The Supportive Role of Dietary Carotenoids, Lutein and Zeaxanthin, against AMD: Science Brief
The Supportive Role of Dietary Carotenoids, Lutein and Zeaxanthin, against AMD: Science Brief

Age-related Macular Degeneration (AMD) is a common medical condition of the eye which usually affects older adults (> 50 years) resulting in the loss of vision in the centre of the visual field, the macula. It is the leading cause of blindness in the developed countries, and its prevalence is likely to rise as a result of increasing longevity. This causes concern about the future of visual dysfunction. It is well established that lutein and zeaxanthin, the oxygenated carotenoids called xanthophylls, are the major pigments that play critical roles in reducing the development and progression of this disease. Ample evidence has been gathered on the benefits offered towards eye health by the consumption of these supplements, their high concentration in the serum, and specific distribution in the body tissues, particularly the retina. Increased levels of macular pigment density have been linked to the delay or even reversal of AMD.

The carotenoids, lutein and zeaxanthin are naturally found in dark green leafy vegetables and fruits such as broccoli, kale, yellow and orange peppers, sweet yellow corn, kiwi, pumpkin, mango, orange, and peach, etc. These form the major dietary sources for the human and the commercial exploitation of these ingredients has been achieved through extraction and purification from the flowers of Tagetes erecta (Marigold) and the fruits of Lycium barbarum (Goji berry).

Fig 1: Chemical Structures of Macular Carotenoid Pigments

Lutein is far more prevalent than zeaxanthin in both the human body and the diet, although zeaxanthin appears to be a more chemically potent anti-oxidant. Long-term depletion of zeaxanthin and lutein has been associated with eye diseases, ageing skin, atherosclerosis, and bladder cancer. This may be due to the diminished ability to defend against free radical assault in certain body tissues notably, the eyes.

This white paper provides a comprehensive report on the various clinical and in-vitro biochemical studies on the effects of lutein, zeaxanthin, and its diastereomer, meso-zeaxanthin, in AMD, with special emphasis on the AREDS clinical studies and biochemical investigations on carotenoid binding proteins such as pi isofrom of glutathione - S - transferase (GSTP1) and Steroidogenic Acute Regulatory Domain 3 protein (SIARD3) whose interactions with lutein and zeaxanthin potentiate these carotenoids’ anti-oxidant effects.

What are Macular Pigments?

The carotenoid pigments of the macula are collectively known as macular pigments. The predominant carotenoids of the macular pigments are composed of oxygenated carotenoids viz., Lutein and Zeaxanthin. They protect the central retina from free radical damage and prevent the risk of Age Related Macular Degeneration (AMD). In addition to their antioxidant properties, these act as a blue-light filter and protect the retinal photoreceptors. Macular pigments improve visual including:

- **Visual acuity/Sharpness**
- **Contrast sensitivity**
- **Light sensitivity**
- **Gaze recovery**

The human body cannot synthesize the macular pigments and hence completely rely on dietary intake for its supplementation.

Clinical Studies - AREDS

AMD is a disease of oxidative stress that can damage the highly unsaturated lipids of the retina and retinal pigment epithelium (RPE). This prompted, ophthalmic clinicians to conduct various clinical studies using anti-oxidant supplements world over. The first study called AREDS (2001) showed that formulations containing anti-oxidants (vitamins C, E and beta-carotene) and minerals including zinc and copper helped to reduce the risk of vision loss among patients with high risk for advanced AMD. The typical AREDS composition in the study included Vitamin C (500 mg), Vitamin E (400 IU), beta-carotene (15 mg equivalent to 25000 IU of Vitamin A), Zinc as zinc oxide (80 mg), and copper as copper oxide (2 mg). This study did not investigate the effects of lutein and zeaxanthin or omega-3 fatty acids, however. Although beta-carotene was a component of the successful AREDS formulation, the observation that this pro-vitamin increased risk of lung cancer in smokers stimulated interest in replacing this carotenoid with suitable anti-oxidant lutein and zeaxanthin because they had a better potential efficacy and safety profile. Thus was born, the AREDS 2 study (2006-2012) which will be discussed below.

Key summary points on the outcome of the original AREDS study include:

- **Without anti-oxidant supplementation**, 18% patients with intermediate AMD progressed to advanced AMD during the study.
- **Without treatment**, 43% patients with advanced AMD in one eye progressed to advanced AMD in the other eye as well.
- **With treatment**, the risk of moderate or severe vision loss decreased by 19% over 5 years.
- **With treatment**, there was significant delay in the risk of progression to advanced AMD in selected high risk patients.
- **With treatment**, no evidence of reversal of vision loss or disease progression was noted.

The study, thus, demonstrates some positive benefits in supplementing with anti-oxidants. The next study, AREDS 2, was conducted to evaluate if the addition of lutein and zeaxanthin and/or omega-3 fatty acids (EPA and DHA) to the original AREDS study composition provided any further benefit. It also evaluated whether removal of beta-carotene and/or the reduction of dosage of zinc provided additional benefits. The key findings of the AREDS 2 study were the following:

1. Addition of omega-3 fatty acids did not provide any benefit.
2. Lutein and zeaxanthin provided a small benefit significantly greater for those who had the lowest intake of dietary lutein.
3. In another subgroup, β-carotene was removed from original AREDS formulation and replaced with lutein and zeaxanthin. An 18% additional reduction to the risk of progression of late stage AMD was observed.

4. The combination of lutein and zeaxanthin is a safe addition to the AREDS formula and is an effective replacement for β-carotene.

5. Lower dose of zinc did not show any significant beneficial effect on the progression of AMD.

Thus AREDS 2 study recommended:

- Removal of β-carotene from the original AREDS composition.
- Inclusion of Lutein and Zeaxanthin.
- No supplementation with omega-3-fatty acids beyond dietary consumption
- Supplementation with:
  - Zinc (80 mg)
  - Copper (2 mg)
  - Vitamin E (400 IU)
  - Vitamin C (500 mg)
  - Lutein and Zeaxanthin 10 mg and 2 mg respectively in individuals at significant risk for visual loss from AMD

Other studies

A clinical research group in Ireland published in Experimental Eye Research a study on the effect of a combination of the 3 macular carotenoids on 31 subjects with atypical macular pigment profiles randomly assigned to one of 3 groups. Group -1 received daily supplement of 20 mg of lutein and 2 mg of zeaxanthin. Group - II received 10 mg of lutein, 2 mg of zeaxanthin and 10 mg of meso-zeaxanthin, and Group - III received 3 mg of lutein, 2 mg of zeaxanthin and 17 mg of meso-zeaxanthin.

After 8 weeks of supplementation, Group - I did not have any significant increase or changes of macular pigments distribution. On the other hand, increases were observed for the other 2 groups at select position on the retina, particularly the ‘central dip’. This suggested that meso-zeaxanthin might play a role in normalizing macular pigment distributions in individuals with no observable typical central peak of macular pigment, and they recommended supplementation with all three macular carotenoids: meso-zeaxanthin, lutein, and zeaxanthin7.

Carotenoid Binding Proteins

While human clinical trials (AREDS) were in progress, an in-vitro research relating to carotenoid binding proteins8 was conducted to understand the role of protein binding to ocular xanthophylls. Deposition of dietary carotenoids to specific target tissues in the human body is regulated and mediated by high affinity carotenoid binding proteins. These act as cell surface receptors, as metabolic enzymes, as intracellular mediators for biological action or as sites for deposition and stabilization of the carotenoids.

The uptake, metabolism, and stabilization of xanthophylls in the retina are believed to be mediated by these specific xanthophyll binding proteins. Through a sequence of purification steps, a π-isomer of human glutathione-S-transferase (GSTP1) was identified and characterized as the specific binding protein for the zeaxanthins. Zeaxanthin had the highest affinity binding, followed closely by meso-zeaxanthin, while lutein did not have appreciable affinity for GSTP1. [Fig 2]
Another protein (StAR-D3), one of 15 members of the human steroidogenic regulatory domain (StAR-D) protein family, was identified as the human retinal lutein binding protein and its selectivity to bind lutein in preference to zeaxanthin was demonstrated [Fig 3]. Thus, these class-1, highly selective, high affinity binding proteins for zeaxanthin, meso-zeaxanthin and lutein (GSTP1 and StARD3) are now recognized as essential agents for the enrichment of these pigments in the macula. These and other ocular xanthophyll-binding proteins are likely to be responsible for:

- Selective uptake of lutein and zeaxanthin from blood stream to the macula.
- Pigment stabilization.
- Metabolic interconversion.
- Enhanced anti-oxidant effects.

**Significance of xanthophylls proportion**

The highest concentrations of lutein and zeaxanthin in the human body is in the macula, while the levels in the lens, ciliary body, iris, RPE/choroid and in the peripheral retina are substantially lower. The carotenoid ratios of lutein, trans-zeaxanthin, and meso-zeaxanthin in the serum and liver are 3:1:0, and in the peripheral retina they are 2:1:0.5, while in the macula they are 1:1:1. This suggests that an as yet unidentified ocular tissue specific enzyme may convert lutein to meso-zeaxanthin and that GSTP1 and/or StARD3 may even facilitate this reaction.

Human retinal extracts from over 100 subjects analyzed by HPLC revealed that zeaxanthin is uniquely concentrated within the central fovea where the concentration exceeds that of lutein. A complexity of this observation is that the lutein:zeaxanthin ratio increases across the fovea from the central foveal value of approximately 0.2 to nearly 2.2 in the peripheral retina [Fig 4]. This can be explained in part by the bio-transformation of lutein to meso-zeaxanthin and suggests that a higher ratio of zeaxanthin to lutein in a dietary supplement is considered to enhance delivery of macular pigment to the eye.

**XanMax® clinical trial report**

“A Single center, randomized, double blind, placebo controlled, parallel group pilot study to evaluate the Efficacy and Safety of four different lutein/zeaxanthin formulations for the improvement of Macular Pigment Density”

**Primary objective** was to evaluate the efficacy of 4 different lutein/zeaxanthin formulations for improvement of Macular Pigment Optical Density

**Secondary Objective** was to evaluate the safety of 4 different lutein/zeaxanthin formulations for improvement of Macular Pigment Optical Density and also to evaluate the efficacy of trans lutein/ trans-zeaxanthin formulations as compared to trans-lutein/meso-zeaxanthin formulation for the improvement of Macular Pigment Density.
The Supportive Role of Dietary Carotenoids, Lutein and Zeaxanthin, against AMD: Science Brief

The 4 formulations of XanMax® tested were

1. Trans-lutein: Trans-zeaxanthin - 5mg:0.3
2. Trans-lutein: Trans-zeaxanthin - 5mg:0.5mg
3. Trans-lutein: Trans-zeaxanthin - 5mg:1 mg
4. Trans-lutein: Meso-zeaxanthin - 5mg:1 mg

Subjects were instructed to take one capsule twice a day with food for 2 months.

XanMax® clinical trial conclusion

From the study conducted for the 4 formulations of XanMax®, the following conclusions are drawn.

- After 8 weeks of treatment, greater improvement was seen in MPOD in treatment arms receiving higher dosage of trans-zeaxanthin i.e. TL/TZ 5:1 and TL/TZ 5:0.5, as compared to TL/TZ 5:0.3 and placebo in the Right Eye.
- Though the increase was marginal in TL/ MZ 5:1 group in the right eye, the results of the left eye suggested a sustainable improvement of MPOD in the 3 groups viz., TL/TZ 5:1, TL/TZ 5:0.5 and TL/MZ 5:1.

XanMax® clinical trial summary

- An oral consumption of a supplementation of 5mg of trans-lutein and 1mg of trans-zeaxanthin favorably influences the deposition of carotenoids in macula and provides significant improvement in MPOD as compared to the lower dosage of trans-zeaxanthin.
- Meso-zeaxanthin which is not available as a dietary constituent, but is a bio-transformed active of natural trans-Lutein and is proven to get depleted in older adults, is a key nutrient besides trans-lutein and trans-zeaxanthin. Meso-zeaxanthin has a key role to play in the macular health of AMD volunteers, besides the xanthophylls trans-lutein and trans-zeaxanthin.

Conclusion

In conclusion, the AREDS 2 study has demonstrated that lutein and zeaxanthin are the two most appropriate anti-oxidant substitutes for β-carotene and omega-3 fatty acids (DHA/EPA) in supplements designed to improve macular health. Carotenoid-protein binding studies reveal that GSTP1 and STARD3 proteins are vital for enrichment of xanthophylls in the macula and to enrich their anti-oxidant effects. Higher concentration of zeaxanthin in a lutein-zeaxanthin combination of dietary supplement may favorably enrich macular pigment. Meso-zeaxanthin may selectively raise MPOD and is recommended by some clinicians as a key addition to the defenses against AMD beyond just lutein and zeaxanthin. Commercial carotenoid supplements deliver widely varied concentrations of lutein and zeaxanthin. Marigold flowers have generally yielded a 95:5 lutein: zeaxanthin product, but technological interventions have helped to develop higher concentration of zeaxanthin with ratios ranging from 90:10 to 80:20, providing further opportunities to optimize macular health.

Given the synergistic antioxidant properties of the three macular carotenoids, and that meso-zeaxanthin is a major carotenoid component in the foveal center where a lack of macular pigment is associated with increased risk of AMD, one can conclude that a supplementation with all three macular carotenoids may be more beneficial in preventing AMD. This is also supported by safety and toxicity assessment and clinical evidence studies.

Based on the synergistic anti-oxidant properties of lutein, zeaxanthin and meso-zeaxanthin and that meso-zeaxanthin is a critical carotenoid in the central fovea moreover, XanMax® 10:1:1 was formulated. Our unique analytical technique validates the presence of lutein, trans & meso-zeaxanthin in our product and ensures batch to batch consistency.

HPLC chromatogram of XanMax® 10:1:1 containing Lutein & Zeaxanthin

This paper is intended to provide scientific and educational information only. It is not intended for use to promote or sell any product. These statements have not been evaluated by the Food and Drug Administration. Consumption of XanMax® is not intended for use to diagnose, treat, cure or prevent any disease.
**XanMax® and its applications**

Lifestyle modification with nutritional supplements adequately laced with anti-ageing phytonutrients which are natural anti oxidants and anti inflammatory ingredients is the key. XanMax® containing enhanced ratio of Zeaxanthin in combination with Lutein, could be an ideal dietary supplement for ‘Healthy ageing’.

Research involving cell cultures, animal models, and human studies has been directed to the potential anti-oxidant role of XanMax®, containing Lutein and Zeaxanthin, in protecting against several chronic diseases, particularly age-related macular degeneration (AMD), cataract, and diabetic retinopathy, cardiovascular disorders and in neuro-protection.

During ageing, skin is one of the vital organs that gets affected. Research studies on our XanMax® formulations and literature review have shown that oral and topical administration demonstrates a remarkable improvement in skin elasticity, hydration, skin lipid levels, contributing to Healthy skin.

---

**References**

1. Keyvan Koushan et. al., The Role of Lutein in Eye-Related Disease, Nutrients 2013, 5, 1823-1839.
2. Seddon JM et. al., Dietary carotenoids, vitamin A,C and E, and advanced age-related macular degeneration. Eye Disease Control Study Group. JAMA, 1994, 272 (18): 1413-20

---

For further information please contact XanMax®’s European Distributor Geelawson

www.geelawson.com | marketing@geelawson.com

---

XanMax® is manufactured by Katra Phytochem (India) Pvt., Ltd.

For further information please contact Katra Phytochem (India) Pvt., Ltd.

www.katraphyto.com | marketing@katraphyto.com

---

This paper is intended to provide scientific and educational information only. It is not intended for use to promote or sell any product. These statements have not been evaluated by the Food and Drug Administration. Consumption of XanMax® is not intended for use to diagnose, treat, cure or prevent any disease.

XanMax® is manufactured by Katra Phytochem (India) Pvt., Ltd. ©2017 All rights reserved