Oasis TEARS **VISION®**

DIETARY SUPPLEMENT

The ingredients in the formula of Oasis TEARS VISION® were carefully chosen for their safety and efficacy in helping to support optimal visual health.

KEY POINTS

1. Vision loss is a major global health concern.
2. It is critical to address all types of vision changes as they often progress to serious disease.
3. Age related vision changes including dry eye disease and vision loss have been associated with oxidative stress and inflammation.
4. Age-related macular degeneration (AMD) onset and progression are associated with low levels of carotenoids, antioxidant vitamins, and omega-3 fatty acids, and reduced intake of fruit, vegetables, and fish.
5. Intake of antioxidant and anti-inflammatory compounds may be beneficial in supporting vision health.
6. The ingredients in the formula of Oasis TEARS VISION® were carefully chosen for their safety and efficacy in helping to support optimal vision health.

INTRODUCTION

The prevalence of vision loss regardless of cause increases with age, it is estimated that 37 million Americans older than 50 years are affected and 25% of those older than 80 years are affected. The impact of the vision loss can significantly impact quality of life as approximately 7% of adults 65 years and older report disability related to impaired vision.[1] The increasing prevalence of vision loss and impairment worldwide has made eye health a global public health priority. The Lancet Global Health Commission on Global Eye Health defines eye health as "the state in which vision, ocular health, and functional ability are maximized, thereby contributing to overall health and wellbeing, social inclusion, and quality of life". [2]

The four major age-related eye diseases are age-related macular degeneration (AMD), cataracts, diabetic retinopathy (DR), and glaucoma. Although over a third of adults experience significant vision loss, not all vision impairment is associated with disease. [3] According to the World Report on Vision for 2020, globally there are an estimated 596

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million people with distance vision impairment and a further 510 million, or 22% of people over 50 years of age, with uncorrected presbyopia. [2,4,5] Straylight is known to increase after the age of 45, almost doubling by age 65.[6] Greater straylight increases glare, impacts vision quality, leads to loss of color contrast and can impact one's ability to drive a vehicle safely, especially at night.[7]

Myopia is the leading cause of distance vision impairment globally affecting an estimated 22.9% of the world population. Prevalence is higher in some populations, particularly in Asian populations and appear to be affecting younger people at an increased rate globally.[8] It is estimated that the prevalence will increase substantially by 2050 especially in these at-risk populations.[4] This is of great concern because myopia has the potential to cause vision impairment by myopic macular degeneration or its comorbidities, cataract, retinal detachment, and glaucoma.[9] The increased prevalence is thought to be due to several factors including decreased time outdoors, increased time spent in "close up" activities such as screen viewing and a diet low in fruits and vegetables.[4,10]

Presbyopia results in a loss of "up close vision" that begins around age 40 and is usually associated with aging. While there is not one agreed upon definition, it is said that it "occurs when the physiologically normal age-related reduction in the eyes focusing range reaches a point, when optimally corrected for distance vision, that the clarity of vision at near is insufficient to satisfy an individual's requirements".[11] It is a global problem affecting one quarter of the world's population. The exact etiology is unknown though most theories agree that it involves anterior central lens capsule steepening during accommodation. Clinically, patients report a progressively difficult ability to read fine print and at the usual distance.[12] While age related changes in vision are inevitable, allowing them to go unmanaged by either corrective glasses, contact lenses or surgery can increase the likelihood of a progression to cataract formation. Furthermore, protection of the eyes from harmful light and chemicals can help to maintain visual health. This is supported by the knowledge that photoreceptors are exposed to extensive oxidative stress in the form of light and oxygen.[13] Additionally, ultraviolet light exposure and smoking are associated with accelerated cataract formation.[14,15] There is no agreed upon effective strategy to prevent the progression from age related vision changes to cataract. However, several have been suggested, such as dietary modification and supplementation with a specific focus on antioxidants. [16]

THE ROLE OF DIET

Age-related vision changes including dry eye disease and vision loss have been associated with oxidative stress and inflammation, suggesting that intake of antioxidant and anti-inflammatory compounds may be beneficial in supporting vision health. [17] A high intake of fruits and vegetables has been associated with the preservation of vision. The beneficial effects have been linked to phytochemicals such as polyphenols and carotenoids, specifically their antioxidant anti-inflammatory effects. [18,19]

AMD onset and progression are associated with low levels of carotenoids, antioxidant vitamins, and omega-3 fatty acids, and reduced intake of fruit, vegetables, and fish. [20] The Age-Related Eye Disease Studies (AREDS) demonstrated that high intake of vitamin A, vitamin, C, zinc, copper, and carotenoids could reduce the progression of AMD by approximately 25%. This supports studies that demonstrate that age-related cataract formation is linked to vitamin and carotenoid status [21,22] and to micronutrient status. [22,23] Some cohort studies have associated vitamins A, C, and E, lutein, zeaxanthin, and β-carotene with reduced cataract risk, however several randomized-controlled trials (RCTs) have reported inconsistent results. [23] Observational cohort studies suggest that regular consumption of nitrate-rich leafy green vegetables is associated with reduced risk of glaucoma development. [24] There is also evidence that vitamins A and C are protective against glaucoma. [25] Observational studies indicate that maintaining adequate levels of omega-3 fatty acids (i.e., with 2 servings/week of fish) or a low glycemic index diet may be particularly beneficial for early AMD and that higher levels of carotenoids may be protective against neovascular AMD. [21] A systematic review found that components of dark-green leafy vegetables, specifically glutathione, flavonoids, and nitric oxide, were significantly associated with decreased risk for glaucoma. [26]

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(Figure #1: Image of Maqui Berry)

MAQUI BERRY

Maqui berry (Aristotelia chilensis) is grown in southern Chile and is rich in anthocyanins, particularly delphinidin-3,5,-O-diglucoside (DS) which is reported to have potent antioxidant activities. [27,28] Anthocyanins are pigments that contribute to the color of many fruits, particularly berries. They are water soluble and are divided into 6 classes: malvidin, delphinidin, petunidin, pelargonidin, cyanidin, and peonidin. The position and number of the hydroxyl and methyl groups in the skeleton dictate the radical scavenging activities of anthocyanins, and DS contains 3 hydroxylations in the B ring and thus has demonstrated the highest antioxidant activity among the classes.[29] Maqui berry is high in DS and therefore has strong antioxidant capabilities.

Several clinical studies have been conducted in support of the antioxidant benefits of maqui berry. In one study, supplementation of 450 mg maqui berry containing 162mg anthocyanins for 4 weeks improved lipid peroxidation in healthy overweight adults. [30] Similarly, an in vitro study showed that maqui berry extract led to a reduction of nitric oxide (NO) production, inhibition of the induction of nitric oxide synthase (NOS) and TNF-alpha, and induction of interleukin 10 (IL-10) gene expression. [31] Additionally, a randomized, double-blind, placebo-controlled trial was conducted to determine the effect of supplementation with a maqui berry supplement on eye dryness and fatigue. Seventy-four subjects aged 30-60 years experiencing eye dryness, eye fatigue and > 4h of visual display terminal (VDT) work daily were randomly assigned to receive one 60 mg capsule of maqui berry daily or placebo for 4 weeks. The group taking the supplement demonstrated significantly more lacrimal fluid production in both eyes compared to the placebo group before VDT load (playing a video game) at 4 weeks after intake. After VDT load, the reduction of subjective symptoms for eye fatigue, bothersome ocular symptoms and stiff shoulders were significantly improved in the treatment group compared to the placebo group. The authors concluded that, supplementation of 60 mg of MaquiBright® per day for 4 weeks reduced eye dryness and seemed to alleviate eye fatigue. [32] Similarly, a pilot study of 13 healthy subjects with moderately dry eyes was conducted. Subjects were assigned to receive either 30 mg or 60 mg maqui berry extract for 60 days. Both groups showed significantly improved tear fluid volume after 30 days of treatment. The Schirmer's test was used to assess tear production and showed an increase from a baseline of 16.3±2.6 mm to 24.4±4.8 mm ($P<0.05$) with 30 mg of maqui berry

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extract daily and from 18.7±1.9 mm to 27.6±3.4 mm with 60 mg (P<0.05). Following treatment with 30 mg maqui berry extract for an additional 30 days, tear fluid volume dropped slightly to 20.5±2.8 mm, but the improvement in tear fluid volume persisted with 60 mg treatment at 27.1±2.7 mm after 60 days treatment (P<0.05 vs. baseline). The results of this study demonstrate that daily intake of maqui berry extract at both 30 mg and 60 mg doses showed significant improvement in tear fluid volume in 30 days. [33]

ASTAXANTHIN

Carotenoids are associated with a variety of physiological effects according to their polarity which dictates how they configure with cellular membranes.[34] Lycopene and β-carotene are non-polar and can cause disruption of the membrane structure and oxidation of lipids in any membrane that is high in polyunsaturated fatty acid. In contrast, astaxanthin is polar, and therefore maintains the structure of the membrane.[34] Astaxanthin is a strong antioxidant, it is 550 times more potent than vitamin E. It is 11 times more powerful as a singlet oxygen quencher than β -carotene.[35] This may be directly related to its structure [36] and account for its increased potency compared to other carotenoids such as β -carotene [35,37] vitamin C, zeaxanthin, lutein and canthaxanthin. [38] Astaxanthin contains a conjugated polyene chain at the center and hydroxy and keto moieties on each ionone ring. This unique structure allows it to link the cell membrane from the inside to the outside and helps explain why its antioxidant effects are superior to other carotenoids. [39,40] Astaxanthin has three stereoisomers: (3R,3'R), (3R,3'S) and (3S,3'S). Astaxanthin produced by natural sources such as the microalgae Haematococcus pluvialis (H. pluvialis) consists of the (3S,3'S) stereoisomer. It has been shown that astaxanthin

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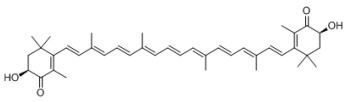

(Figure #2: Structure of Astaxanthin)

functions as an antioxidant by directly scavenging cellular reactive oxygen sub-species (ROS) that are contained in the phospholipid membrane and, at the cell surface, protecting the mitochondrial redox state and functional integrity and activating antioxidant signaling. [41-44] The precise cellular mechanism by which it exerts its antioxidant effect is not known.

Many age-related visual disorders are said to be related to oxidative and inflammatory processes. [45] Diets high in carotenoids including lutein and zeaxanthin have been associated with a decreased risk for such conditions mostly because they are concentrated in the macula of the eye. [46,47] Astaxanthin is similar in structure to these carotenoids, however demonstrates stronger antioxidant activity in restoring cells after UVA light damage. [48] Whether that translates directly to ocular health is unclear, but some evidence does support its role in visual health.

A study of 49 subjects over 40 years of age taking either 4 mg or 12mg of astaxanthin for 28 days reported significantly improved far visual acuity and shortened accommodation time. [49] Similarly, Sawaki et al. reported significantly improved deep vision and critical flicker fusion of healthy adult male volunteers taking astaxanthin. [50] Nagaki et al. found that 6 mg of astaxanthin per day improved eye fatigue in VDT workers. [51] It was also shown that astaxanthin might increase retinal capillary blood flow in the eyes of healthy subjects. [52]

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ZEAXANTHIN & LUTEIN

The xanthophyll compounds, lutein and zeaxanthin, are found throughout the retina and the macula of the eye. They are found in high concentrations in fibers in the fovea in the retina of the eye, where visual acuity is highest. Lutein and zeaxanthin accumulate in the retina to form the macular pigment, where their chemical structure allows the macular pigment to absorb and filter blue light. This is the main mechanism by which they are thought to aid in maintaining eye health. [53-59] The macular pigment has several functions that help improve visual performance. Macular pigment optimizes visual performance in non-diseased eyes because its ability to filter blue light reduces chromatic aberration (the refraction of difference wavelengths), which can enhance visual acuity and contrast sensitivity. Macular pigment may also reduce discomfort associated with glare and improve visual acuity. By absorbing blue light, the macular pigment also protects the underlying cell layer from oxidative damage. [53-57,60]

Lutein and zeaxanthin have antioxidant activity, which also protect the eye against photooxidative damage caused by sunlight. Oxidative stress can damage the retina by generating oxidation products of retinal fatty acids which then can trigger an inflammatory response and promote the initiation and progression of AMD. Digital devices, as well as fluorescent lamps, have light- emitting diodes (LED) that radiate blue wavelength light (430 nm). Research suggests that regular, prolonged exposure to the blue light emitted from backlit displays can damage retinal cells. [61] Short-wavelength blue visible light damages the retinas through a photooxidation reaction in which singlet oxygen and lipid peroxy radicals are produced by aging pigments called lipofuscin. Accumulation of lipofuscin is one of the most characteristic features of ageing observed in retinal pigment epithelial (RPE) cells [62]. Lutein and zeaxanthin supplementation has been shown to protect the fovea from blue light–induced damage in an animal model [53] and to modulate inflammatory response to photooxidation in retinal pigment epithelial cells. [60]

Epidemiological, clinical and interventional studies, plus numerous reviews, have established that lutein and zeaxanthin can benefit eye health. A comprehensive review of the epidemiological evidence of for the protection of eye health by lutein and zeaxanthin concluded that the macular pigment can be increased either by increasing the intake of foods that are rich in lutein and zeaxanthin, such as dark-green leafy vegetables, or by supplementation with lutein or

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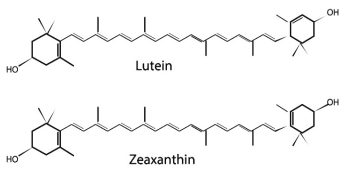

(Figure #3: Structures of Lutein and Zeaxanthin)

zeaxanthin. [56] Epidemiological studies suggest that adequate consumption of lutein and zeaxanthin might be associated with lower risk of AMD. [58] A prospective cohort study of 63,000 women and 38,000 men over 50 years of age, concluded that a higher intake of bioavailable lutein/zeaxanthin is associated with a long-term reduced risk of advanced AMD [63]. A systematic review and meta-analysis of 5 trials pertaining to lutein and zeaxanthin intake and risk of AMD reported that although dietary lutein and zeaxanthin is not significantly associated with a reduced risk of early AMD, high intake of these carotenoids may be protective against late AMD. [64] Similarly, a review of the effect of lutein and zeaxanthin on eye health reported that randomized, placebo-controlled clinical trials have demonstrated that xanthophyll supplementation increases macular pigment levels, improves visual function, and decreases the risk of progression to late AMD. In addition, observational studies have shown that there is a correlation between increased dietary intake of lutein and zeaxanthin and higher serum levels, which are also associated with lower risk of age-related macular degeneration (AMD), especially late AMD. [57] A systematic review and meta-analysis of 20 randomized controlled trials investigating the effect of lutein, zeaxanthin and meso-zeaxanthin on macular pigment optical density (MPOD) in both healthy subjects and patients with AMD, concluded that lutein, zeaxanthin and meso-zeaxanthin supplementation improved MPOD both in AMD patients and healthy subjects with a dose-dependent manner. The dosage of lutein, zeaxanthin and/or meso-zeaxanthin in the intervention groups in various trials ranged from 0 mg/day to 20 mg/day. The duration of intervention and follow-up ranged from 8 weeks to 2 years. [65]

In a study of 150 healthy subjects supplemented with 10 mg lutein plus 2 mg zeaxanthin, macular pigment density was significantly related to serum lutein and zeaxanthin concentrations with increased macular pigment density also significantly correlated with improved glare disability, photostress recovery, and chromatic contrast. [66] In a 12-month supplementation study, 115 young, healthy subjects were randomly assigned either 10 mg of lutein FloraGLO® lutein combined with 2 mg of OPTISHARP® zeaxanthin daily or a placebo. Significant increases in serum lutein and zeaxanthin concentration were observed as a result of supplementation with FloraGLO® lutein and OPTISHARP® zeaxanthin compared to baseline and placebo treatment. This increase in blood levels of lutein and zeaxanthin was accompanied by significant increases

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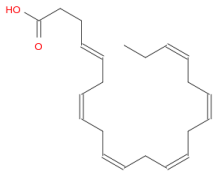
in MPOD values across the entire retinal area assessed. Glare disability energy (the amount of light that subjects could withstand and still see the target) increased in supplemented subjects but was not found to be significant compared to placebo. Furthermore, the study found a significant improvement in photostress recovery with lutein and zeaxanthin supplementation compared to baseline as well as to the placebo group. In addition to these visual performance parameters, this study also found that lutein and zeaxanthin supplementation resulted in significant improvements in chromatic contrast. [67]

DHA

Aside from the brain, the highest level of docosahexaenoic acid (DHA) in the human body is found in the eye, especially the retina. DHA is required for the process of transforming light into an electrophysiological signal and for the regeneration of the light sensitive pigment in the retina – rhodopsin. [68] Biological effects of omega-3 fatty acids such as DHA and eicosapentaenoic acid (EPA) include protection against lipid peroxidation, anti-inflammatory activity, and support of endothelial function by promoting nitric oxide from endothelial cells. At high doses they also have anti-thrombotic activity. [69] EPA and DHA form part of the cell membrane, thereby modulating cellular function. Such changes in cellular function pertaining to cardiovascular health include vasodilation, anti-inflammatory activity, anti-arrhythmic effects, and reduction in pro-atherogenic cytokines. [70] DHA is found in significant amounts in the retinal and neuronal cell membranes due to its high fluidity and therefore DHA may have neuroprotective properties against brain aging and neurodegenerative diseases. [71,72] As a major lipid component of retinal photoreceptor outer membranes, EPA (as a precursor to DHA) may have a protective role against age-associated changes to eye health. [73]



(Figure #4: Structure of DHA)

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A triple-blind placebo-controlled randomized repeated-measures trial was conducted with 74 healthy participants, aged 45-77 years. Cognitive and visual acuity measures and plasma levels of DHA were determined at baseline and after 90 days of administration of either 1000 mg of tuna oil (252 mg DHA, 60 mg EPA and 10 mg vitamin E) or placebo (1000 mg soybean oil). There was a significant increase in plasma DHA and total N-3 plasma level in the treatment group compared to controls. However, no significant effects of DHA supplementation on cognitive functioning were found. For participants with corrected vision, the group receiving DHA were found to have significantly better right eye visual acuity posttreatment in comparison with the placebo group. [74] A Cochrane review including 34 RCTs involving 4314 adults from 13 countries published from February 2018 to October 2019 with dry eye of varying cause and severity reported "a possible role for long-chain omega-3 supplementation in managing dry eye disease, although the evidence is uncertain and inconsistent". [75] A pooled analysis of data from two double blind, placebo-controlled RCTS in Australia and New Zealand aimed at investigating the efficacy and safety of oral N-3 supplementation for the treatment of ocular surface inflammation was conducted. Participants were randomized to receive either an oral omega-3 supplement (n = 72) consisting of krill oil (945 mg/day EPA + 510 mg/day DHA), fish oil (1000 mg/day EPA + 500 mg/day DHA or 900 mg/day EPA + 600 mg/day DHA), or fish plus flaxseed oils (900 mg/day EPA + 600 mg/day DHA + 900 mg/day ALA); or an oral placebo supplement (n = 33, 1500 mg/day olive oil) for 3 months. They reported that omega-3 supplementation for 3 months significantly reduced intraocular pressure in normotensive adults. [76]

SUMMARY

Age related vision loss is common and can progress to serious disease and blindness. These changes are often related to oxidative stress, poor diet and the associated inflammation. Therefore, antioxidants may be beneficial to support eye health by offsetting excessive oxidation and thereby supporting a healthy inflammatory response. Adequate dietary intake is not always achievable therefore supplemental antioxidants may be beneficial. The ingredients discussed here were chosen for their efficacy as powerful antioxidants and for their ability to support optimal eye health throughout aging. The evidence clearly suggests they play a supportive role in maintaining eye health.

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(844) 820-8940 (USA Toll Free) | (909) 305-5400
oasis@oasismedical.com | www.oasismedical.com
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