Meso-Zeaxanthin (MZ): Current Perspectives and New Insights

Abstract

Recent in vitro, in vivo and human studies indicate that dietary meso-zeaxanthin (MZ) may be of benefit in maintaining vision and provides antioxidant and anti-inflammatory support. MZ is a macular carotenoid with additional protective effects such as antioxidant, anti-mutagenic, singlet oxygen quenching and inhibitory effects on specific CYP450 isoenzymes, potential to induce phase II enzymes, chemo-protective and anti-carcinogenic effects. MZ scavenges superoxide, hydrosulf, nitric oxide diphenyl-2-picylhydrazyl (DPPH) radical, and 2, 2'-azino-bis (3-ethylbenothiazoline-6-sulfonic acid) radicals, inhibits tissue lipid peroxidation and prevents cellular damage. MZ increase the levels of antioxidant enzymes like catalase, superoxide dismutase and glutathione peroxidase. MZ supplementation will provide benefit for maintaining visual performance in health and disease. Recent data strongly support the observation that adequate macular carotenoid supplementation may significantly reduce the risk of macular degeneration and age related macular degeneration mediated by reactive oxygen species. This review will focus on the effect of macular carotenoids and MZ in the context of carotenoids’ unique visual health including antioxidant and anti-inflammatory properties.

Keywords

Meso-zeaxanthin; Macular carotenoids; Antioxidant; Eye health

Abbreviations

MZ: Meso-Zeaxanthin; L: Lutein; RZ: RR-Zeaxanthin; AMD: Age-related Macular Degeneration; MD: Macular Degeneration; NAFL: Non-Alcoholic Fatty Liver; NASH: Nonalcoholic Steatohepatitis; DPPH: Diphenyl-2-Picylhydrazyl; ABTS: 2, 2'-Azino-bis (3-Ethylbenothiazoline-6-Sulfonic acid); GST: Glutathione-S-Transferase; UDPGT: Uridine Diphosphate Glucuronyl Transferase; SGPT: Serum glutamic-oxaloacetic transaminase; SGOT: Serum glutamic-Pyruvic Transaminase

Introduction

Visual function

Healthy eyes and vision are the most important factors for quality of life. The morphological and physiological changes in visual function occur in aging due to several risk factors such as diet, family history, smoking, exposure to environmental affluents and chronic conditions. Visual changes occur at any age. The common morphological and physiological changes include average refractive error, decrease in corneal sensitivity, transmission of light and volume of the anterior chamber. In addition, pupil size decreases in dim light conditions. With aging, the ocular lens becomes more yellow and absorbs more light, significantly changing the amount and quality of light reaching the retina. The amplitude of accommodation (expressed in diopters), photoreceptor density and visual field size decrease with age as well. The vitreous commonly detaches from the retina after the age of 60. Lipofuscin (aging pigment) accumulates in the retina with age; other retinal cell layers become disordered and visual acuity declines, with age. During aging the ability to adapt to darkness is slowed, the ability to recover visual sensitivity from bright lights and to see rapid flicker worsens and one experiences more glare problems. Over two decades of research suggest the role of macular carotenoids and its correlation with macular pigment to improve visual performance in eye health and disease. Lutein (L), RR-Zeaxanthin (RZ) and Mesozeaxanthin (MZ) carotenoids that have antioxidant properties and cells are protected from oxidative stress and free radicals.

The three carotenoids involved in eye health, especially macular health, are 3R, 3’S-zeaxanthin or meso-zeaxanthin (MZ), 3R, 3’R-zeaxanthin or RR-zeaxanthin (RZ) and lutein (L). These carotenoids are distributed in the macula at epicenter, mid- periphery, and periphery areas, respectively. The protective substance in the macula is macular pigment (MP). Macular pigment (MP) consists of L, RZ and MZ macular carotenoids. Macular pigment acts as an antioxidant in the eye to help maintain healthy vision. It has unique properties such as blue light filtering from different energy sources, and it modulates other photo-physical properties. It is important to consider fortification of xanthophylls as antioxidants for infant and adult eye health. Macular carotenoids augment MP and enhance visual performance in aging.

The physiological and morphological changes includes anatomical structure or function in the eye and vision includes changes in co ordinations, wrong field assessment and observing the aids very closely and reading the materials very close to the eyes, unusual observational positions which will interfere with daily activities.

Macular degeneration

Macular degeneration (MD) is one of the causes for blindness. It is the third most important cause of blindness in the world. More people will go blind from retinal degeneration and visual...
impairment than from cataracts and glaucoma combined. Recent observational and epidemiological data suggest that 60 million people may be affected with blindness. In the U.S it was reported that over 14 million children (aged 12y) and older people developed retinal degeneration and visual health problems with visual acuity of 20/50. It is possible to bring changes in over 11 million Americans to visual acuity of 2040 with refractive correction. The Center for Disease Control (CDC) predicts that number will double by 2020 [1]. This number increases every year by 1 million in North America. According to Wong and Colleagues [2], age-related macular degeneration (AMD) will affect 119 million people by 2020 and expected to affect 288 million people in 2040.

Age, sex, race, smoking, family history, high blood pressure, prolonged sun exposure and chronic disease conditions are risk factors for macular degeneration. Other risk factors include oxidative stress causing free radicals, high energy UVA, LED blue light sources, such as the sun, television, tablet, cell phones, which exposure may cause photochemical reactions and cellular changes in the macula. Release of free radicals in the macula changes the rate of metabolism due to oxidative stress factors. The release of free radicals from oxidative stress damages the retina, retinal pigment and photo-layers of the retina. Changes due to cellular damage in the retina due to oxidative stress factors leave a brownish pigment (called lipofuscin), which accumulates in Bruch’s membrane (BM) and forms drusen. The formation of drusen is the first early sign of dry macular degeneration (DMD). This will lead to loss of field of vision including blurred central vision or a blind spot at any age. The oxidative stress factors that may increase inflammation and cellular changes in the macula causing macular degeneration are seen in Figure 1. The changes in the eye can be determined by an ophthalmologist and the progression of AMD will be categorized as Early AMD (dry AMD) condition, based on several changes and abnormalities including soft drusen, pigment epithelial changes, changes in macula, fatty depots in the retina and thinning of macula, while late AMD (Wet AMD) is characterized by geographic atrophy or neo-vascular AMD and or pigment epithelial detachment.

Macular carotenoids

The biological activity and placement of each of the macular carotenoids - lutein, RR-zeaxanthin and meso-zeaxanthin - in the eye tissue is of interest. The biological role of macular carotenoids includes limiting chromatic aberration at the fovea by filtering out blue light [3], quenching of singlet oxygen or free radicals produced in the retina, protecting the macula from the photo toxicity of blue light [4,5], and protecting against photo-oxidation of lysosomal membranes and reducing the risk of AMD [6].

Xanthophylls are yellow or orange pigments in food and plants. Over 600 carotenoids are observed in nature, but not all are useful for health and disease condition (Table 1). The carotenoids in the retina are lutein (L), RR-zeaxanthin (RZ) and meso-zeaxanthin (MZ). Meso-zeaxanthin (MZ, Figure 2) comprises 33% of the total carotenoid content in the macula. RR-zeaxanthin (RZ) is concentrated in the macular region, whereas lutein (L) is dispersed throughout the entire retina. Meso-zeaxanthin concentration is greatest at the peak and decreases rapidly away from the peak [7]. Substantial quantities of carotenoids are also present in the infant retina. Recent research also suggests that carotenoids from food sources together may play a crucial role in retinal health and visual function in infants [8-11] and abnormal carotenoids may lead to oxidative stress and inflammation [12-15]. Carotenoid levels between individuals vary with advancing age [16]. Figure 1 also shows how macular carotenoids prevent MD and progression of early and late AMD risk.

Dietary Intake of macular carotenoids

The dietary data from National Health and Nutrition Examination Survey (NHANES) 2003-2004 reported that the average intakes of lutein and zeaxanthin isomers from dietary sources are in the range of 1 to 2 mg/day (approximately 0.01 to 0.03 mg/kg body weight/day) and it was observed that their intakes are low compared with the average requirement of 10 mg

Figure 1: Potential mechanism of action of macular carotenoids.

Figure 2: Concentration of macular pigment in the human retina. Source: http://www2.fiu.edu/~landrumj/
L/d to maintain vision health. Studies reported efficacy in AMD is at a dose range of 6-40 mg L/day. In general, the ratio of lutein to zeaxanthin isomers in natural dietary sources is approximately 5:1 [17]. Numerous studies have demonstrated that increased dietary intake of lutein and zeaxanthin isomers is associated with increased macular pigment density (MPOD) in healthy adults [17,18]. A negative correlation was observed with dietary intake of macular carotenoids and with the risk of developing ocular diseases such as early and late age-related macular degeneration (AMD) and cataracts [19-21].

The major dietary sources of carotenoids (Lutein and Zeaxanthin) include yellow and orange fruits and vegetables and dark green leafy vegetables, such as spinach, kale, kiwi and yellow pepper, as well as eggs. The major dietary sources of MZ are shrimp shells, turtle fat 21 species of fish skin, as well as eggs in California and Mexico. MZ absorption may be increased by cooking these dietary sources in a small quantity of oil. MZ belongs to xanthophyll class fortified in chicken feed in Mexico for the last 10 years. Egg consumption in Mexico is approximately one egg/person/day and contributes to dietary intake of MZ in this population [17]. Further epidemiological data and observational studies are required to explore the intakes of dietary MZ in different population groups.

### Bioavailability

Bioavailability is defined as the extent and rate at which the active moiety enters systemic circulation, thereby accessing the site of action. MZ bioavailability was reported in volunteers (ten men and nine women) who received one capsule of 10.8 mg L, 1.2 mg RZ and 8.0 mg MZ/d. Blood was taken at baseline, day 10 and day 22. Concentrations of MZ at day 22 were two folds higher in women than men. A significant variation exists in the absorption of carotenoids and gender response [22]. Although the uptake of L into plasma appeared to be slightly depressed by the presence of MZ, it is difficult to draw a conclusion based on this study that MZ inhibit L absorption. Further, recent studies suggest no inhibition of L or other carotenoids by MZ in intervention studies reported by Nolan et al. and his research group. MZ supplementation increased MZ levels in blood and improved visual performance by increasing MPOD (Table 2). In another study, a significant correlation of MPOD across its spatial profile was observed after supplementation with a formulation containing high doses of MZ (17 mg) in combination with L and RZ compared to L/RZ supplementation alone. There was an improvement in contrast sensitivity with the supplementation of macular carotenoids [23]. Bioavailability of an ingredient is largely determined by the properties of the dosage form and quality of the product, which depend partly on its design and manufacturing process. Further dose response and tissue absorption studies are required.

### Table 1: Macular carotenoids structure and concentration distribution in plasma and retina [48], HK Ophthalmol 2000, 4(1).

| Carotenoid     | Ave. Plasma Concentration (µmol/L) | Retinal Concentration | Structure |
|----------------|------------------------------------|-----------------------|-----------|
| Lutein         | 0.25                               | Central: 17 Medial: 20 Outer: 22 | 59 58%    |
| Meso-zeaxanthin| Trace                              | Central: 10 Medial: 3 Outer: 2 | 15 15%    |
| RR-zeaxanthin  | 0.06                               | Central: 12 Medial: 9 Outer: 7 | 28 27%    |
Meso-Zeaxanthin (MZ): Current Perspectives and New Insights

Biological functions of meso-zeaxanthin

MZ has substantial antioxidant, anti-inflammation and immune functions. Although MZ is primarily associated with visual function and its protective role in eye health, recent studies show a number of additional properties of the macular carotenoid which need further attention, such as anti-cancer/tumors potential, liver health protection and healthy metabolism effects.

Eye health: MZ is able to protect against chronic and cumulative eye damage through its capacity to filter the most energetic and potentially damaging wavelengths of visible light and to neutralize free radicals produced by oxidative stress [24]. In vitro and in vivo studies of this carotenoid showed that it has significant antioxidant potential [25]. Table 2 provides a summary of MZ supplementation studies in combination with L/RZ. Human clinical studies demonstrate MZ’s protective role for eye health and defense against AMD [26-31]. Overall, in these studies, MZ was observed in blood after supplementation. Doses used in these studies vary from 8 mg to 17 mg/d. Improvements in visual performance with MZ supplementation was observed in human clinical trials (Table 2). MZ is absorbed into the serum in visual performance with MZ supplementation was observed after one month MZ supplementation in mice, antioxidative enzymes such as catalase, superoxide dismutase, glutathione and glutathione reductase levels in blood and liver significantly increased. Antioxidative enzyme levels of glutathione peroxidase and glutathione-S-transferase were also found to be increased in the liver in a dose dependent manner [25]. These results suggest antioxidative properties of MZ, and further long term human studies are required to explore its role in health and disease conditions.

Hepatic fibrosis is one of the liver disease during which excess connective tissue will build in liver and up-regulate cytochromes. CYP2E1 is one of the cytochrome gene proteins involved in oxidative stress process and CYP2E1 upregulates collagen I in rat hepatic stellate cells [36]. This process leads to the depletion of antioxidative enzymes and inhibits the antioxidant system. The gene protein cytochrome CYP2E1 upregulates by high fat/low-carbohydrate diets [37]. Over-expressions of cytochrome gene proteins have a significant role in the inhibition of antioxidative system process. Antioxidants play a role in the prevention of conditions associated with liver health and disease [37-39].

Preliminary evidence suggests that oral administration of MZ at different doses significantly increases tumor latency period. In 3-methylcholanthrene (3-MC) control group, animals started developing sarcoma in week 6. However, animals treated with 3-MC and MZ (50 and 250 mg/kg bw) started developing sarcoma only on 15th and 18th week, respectively. Survival of tumor-bearing mice was significantly increased by MZ treatment. Animals in 3-MC control group started dying due to tumor burden from the 9th week. All animals treated with MZ (50 and 250 mg/kg bw) were found to be alive even after 16 and 20 weeks, respectively. Oral administration of MZ inhibited different CYP450 isoenzymes like CYP1A1 (PROD), CYP1A2 (MRD), and CYP2B1/2 (EROD), which are involved in carcinogen metabolism in a dose-dependent manner. Moreover, levels of phase II enzymes like UDP-glucuronyl transferase and glutathione-S-transferase, which are involved in detoxification of carcinogens, were significantly increased by MZ treatment.
Table 2: Summary of MZ human clinical trials.

| Author            | Condition          | Gender | Age     | Study Design | N     | Study Duration | L (mg) | RRZ (mg) | MZ (mg) | Dosage Forms | Outcome Measures                  | Interpretation                                                                 |
|-------------------|--------------------|--------|---------|--------------|-------|----------------|--------|-----------|---------|-------------|-----------------------------------|--------------------------------------------------------------------------------|
| Bone et al. [26]  | Healthy Subjects   | 8M/2F  | 30.5 ± 10.9 y | Parallel; RPC | Supplement: 10 | 120 d | 5.5       | 1.4     | 14.9        | Softgels                          | Serum macular carotenoids, MPOD                                                |
|                   |                    |        | 5M/4 F  |              | Placebo: 9  |       | 0         | 0       | 0          |                                    | • Presence of all three carotenoids in actives supplementation.               |
|                   |                    | 22.1 ± 3.6 y |             |              |                       |       |           |         |             |                                    | • MPOD, measured at 460 nm, rose at average rate of 0.59 +/- 0.79 mi-           |
|                   |                    |         |          |              |                     |       |           |         |             |                                    | aborbance unit/day in supplement group.                                      |
|                   |                    |         |          |              |                     |       |           |         |             |                                    | • MZ absorbed into serum following ingestion. Supplement group significantly   |
|                   |                    |         |          |              |                     |       |           |         |             |                                    | different from placebo group for whom the average rate was -0.17 +/- 0.42     |
|                   |                    |         |          |              |                     |       |           |         |             |                                    | mi-absorbance units/day.                                                      |
|                   |                    |         |          |              |                     |       |           |         |             |                                    | No adverse events reported                                                   |
| Thurnham et al. [22] | Healthy Subjects | 9F     | 27 ± 7 y  | Open label, non randomized | 19         | 22 d [baseline, day 10 and day 22] | 10.8   | 1.2       | 8        | Softgels     | Serum macular carotenoids           | Plasma concentrations per mg dose at day 22 suggested that RR-zeaxanthin      |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | (0.088 μmol/l per mg) was about 50 % more actively retained by the body than  |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | lutein (0.056 μmol/l per mg) (difference not significant in women) and 2.5-3.0x   |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | more than MZ (0.026 μmol/l per mg).                                          |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | • MZ concentrations at day 22 were 2.5x higher in women than men. Plasma      |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | responses from lutein and RR-zeaxanthin in Lutein Plus lower than literature  |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | values. Plasma uptake appeared to be slightly depressed by presence of MZ.    |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | • Plasma concentrations of beta-carotene were depressed by about 50% at day 10 |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | and about 35% at day 22.                                                      |
| Connolly et al. [30] | Healthy Subjects | 9F     | 27 ± 7 y  | Open label, non randomized | 19         | 22 d [baseline, day 10 and day 22] | 10.8   | 1.2       | 8        | Softgels     | Serum macular carotenoids           | Plasma concentrations per mg dose at day 22 suggested that RR-zeaxanthin      |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | (0.088 μmol/l per mg) was about 50 % more actively retained by the body than  |
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|                   |                    |        |          |              |                     |       |           |         |             |                                    | more than MZ (0.026 μmol/l per mg).                                          |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | • MZ concentrations at day 22 were 2.5x higher in women than men. Plasma      |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | responses from lutein and RR-zeaxanthin in Lutein Plus lower than literature  |
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|                   |                    |        |          |              |                     |       |           |         |             |                                    | • Plasma concentrations of beta-carotene were depressed by about 50% at day 10 |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | and about 35% at day 22.                                                      |
|                   |                    |        |          |              |                     |       |           |         |             |                                    | No adverse events reported                                                   |

No adverse events reported
| Connolly et al. [29] | Healthy Subjects | M/F | 18-61 y | RPC | intervention, 1 group: 22 or placebo, P group: 22 | 6 mos [Bl, 3 mos and 6 mos] | 5.9 | 1.2 | 10.6 | Capsule | Serum macular carotenoids, spatial profile of MP optical density | • Subjects supplemented with MZ, L and Z exhibited significant increases in serum concentrations of these carotenoids and subsequent increase in central MPOD. |
|---------------------|------------------|-----|---------|-----|-------------------------------------|-----------------------------|-----|-----|------|---------|-----------------------------------------------|-------------------------------------------------|
| Nolan et al. [31]   | Healthy Subjects with atypical MP spatial profiles | M/F | 18-60 y | Randomized Trial | Group 1: (n = 10) 8 wks [baseline, 4 wks and 8 wks] | 10 | 2 | 0 | Softgels | MP at 0.25°, 0.5°, 1°, 1.75° and 3° | • No statistically significant increase in MP at any eccentricity in Group 1 (p > 0.05, for all eccentricities). • Trend towards increase in MP at all eccentricities in Group 2, with significant increase at 0.25° and 0.5° (p = 0.000 and p = 0.016, respectively). • Statistically significant increase in MP at 0.25° in Group 3 (p = 0.005), but at no other eccentricity (p > 0.05, for all other). • Typical central peak of MP can be realized in subjects with atypical spatial profiles following supplementation with preparation containing all three macular carotenoids, but not with a supplement lacking MZ. |
| Meagher et al. [28] | Normal 54 total Normal 27, AMD 27 20 M, 34 F | 60 ± 10 y | Randomized Trial Double blind | Group 1: 21° 8 weeks [baseline, 4 weeks and 8 weeks] | 20 | 2 | 0 | Softgels | Serum macular carotenoids | • Response as average of 4- and 8-week concentrations (saturation plateau). • Serum L increased significantly in Group 1 (0.036 μmol/l per mg (269 %); P= 0.001) and Group 2 (0.079 μmol/l per mg (340 %); P= 0.001), with no significant change in Group 3 (0.006 μmol/l per mg (7 %); P= 0.466). • Serum RRZ increased significantly in Group 1 (0.037 μmol/l per mg (69 %); P= 0.001) and Group 2 (0.015 μmol/l per mg (75 %); P= 0.001), with no significant change in Group 3 (-0.0002 μmol/l per mg (−6 %); P= 0.384). • Serum MZ increased significantly in Group 1 (0.0094 μmol/l (absolute value); P= 0.015), Group 2 (0.005 μmol/l per mg; P= 0.001) and Group 3 (0.004 μmol/l per mg; P< 0.001). |
| Loughman et al. [31] | Normal Subjects | 19 M, 17 F | 51 ± 13 y | Single-masked placebo-controlled study | Group I: 11a | 6mos [Baseline, 3 mos and 6 mos] | 20 | 2 | 0 | Softgel | MPOD and visual performance |
|---------------------|----------------|------------|-----------|----------------------------------|-------------|-----------------------------------|-----|---|----|---------|---------------------------|
|                     |                |            |           |                                  |             |                                   |     |   |    |         | At 3 and 6 months, statistically significant increase in MPOD at all eccentricities (other than the most peripheral 3° location) in group 2 (P < 0.05 for all), whereas no significant increase in MPOD was demonstrable at any eccentricity for subjects in groups 1 and 3. |
|                     |                |            |           |                                  |             |                                   |     |   |    |         | Statistically significant improvements in visual performance measures including visual acuity and contrast sensitivity with and without glare were observed for group 2 only. |
|                     |                |            |           |                                  |             |                                   |     |   |    |         | Only mesopic contrast sensitivity at one spatial frequency improved significantly by 6 months (P < 0.05) for group 1. |
|                     |                |            |           |                                  |             |                                   |     |   |    |         | No improvements in any parameters of visual performance were observed for subjects supplemented with placebo (P > 0.05 for all). |
|                     |                |            |           |                                  |             |                                   |     |   |    |         | No adverse events reported |

| Loughman et al. [27] | AMD M/F 18-60 y | Randomized trial | Group I: 23 | 36 mos | 20 | 2 | Softgel | MPOD, visual function-visual acuity, letter contrast sensitivity |
|---------------------|-----------------|-----------------|-------------|--------|-----|---|---------|---------------------------------------------------------------|
|                     |                 |                 | Group II: 24 |        | 10 | 2 | 10      | A statistically significant increase in MPOD observed in all measured eccentricities with exception in group I at 1.7. |
|                     |                 |                 | Group III: 20 |        | 3  | 2 | 17      | In group I, statistically significant improvements in letter contrast sensitivity were only seen at 1.5 cpd. |
|                     |                 |                 |             |        |     |         | In Group 2, statistically significant improvements in letter CS were seen at all spatial frequencies except at 2.4 cpd. |
|                     |                 |                 |             |        |     |         | In Group 3, statistical significant improvement in letter CS was seen at 6 cpd, 9 cpd, and 15 cpd. |
|                     |                 |                 |             |        |     |         | 51 of 46 subjects exhibited no change in AMD grade over the three years. |
|                     |                 |                 |             |        |     |         | No subject exhibited beyond stage 8 on the AREDSII step severity scale. |
|                     |                 |                 |             |        |     |         | No adverse events reported |

| Sabour-Pickett et al. [23] | Early age-related macular degeneration | Randomized Trial | Group I: 17 | 12 mos | 20 | 2 | Softgel | MPOD, visual function-visual acuity, letter contrast sensitivity |
|---------------------------|----------------------------------|-----------------|-------------|--------|-----|---|---------|---------------------------------------------------------------|
|                           |                                  |                 | Group II: 21 |        | 10 | 2 | 10      | Statistically significant increase in MPOD at all measured eccentricities in Group 2 (P ≤ 0.005) and in Group 3 (P < 0.05, for all), but only at 1.75° in Group 1 (P = 0.018). |
|                           |                                  |                 | Group III: 14 |        | 3  | 2 | 17      | Statistically significant (P < 0.05) improvements in letter contrast sensitivity at all spatial frequencies (except 1.2 cycles per degree) in Group 3, and at low spatial frequencies in Groups 1 and 2. |
|                           |                                  |                 |             |        |     |         | No adverse events reported |

L: Lutein; RRZ: RR-Zeaxanthin; MZ: Meso-zeaxanthin; R: Randomized; DB: Double Blind; SB: Single Blind; P/C: Placebo Controlled a Group 1; b Group 2; c Group 3; * No MZ was present in the serum baseline.

Source: Juturu V (2014) Advances in Ophthalmology & Visual Systems. Aug 2014 (Submitted).
Results indicated that the mode of action of MZ may be through inhibition of carcinogen activation coupled with enhancement of the detoxification process. MZ may also inhibit promotion phases of carcinogenesis by its antioxidant activity [40].

CYP inhibition is an important consideration for the development of novel therapeutic agents. Clinically important mechanism-based CYP inhibitors include anti-bacterial, anticancer agents, anti-HIV agents, anti-hypertensives, sex steroids and their receptor modulators [41].

Effect of MZ on antioxidant enzymes

Oxidative stress plays a central role in liver disease pathogenesis and progression, and the use of antioxidants has been proposed as therapeutic agents. MZ is one of the macular carotenoids and acts as an antioxidant to protect against cellular damage from free radicals. Recent reports suggest that oxidative stress markers, tissue lipid peroxidation, conjugated dienes and tissue hydroperoxides were enhanced with paracetamol treatment. In an animal study, paracetamol was compared to a control group, and MZ supplementation to these animals improved the level of antioxidative enzymes. In an alcoholic induced animal model study, the levels of antioxidative properties and antioxidant enzymes improved with MZ supplementation (glutathione and antioxidant enzymes, superoxide dismutase, catalase and glutathione peroxidase) in liver tissue. The hepatoprotective potential of MZ was observed in these animals [42]. These results suggest a role of MZ as an antioxidant. Recent human studies also confirmed MZ supplementation will protect liver and renal functions including maintenance of normal lipid profile and hematological indicators [29]. Further long term human studies are required to confirm these findings.

Potential mechanism of action

Visual performance: MZ is required for macular pigmentation for healthy eye function. MZ may reduce the production of reactive oxygen species (ROS), and MZ inhibit spheroxidation and reduces oxidative injury. MZ also filters blue light in the macula. [27].

Antioxidant activity: The mode of action of MZ may be through enhancement of the detoxification process, reducing enzymes such as Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic-pyruvic transaminase (SGPT). Toxin blockade at the membrane level inhibit membrane peroxidation. MZ has been shown to reduce hepatotoxins in the body and to stimulate glutathione, a powerful antioxidant that can help protect liver cells, support detoxification enzymes more effectively and protect the liver from toxins, including certain drugs such as acetaminophen (Tylenol), which can cause liver damage in high doses, have antioxidant and anti-inflammatory properties, and may help the liver repair itself by growing new cells [25,40,42]. In preclinical studies, one month MZ supplementation increases antioxidant enzymes in mice [43,44]. Laboratory studies show that MZ scavenges superoxide, hydroxyl, nitric oxide and DPPH and ABTS radicals, as well as inhibits tissue lipid peroxidation in vitro in a concentration dependent manner [25].

The possible anti-carcinogenic activity of MZ and its effect on phase I carcinogen metabolizing enzymes was studied. The result indicated that MZ could significantly inhibit different CYP450 isoenzymes (CYP1A1, CYP1A2, and CYP2B1/2), which are involved in the activation of many known chemical carcinogens. This inhibitory effect could be one of the mechanisms of action of MZ against chemical carcinogenesis. Another major mechanism of protection against chemical carcinogenesis is mediated by the induction of enzymes involved in the detoxification of chemical carcinogens. Phase II enzymes such as glutathione-S-transferase (GST) and uridine diphospho glucuronyltransferase (UDPGT) are the major enzymes involved in the detoxification process. Transcriptional control of the expression of phase II enzymes is mediated through the antioxidant response element (ARE) found in the regulatory regions of their genes. The binding of transcription factor Nrf2 to ARE in response to treatment with certain phytochemicals appears to be essential for the induction of prototypical phase II enzymes [45].

Safety/Toxicity

MZ is nontoxic and generally regarded as safe. The European Food Safety Authority (EFSA) concludes MZ is a food constituent [46]. Standard protocols of toxicity were used to study the acute and chronic toxicity in animals. There were no adverse events in animal and human studies and no-observed-adverse-effect-level (NOAEL) of MZ was >200mg/kg/day in animal studies. No cytotoxicity, no mutagenesis and no genotoxicity were observed with MZ administration [47-50]. In humans, no adverse events were reported in any of the human clinical trials (Table 2).

Conclusion

MZ, one of the three macular carotenoids, improves visual function and has been shown to be very effective in the early stage of AMD. It is a very strong antioxidant to protect against oxidative stress. In addition to supplementation of macular carotenoids, smoking cessation diet, regular physical activity and protective eye wear such as sunglasses and wide brimmed hats may help reduce the risk of AMD, and regular eye examinations can result in the early detection of early and late age related macular degeneration. The preservation of vision at any age and quality of life are related to a healthy diet including the macular carotenoids, physical exercise and the reduction of exposure time of eyes to high energy sources. Early macular carotenoid interventions that are geared to improve visual performance in healthy and high risk populations are imperative.

Conflict of Interest

Employee, OmniActive Health Technologies Inc.

References

1. http://www.cdc.gov/
2. Wong WL, Su X, Li X, Cheung GMC, Klein R, et al. (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet Global Health 2(2): 106-116.
3. Nussbaum JJ, Pruett RC, Delori FC (1981) Historic perspectives. Macular yellow pigment. The first 200 years. Retina 1(4): 296-310.
Meso-Zeaxanthin (MZ): Current Perspectives and New Insights

4. Handelman GJ, Dratz EA (1986) The role of antioxidants in the retina and retinal pigment epithelium and the nature of pro-oxidant-induced damage. Adv Free Radical Bio Med 2(1): 1-89.

5. Kirschfeld K (1982) Carotenoid pigments: their possible role in protecting against photodamage in eyes and photoreceptor cells. Proc R Soc Lond B Biol Sci 216(1202): 71-85.

6. Brunk UT, Wihlmair U, Wrigstad A, Roberg K,Nilsson SE (1995) Accumulation of lipofuscin within retinal pigment epithelial cells results in enhanced sensitivity to photo-oxidation. Gerontology 41(2): 201-212.

7. Bone RA, Landrum JT, Friedes LM, Gomez CM, Kilburn MD, et al. (1997) Distribution of lutein and zeaxanthin stereoisomers in the human retina. Exp Eye Res 64(2): 211-218.

8. Bone RA, Landrum JT, Tarsis SL (1985) Preliminary identification of the human macular pigment. Vision Res 25(11): 1531-1535.

9. Choi SS, Doble N, Hardy JL, Jones SM, Keltner JL, et al. (2006) In vivo imaging of the photoreceptor mosaic in retinal dystrophies and correlations with visual function. Invest Ophthalmol Vis Sci 47(5): 2080-2092.

10. Izumi-Nagai K, Nagai N, Ohgami K, Satofuka S, Ozawa Y, et al. (2007) Macular pigment lutein is antiinflammatory in preventing choroidal neovascularization. Arterioscler Thromb Vasc Biol 27(12): 2555-2562.

11. Zimmer JP, Hammmond BR Jr (2007) Possible influences of lutein and zeaxanthin on the developing retina. Clin Ophthalmol 1(1): 25-35.

12. Jewell VC, Mayes CB, Tubman TR, Northrop-Clewes CA, Thurnham DI (2004) A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. Eur J Clin Nutr 58(1): 90-97.

13. Hammmond BR (2008) Possible role for dietary lutein and zeaxanthin in visual development. Nutr Rev 66(12): 695-702.

Vogelsang A, van Lingen RA, Slootstra J, Dikkeschei BD, Kollen BJ, et al. (2009) Antioxidant role of plasma carotenoids in bronchopulmonary dysplasia in preterm infants. Int J Vitam Nutr Res 79(5-6): 288-296.

15. Perrone S, Longini M, Marzocchi B, Picardi A, Belleni CV, et al. (2010) Effects of lutein on oxidative stress in the term newborn: a pilot study. Neonatology 97(1): 36-40.

16. Handelman GJ, Dratz EA, Reay CC, van Kuijk JG (1988) Carotenoids in the human macula and whole retina. Invest Ophthalmol Vis Sci 29(6): 850-855.

17. Thurnham DI (2007) Macular zeaxanthins and lutein -- a review of dietary sources and bioavailability and some relationships with macular pigment optical density and age-related macular disease. Nutr Res Rev 20(2): 163-179.

18. Whitehead AJ, Mares JA, Danis RP (2006) Macular pigment: a review of current knowledge. Arch Ophthalmol 124(7): 1038-1045.

19. Barker FM (2010) Dietary supplementation: effects on visual performance and occurrence of AMD and cataracts. Curr Med Res Opin 26(8): 2011-2023.

20. Lien EL, Hammmond BR (2011) Nutritional influences on visual development and function. Prog Retin Eye Res 30(3): 188-203.

21. Wong IV, Koo SC, Chan CW (2011) Prevention of age-related macular degeneration. Int Ophthalmol 31(1): 73-82.

22. Thurnham DI, Tremel A, Howard AN (2008) A supplementation study in human subjects with a combination of meso-zeaxanthin, (3R,3'R)-zeaxanthin and (3R,3'R,6'R)-lutein. Br J Nutr 100(6): 1307-1314.

23. Sabour-Pickett S, Beatty S, Connolly E, Loughman J, Stack J, et al. (2014) Supplementation with three different macular carotenoid formulations in patients with early age related macular degeneration. Retina 34(9): 1757-1766.

24. Krinsky NL, Landrum JT, Bone RA (2003) Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 23: 171-201.

25. Firdous AP, Preethi KC, Kuttan R (2010) Antioxidant potential of meso-zeaxanthin in a semi synthetic carotenoid. Food Chem 119 (3): 1096-1101.

26. Bone RA, Landrum JT, Cao Y, Howard AN, Alvarez-Calderon F (2007) Macular pigment response to a supplement containing meso-zeaxanthin, lutein and zeaxanthin. Nutr Metab (Lond) 4: 12.

27. Loughman J, Beatty S, Howard A, Connolly E, Nolan JM (2012) Effect of carotenoid supplementation on macular pigment optical density and visual performance in normal observers: the most vision trial. Invest Ophthalmol Vis Sci 53: E-Abstract 3376.

28. Meagher KA, Thurnham DI, Beatty S, Howard AN, Connolly E, et al. (2013) Serum response to supplemental macular carotenoids in subjects with and without age-related macular degeneration. Br J Nutr 110(2): 289-300.

29. Connolly EE, Beatty S, Loughman J, Howard AN, Louw MS, et al. (2011) Supplementation with all three macular carotenoids: response, stability, and safety. Invest Ophthalmol Vis Sci 52(12): 9207-9217.

30. Connolly EE, Beatty S, Thurnham DI, Loughman J, Howard AN, et al. (2010) Augmentation of macular pigment following supplementation with all three macular carotenoids: an exploratory study. Curr Eye Res 35(4): 335-351.

31. Nolan JM, Akkali MC, Loughman J, Howard AN, Beatty S (2012) Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment. Exp Eye Res 101: 9-15.

32. Cheng KS, Tang HL, Chou FT, Chou JW, Hsu CH, et al. (2009) Cytokine evaluation in liver cirrhosis and hepatocellular carcinoma. Hepatogastroenterology 56(93): 1105-1110.

33. Misra UK, Bradford BU, Handler JA, Thurnham RG (1992) Chronic ethanol treatment induces H202 production selectively in pericentral regions of the liver lobule. Alcohol Clin Exp Res 16(5): 839-842.

34. Firdous AP, Sinhu ER, Ramnath V, Kuttan R (2010) Anti-mutagenic and anti-carcinogenic potential of the carotenoid meso-zeaxanthin. Asian Pac J Cancer Prev 11(6): 1795-1800.

35. Lopez-Saiz CM, Suarez-Jimenez GM, Plascencia-Jatomea M, Burgos-Hernandez A (2013) Shrimp lipids: a source of cancer chemopreventive compounds. Mar Drugs 11(10): 3926-50.

36. Nieto N, Friedman SL, Greenwel P, Cederbaum AI (1999) CYP2E1-mediated oxidative stress induces collagen type I expression in rat hepatic stellate cells. Hepatology 30(4): 987-996.

37. Robertson G, Leclercq I, Farrell GC (2001) Nonalcoholic steatosis and hepatic stellate cells. Hepatology 30(4): 987-996.

38. Niskanen LK, Salonen JT, Nyysönen K, Uusitalo MI (1995) Plasma lipid peroxidation and hyperglycaemia: a connection through hyperinsulinaemia? Diabet Med 12(9): 802-808.
39. Chitturi S, Farrell GC (2001) Etiopathogenesis of nonalcoholic steatohepatitis. Semin Liver Dis 21(1): 27-41.

40. Firdous AP, Sindhu ER, Ramnath V, Kuttan R (2013) Anticarcinogenic activity of meso-zeaxanthin in rodents and its possible mechanism of action. Nutr Cancer 65(6): 850-856.

41. Zhou S, Chan E, Lim LY, Boelsterli UA, Li SC, et al. (2004) Therapeutic drugs that behave as mechanism-based inhibitors of cytochrome P450 3A4. Curr Drug Metab 5(5): 415-442.

42. Firdous AP, Sindhu ER, Kuttan R (2011) Hepato-protective potential of carotenoid meso-zeaxanthin against paracetamol, CCl4 and ethanol induced toxicity. Indian J Exp Biol 49(1): 44-49.

43. Sindhu ER, Firdous AP, Preethi KC, Kuttan R (2010) Carotenoid lutein protects rats from paracetamol-, carbon tetrachloride- and ethanol-induced hepatic damage. J Pharm Pharmacol 62(8): 1054-1060.

44. Sindhu ER, Preethi KC, Kuttan R (2010) Antioxidant activity of carotenoid lutein in vitro and in vivo. Indian J Exp Biol 48(8): 843-848.

45. Talatay P, Fahey JW (2001) Phytochemicals from Cruciferous Plants Protect against Cancer by Modulating Carcinogen Metabolism. J Nutr 131: 3027S-3033S.

46. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2010) Scientific Opinion on the substantiation of health claims related to meso-zeaxanthin and maintenance of vision (ID 2096) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 8(2): 1483.

47. Howells O, Eperjesi F, Bartlett H (2011) Measuring macular pigment optical density in vivo: a review of techniques. Graefes Arch Clin Exp Ophthalmol 249(3): 315-347.

48. Thurnham DI, Howard AN (2013) Studies on meso-zeaxanthin for potential toxicity and mutagenicity. Food Chem Toxicol 59: 455-463.

49. http://www.howard-foundation.com/Covance%20Final%20Report-Mesozeaxanthin-SP.pdf

50. Loughman J, Nolan JM, Howard AN, Connolly E, Meagher K, et al. (2012) The impact of macular pigment augmentation on visual performance using different carotenoid formulations. Invest Ophthalmol Vis Sci 53(12): 7871-7880.