeaxanthin recommended by the National Eye Institute (NEI) based on the results of the Age-Related Eye Disease Study 2 (AREDS2)(*28*). The NEI recommendation on the supplement formulation levels of lutein and zeaxanthin is consistent with the 5:1 ratio of lutein:zeaxanthin that is observed in the diet.

Table 2. Published Human Trials Examining the Effects of Zeaxanthin Supplementation on Parameters of Eye Health.

Trial	Cohort[a]	Protocol[b]	Results[c,d]
AREDS2 Research Group *et al.* (2013) (***29***)	1044 adults with moderate to advanced AMD	10 mg FloraGLO Lutein + 2 mg zeaxanthin (synthetic) daily for 5 years	• Significant 10% reduction in progression to advanced AMD as compared to subjects who did not receive lutein + zeaxanthin • Significant 26% reduction in progression to advanced AMD in the lowest quintile of dietary lutein and zeaxanthin as compared to subjects who did not receive lutein + zeaxanthin

Tanito *et al.* (2012) ***(30)***	11 healthy adults	10 mg zeaxanthin (from peppers) daily for 3 months	No change in MPOD compared to baseline
Richer *et al.* (2011) ***(31)*** and Richer *et al.* (2012) ***(32)***	25 adults with mild to moderate AMD	8 mg ZeaONE Zeaxanthin (from marigold flowers) daily for 1 year[f]	• Significant improvement in MPOD, high contrast visual acuity, shape discrimination, and clearing of central scotomas as compared to baseline • Trend in the self-described ability to drive a car (p = 0.057)
Bucheli *et al.* 2011 ***(33)***	75 healthy elderly subjects	10 mg zeaxanthin (from goji berries) daily	• Significant decrease in macula hypopigmentation as compared to placebo • Significant decrease in soft drusen as compared to placebo • Significant 26% increase in plasma zeaxanthin from baseline • Significant 57% increase in plasma antioxidant capacity from baseline. Values were significantly greater than placebo at 1 and 3 months.
Stringham and Hammond 2008 ***(34)***	40 healthy adults	10 mg FloraGLO Lutein + 2 mg zeaxanthin (synthetic) daily for 6 months	• Significant increase in MPOD • Significant increase in glare tolerance • Significant decrease inphotostress recovery time
Huang *et al.* 2008 ***(35)***	20 adults with AMD	10 mg FloraGLO Lutein + 2 mg zeaxanthin (synthetic) daily for 6 months	• Significant increase in serum zeaxanthin from baseline • No significant improvement in visual acuity
Van de Kraats *et al.* (2008) ***(36)***	3 healthy male adults	20 mg zeaxanthin daily (from peppers) for 6 months	Significant increase in MPOD in all subjects from baseline
Schalch *et al.* (2007) ***(37)***	23 healthy male adults	10 mg zeaxanthin (synthetic) daily for 6 months	• Serum zeaxanthin increased 27-fold from baseline[e] • Increase in MPOD (2.7%) was not significant compared to placebo
Kvansakul *et al.* (2006)***(38)*** and Rodriguez-Carmona *et al.* (2006) ***(39)***	5 healthy males	10 mg zeaxanthin (synthetic) daily for 6 months (phase I) followed by 20 mg zeaxanthin/day for an additional 6 months (phase II)	• Decreasing trend in light scatter, wavefront aberration, and contrast acuity threshold from end of phase I • Significant increase in MPOD as compared to placebo at the end of phase II
Cheng *et al.* (2005) ***(40)***	14 healthy subjects	3 mg zeaxanthin (from goji berries) per day for 28 days	Significant 2.5-fold increase in serum zeaxanthin from baseline
Breithaupt *et al.* (2004) ***(41)***	12 healthy adults (6 male, 6 female)	5 mg zeaxanthin (from goji berries) in a single dose	Significant increase in serum zeaxanthin from baseline
Hartmann *et al.* (2004) ***(42)***	20 healthy adults (10 male, 10 female)	1 mg or 10 mg zeaxanthin per day (synthetic) for 42 days	Significant increase in serum zeaxanthin in both the 1 mg and 10 mg groups (4-fold and 20-fold, respectively) from baseline
Bone *et al.* (2003) ***(43)***	Two healthy male adults	30 mg zeaxanthin per day (from Flavobacterium) for either 60 or 120 days	Serum zeaxanthin rose 5- to 6-fold. MPOD increased in both subjects[e]

[a]Only subjects who received zeaxanthin supplementation are listed.
[b]Only zeaxanthin dose is listed. Trial may have included other nutrients or placebo.
[c]Change from baseline to end of zeaxanthin supplementation period
[d]Significance defined as $p < 0.05$

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[e]Significance not noted
[f]Study conducted with EZEyes® Zeaxanthin which was sourced from the same patented, hybrid marigold flowers as those used in ZeaONE and has a comparable carotenoid composition to ZeaONE

DIET-BASED SCIENCE

The intervention trials corroborate epidemiological studies that provide evidence that zeaxanthin is beneficial for eye health. Many of these studies evaluated the benefit of zeaxanthin in combination with lutein as these are very closely related molecules and are found together in the diet. Assuming dietary exposures to zeaxanthin to be at approximately 1/5 of the levels of dietary intakes of zeaxanthin, these studies support that supplementation with higher levels of zeaxanthin can positively impact eye health and function.

Early indications of the role of lutein and zeaxanthin in eye health came from Seddon *et al.* in 1994 which showed a 57% reduction in the risk of developing advanced AMD with the consumption of 6 mg lutein and zeaxanthin daily from the diet as compared to a daily intake of 1 mg. Since then, numerous observational studies have been published showing increased consumption of lutein and zeaxanthin is linked to a reduced incidence of age-related eye diseases, particularly age-related macular degeneration (AMD) and cataract. A summary of these studies can be found below in Table 3. There were two studies that found a significant reduction in risk of AMD with higher serum zeaxanthin independent of lutein.(*44, 45*) A study by Fletcher *et al.* demonstrated a significant association between blue light exposure and neovascular AMD in individuals in the quartile of lowest serum levels of zeaxanthin.(*46*)

In addition to being associated with reduced AMD risk, several studies have also found that high zeaxanthin in the diet and serum can reduce the risk of cataract. A summary of these studies can be found in Table 4.

Table 3. Summary of Epidemiology Studies Investigating the Relationship between Lutein and Zeaxanthin and AMD Risk

Study	Cohort	Result
AMD and Dietary Intake of Lutein and Zeaxanthin		
Ho *et al.* 2011 (***47***)	2167 ≥ 55 years genetically at risk for AMD from the Rotterdam Study	Highest intake of lutein/zeaxanthin reduced the risk of early AMD (from 2.63 to 1.72) in carriers of CFH Y402H ($p = 0.05$)
Cho *et al.* 2008 (***48***)	Up to 18 years follow-up of 71,494 women and 41,564 men aged ≥ 50 y and had no diagnosis of AMD or cancer.	Lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD. There was a statistically non-significant and nonlinear inverse association between lutein/zeaxanthin intake and neovascular AMD risk
Tan *et al.* 2008 (***49***)	Cohort of the Blue Mountains Eye Disease Study (2,454)	Significant inverse relationship between lutein/zeaxanthin intake and risk of long-term AMD
SanGiovanni *et al.* 2007 (***50***)	AREDS participants (4,519)	Significant inverse relationship between lutein/zeaxanthin intake and likelihood to have advanced AMD, geographic atrophy, and large or extensive intermediate drusen
Moeller *et al.* 2006 (***51***)	Cohort of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (1,787)	Significant inverse relationship between intake of lutein/zeaxanthin and AMD risk in women less than 75 years old with stable intake of lutein/zeaxanthin and no history of chronic diseases that are often associated with dietary changes
Vu *et al.* 2006 (***52***)	183 subjects with early (147) or late (36) AMD *versus* 1,789 healthy controls	Possible protection of high lutein/zeaxanthin intake on AMD among those with low level of linoleic acid intake
Snellen *et al.* 2002 (***53***)	72 patients with neovascular AMD *versus* 66 healthy controls	Prevalence rate of AMD in patients in low lutein/zeaxanthin intake was about twice those with high intake ($p < 0.05$)

Seddon *et al.* 1994 (***54***)	356 patients with advanced AMD *versus* 520 healthy controls	Significant inverse relationship between lutein and zeaxanthin intake and risk for AMD
AMD and Serum Lutein and Zeaxanthin		
Zhou *et al.* 2011 (***45***)	267subjects (82 cases of exudative AMD, 92 cases of early AMD, and 93 controls)	Significant inverse relationship for exudative AMD and serum zeaxanthin levels. No association between serum lutein levels and early or exudative AMD.
Michikawa *et al.* 2009 (***55***)	722 subjects(32 subjects with early, 8 with late AMD and 682 with nomaculopathy)	No difference in serum lutein and zeaxanthin levels between AMD patients and normal subjects. The carotenoid family of beta-cryptoxanthin, alpha and beta-carotene, lycopene, lutein and zeaxanthin were protective against late AMD.
Fletcher *et al.* 2008 (***46***)	Cross-sectional analysis of 4753 elderly with early (2,182) or neovascular AMD (101) or controls (2,117) in the European Eye Study	No relationship between serum lutein or zeaxanthin levels and incidence of AMD. However, a significant association was found between blue light exposure and neovascular AMD in individuals in the quartile of lowest serum levels of zeaxanthin
Delcourt *et al.* 2006 (***56***)	Cohort of the Pathologies Oculaires Liées à l'Age (POLA) Study [640 for Age-Related Maculopathy (ARM); 815 for cataracts]	Significant inverse relationship between plasma lutein and plasma zeaxanthin levels and risk of AMD (p = 0.005)
Cardinault *et al.* 2005 (***57***)	37 patients with AMD (9 with early AMD and 28 with late stage AMD) *versus* 24 healthy controls	No relationship between serum lutein or zeaxanthin and incidence of AMD.
Gale *et al.* 2003 (***44***)	78 subjects with early (64) or late (14) AMD *versus* 302 controls	Significant inverse relationship between zeaxanthin serum levels and risk for AMD. Trend for inverse relationship between lutein serum levels and risk for AMD
EDCC Study Group, 1993 (***58***)	421 patients with neovascular AMD *versus* 615 healthy controls	Significant inverse relationship between lutein and zeaxanthin serum levels and antioxidant index and risk for AMD
AMD and Macular Pigment		
Puell *et al.* 2013 (***59***)	22 subjects with early AMD and 27 healthy control subjects	No significant difference was found in foveal macular pigment optical density (MPOD), composed of dietary lutein/zeaxanthin, between control eyes and eyes with early AMD
Kaya *et al.* 2012 (***60***)	85 healthy subjects and 96 patients with AMD	Significant reduction in MPOD in AMD patients as compared to the healthy control group
Raman *et al.* 2012 (***61***)	33 patients with wet AMD and 29 age-matched controls >50 years	Significant inverse association between wet AMD and MPOD
Tsika *et al.* 2011 (***62***)	33 patients with bilateral dry AMD and 35 elderly subjects without any signs of retinal disease	Mean MPOD of the fellow eye of patients with unilateral wet AMD was found to be significantly higher than that of patients with bilateral dry AMD. There was no difference between MPOD of healthy patients as compared to those with bilateral dry AMD.
Dietzel *et al.* 2011 (***63***)	369 participants from the Muenster Aging and Retina Study	No relationship between macular pigment and AMD
Nolan *et al.* 2010 (***64***)	17 subjects with early AMD and 62 with no signs of AMD	MPOD in subjects with no signs of AMD was significantly higher when compared to subjects with early stage AMD
LaRowe *et al.* 2008 (***65***)	Women in the cohort of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (1,698)	Significant inverse trend between macular pigment optical density (composed of dietary lutein/zeaxanthin) and pigment abnormalities. Decreased risk for intermediate AMD in women less than 70 years old with stable diets

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Obana *et al.* 2008 (***66***)	100 normal eyes and 187 eyes with ARM; all were Japanese	Macular lutein and zeaxanthin levels in AMD patients were significantly lower than those in healthy volunteers. Levels in later AMD patients were significantly lower than levels found in patients with early AMD (p < 0.0001).
Bernstein *et al.* 2002 (***67***)	93 AMD eyes from 63 patients *versus* 220 normal eyes from 138 subjects	Significant inverse relationship between average levels of lutein and zeaxanthin in AMD eyes versus normal elderly control eyes among the subjects not consuming high-dose lutein supplements (p = 0.001)
Beatty et al. 2001 (***68***)	46 healthy eyes and 9 eyes at high risk for AMD due to advanced disease in the fellow eye	Significantly less macular lutein and zeaxanthin in eyes at high risk for AMD because of advanced disease in the fellow eye as compared to eyes with no known risk (p = 0.015)
Bone *et al.* 2001 (***69***)	112 AMD eyes from 56 patients and 112 normal eyes from 56 healthy subjects	Significant inverse relation between lutein and zeaxanthin concentrations in the central retina and AMD risk

[a]Significance defined as $p < 0.05$ unless otherwise noted
[b]Significance not noted

Table 4. Summary of Epidemiology Studies Investigating the Relationship between Lutein and Zeaxanthin and Cataract Risk

Study	Cohort	Result
Cataract and Dietary Intake of Lutein and Zeaxanthin		
Christen *et al.* 2008 (***70***)	Cohort of the Women's Health Study (39,876)	Significant inverse relationship between nuclear cataract and higher dietary intake of lutein/zeaxanthin
Moeller *et al.* 2008 (***71***)	Women in the cohort of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (1,802)	Significant inverse relationship between nuclear cataract and those in highest quintile category of diet or serum levels of lutein/zeaxanthin as compared to those in the lowest quintile category
Brown *et al.* 1999 (***72***)	Cohort of male health professionals (36,644)	Significant inverse relationship between lutein and zeaxanthin dietary intake and risk of cataract extraction
Chasan-Taber *et al.* 1999 (***73***)	Cohort of female health professionals (50,461)	Significant inverse relationship between lutein and zeaxanthin dietary intake and risk of cataract extraction
Cataract and Serum Lutein and Zeaxanthin		
Karppi *et al.* 2011(***74***)	1689 subjects age 61-80 (113 cases of incident age-related nuclear cataracts of which 108 were nuclear cataracts)	Individuals in the highest tertile of lutein and zeaxanthin plasma concentrations had a significantly lower risk of nuclear cataracts compared to those in the lowest tertile
Dherani *et al.* 2008 (***75***)	1,112 northern Indians with or without cataract	Significant inverse association between serum zeaxanthin and lutein levels and cataract incidence
Delcourt *et al.* 2006 (***56***)	Cohort of the Pathologies Oculaires Liées à l'Age (POLA) Study [640 for Age-Related Maculopathy (ARM); 815 for cataracts]	Significant inverse relationship between plasma zeaxanthin and both nuclear and any type of cataract

CONCLUSION

The data from epidemiological and intervention trials suggest the antioxidant and blue light filtering functions of zeaxanthin in the macula, along with lutein, improve visual function and may reduce the risk of certain eye conditions such as AMD and cataracts. Increasing levels of zeaxanthin in the macula either through a diet high in zeaxanthin and/or zeaxanthin supplementation can improve visual function and may help protect against AMD and cataract. As the average dietary intake of zeaxanthin is well below the 2 mg per day supported by the scientific literature and dietary ratios, for many people an eye vitamin is the best source for their daily supply of zeaxanthin. Many formulations don't provide the clinically studied amounts of dietary zeaxanthin needed for optimal vision. Supplements formulated with the same "free" form as is found naturally in our diet, as found in ZeaONE™ from marigolds, help provide clinically proven benefits of the zeaxanthin nutrient the way nature intended.

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