



INCREASING THE FLORAGLO® LUTEIN INCLUSION LEVEL TO 10 MG FOR IMPROVED EYE HEALTH AND FUNCTION

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KEY CONCLUSIONS

- *Human studies published in peer-reviewed scientific journals show that daily consumption of 10 mg FloraGLO® Lutein may provide significant benefits to the eyes.*
- *10 mg/day FloraGLO Lutein intake has resulted in increased plasma lutein levels and greater macular pigment optical density (MPOD).*
- *Visual function improvements have been observed in both healthy individuals and in patients suffering from age-related macular degeneration (AMD) following ingestion of 10 mg FloraGLO Lutein daily.*
- *No toxicological side effects were reported in any of these studies.*

INTRODUCTION

The use of over-the-counter complementary medicines and supplements is growing as patients seek natural non-invasive approaches to improve health and reduce disease risk. Patients with age-related macular degeneration (AMD), the leading cause of visual impairments and blindness in industrialized countries among people \geq age 65 (15), may already be aware of the benefits of taking supplements such as lutein to increase their chances of retaining useful eyesight (10). However, medical professionals are increasingly called upon to recommend safe and effective approaches to healthy individuals experiencing age-related low vision or who are at risk for ocular disease. A recent market evaluation showed that overall medical professional and consumer awareness regarding what constitutes a safe and beneficial dosage regimen of lutein to improve visual function remains low (7).

Lutein, a major component of the macula lutea, is a carotenoid also deposited in the lens. It absorbs blue light and acts as a filter that may reduce photochemical damage caused by short-wavelength visible light (13,15,26). Additionally, lutein's powerful anti-oxidant properties may offer protection against light-induced oxidative damage by quenching reactive oxygen species (15,22). Chucair *et al.* have recently published the first direct evidence that lutein efficiently protects photoreceptors from cell death due to oxidative stress in rat retinal cell culture supplemented with lutein (6). Obana *et al.* observed that even healthy individuals experience a decrease in macular lutein over time and patients with age-related macular disease have lower macular lutein levels than healthy people (15).

Early lutein formulations developed using 2-6 mg of lutein were based upon historic epidemiological data showing reduced risks for AMD as lutein intake reached 6 mg (24). However, more recent randomized controlled trials in peer-reviewed scientific journals support increasing the lutein inclusion level above 6 mg to a 10 mg daily dosage.

Clinical studies show positive relationships between 10 mg FloraGLO Lutein supplementation and plasma concentrations of lutein, macular pigment accumulation, and visual function improvements in healthy individuals (14,20,23), as well as those affected by ocular diseases (2,17,18) such as AMD. In the widely anticipated Age-Related Eye Disease Study 2 (AREDS2) sponsored by the National Eye Institute, FloraGLO Lutein at 10 mg is the selected dosage of choice to investigate the potential benefits of lutein in reducing the progression of AMD in 4,000 AMD patients over a



5-year period. While there is a growing body of clinical evidence showing that daily consumption of 10 mg FloraGLO Lutein may provide significant benefits to the eyes, many commercially available products are not formulated or do not indicate directions for use consistent with the effective levels utilized in clinical trials (10).

Following are summaries of the scientific research (**Table 1**) that support increasing the inclusion level of FloraGLO Lutein in dietary supplements to a dosage of 10 mg/day.

LUTEIN LEVELS IN THE SERUM OR PLASMA

Early Evidence for a 10 mg Dosage

Research supplementing lutein at 10 mg per day has been published as early as 1995 and discussed further in 2006 by Khachik (11,12) and in 1999 by van het Hof (27) demonstrating changes in lutein levels in the serum or plasma. The former research conducted at the USDA Human Nutrition Research Center in Beltsville, MD, supplemented three subjects with 10 mg/day of FloraGLO Lutein (in olive oil) for 18 days (12).

Results: The serum lutein level increased significantly after one week of supplementation with FloraGLO Lutein. Similarly, ingestion of lutein resulted in increased concentration of lutein metabolites, suggesting lutein acts as an antioxidant in vivo. No toxicological side effects were reported.

The van het Hof group from Unilever Research Vlaardingen, Netherlands, examined the bioavailability of lutein from vegetables or a lutein-containing supplement. Subjects ingested a low-vegetable diet (containing approximately 3 mg dietary lutein/day), a high-vegetable diet (including spinach, broccoli, and other greens; equivalent to approximately 11 mg dietary lutein/day), or a carotenoid supplement (containing approximately 11 mg FloraGLO Lutein/day), for four weeks. Bioavailability of a variety of antioxidants was determined by measuring the change in serum levels (27).

Results: Low-vegetable intake increased serum lutein the least (0.068 ± 0.008 mmol/L), followed by a dramatic increase in serum lutein from high-vegetable intake (0.40 ± 0.027 mmol/L). However, serum lutein increased the most in the lutein supplemented group (0.64 ± 0.048 mmol/L), more than 50% higher than the high-vegetable group. This study supports the idea that FloraGLO Lutein may be more bioavailable than that from vegetable sources.

The data generated by these early studies provided the first evidence of the safety and greater bioavailability of lutein when taken as a food supplement at 10 mg/day.

Lutein Dose Response Studies

In 2006, Rosenthal *et al.* published a dose ranging study to examine the relationship between oral lutein supplementation and serum lutein concentration. Forty-five participants aged 60-91 with no AMD, large drusen, or advanced AMD were randomized to receive one of three lutein doses of lutein (2.5, 5, or 10 mg per day) for 6 months (21).

Results: Serum lutein levels peaked at 3 months with highly significant increases at all dosages at month 6. Mean serum lutein concentrations from baseline to 6 months in the 2.5, 5, and 10 mg groups increased 2-fold (19 to 35 $\mu\text{g/dl}$), 3-fold (18 to 59 $\mu\text{g/dl}$), and 4-fold (15 to 67 $\mu\text{g/dl}$), respectively (all $p < 0.001$). No toxicity was observed during or for 6 months after treatment. Rosenthal demonstrated the link between increasing doses of lutein supplements and significantly increased serum levels of lutein.

Khachik *et al.* investigated the distribution and metabolites of carotenoids in the serum following lutein supplementation (12).

Results: Khachik observed a highly significant ($p < 0.0001$) increase in metabolites of lutein that have previously been identified in ocular tissue. The levels of these oxidative metabolites of lutein were not correlated to dosage likely due to their rapid reversion back to the parent molecule consistent with the mode of action of antioxidants. While serum lutein concentration gradually declined, the mean concentration of lutein metabolites remained significantly higher than baseline six months after supplementation. In this study, lutein up to 10 mg/day did not interact with mean serum concentration of other dietary carotenoids identified and quantitated in the serum including α -carotene, β -carotene, phytofluene, phytoene, and lycopene, α -cryptoxanthin, and β -cryptoxanthin (12).



Rosenthal and Khachik concluded independently that older individuals with and without AMD can be safely administered 10 mg of lutein for 6 months with no toxicity or side effects. This research was part of the fundamental evidence supporting the use of a 10 mg dosage of FloraGLO Lutein in a large long-term supplementation trial to investigate the efficacy of lutein in reducing the risk of the developing advanced AMD (see AREDS2 below).

The Age-Related Eye Disease Study 2 (AREDS2)

The National Eye Institute, one of the Federal government's National Institutes of Health, initiated the first large randomized, double blind, placebo-controlled study specifically to evaluate the safety and eye health benefits of long-term lutein supplementation. By summer 2008, 80 participating US centers are expected to complete recruitment of 4,000 AMD patients for the study with each patient receiving treatment for 5 years. Patients are randomized to four possible treatments: 10mg/day of FloraGLO Lutein, 2 mg/day of zeaxanthin, 1 gm/day of omega 3 fatty acids, combined xanthophyll and omega 3 treatment, or placebo in combination with various forms of the original AREDS supplement (5).

The AREDS2 aims to refine the findings of the earlier NIH sponsored AREDS, which showed a 25% reduction in risk of advanced AMD associated with oral supplementation with high-dose antioxidants, vitamins and minerals (5). The rate of disease progression will be evaluated in individuals aged 50 to 85 years with advancing AMD categories 3 and 4 (bilateral large drusen, or large drusen in one eye and advanced AMD in the fellow eye). Other outcomes that will be simultaneously evaluated include effects of treatment on cognitive function, cataracts, cardiovascular disease, vision loss, visual function, and genetic risk factors. In this critical study, 10 mg of FloraGLO Lutein was the selected dosage of choice.

LUTEIN EFFECTS ON MPOD AND VISUAL FUNCTION

The amount of lutein and zeaxanthin present in the macula is referred to as the macular pigment optical density (MPOD). Of the lutein isomers found in human serum, only trans-lutein accumulates at the macula (3), the central portion of the retina upon which light is focused. Published studies suggest an inverse association between the levels of MPOD and the risk of developing AMD (4,17-19). MPOD has also been shown to contribute to visual function improvements in healthy individuals (15,23,26).

The LAST Study

The Lutein Antioxidant Supplementation Trial (LAST) conducted by Stuart Richer, M.D., from the Department of Veterans Affairs Medical Center in Chicago was a double-blind, placebo-controlled trial in which AMD patients were supplemented with 10 mg FloraGLO Lutein for 12 months (18,19). Ophthalmic testing of MPOD, glare recovery, near and distance visual acuity, and contrast sensitivity were conducted at baseline and at 4, 8, and 12 months. Activities of daily living, night driving, and glare recovery symptoms were evaluated on a rating scale used by the National Eye Institute. Subjects were also provided with an Amsler grid to monitor changes in central vision over time.

Results: In this study, AMD patients experienced a significant increase in MPOD after 10 mg FloraGLO Lutein supplementation alone or together with other antioxidants (36 % and 43% respectively; $p=0.03$ between baseline and final visit) (18). Patients in both groups receiving FloraGLO Lutein supplements were also found to have improvements in visual function (i.e. better photostress glare recovery, contrast sensitivity, visual acuity) and quality of vision over time. Further analysis of the LAST results revealed that among the study participants, MPOD continued to increase through the 12-month period of supplementation (19). Furthermore, it was found that patients with the lowest baseline values of MPOD exhibited the greatest increases in MPOD over time. Supplementation with 10 mg FloraGLO Lutein did not result in a plateau of accumulation even after 12 months of daily intake. The authors conclude that the improvements seen in this study may be due to lutein's dual role in the body as a blue light filter and antioxidant. The results of this landmark study also suggest that AMD may be a nutrition responsive disorder.



Table 1. Published human studies with 10 mg daily lutein supplementation

Study	Study population	Dosage & study design	Duration	Key outcomes
Richer <i>et al.</i> (2004, 2007) <i>n</i> = 59	AMD patients (LAST)	10mg/d <i>all-trans</i> lutein; randomized, controlled	12 months	Significant 36% increase in MPOD with no plateau after 12-mo lutein; lowest baseline MPOD showed greatest MPOD increases; no significant difference in adverse effects vs. placebo. (18,19)
Schalch <i>et al.</i> (2007) <i>n</i> = 92	Healthy adults (LUXEA)	10mg/d [followed by 20mg/d] <i>all-trans</i> lutein; randomized, controlled	6-12 months	7-fold increase in plasma lutein level and significant 14.5% increase in MPOD vs. Placebo ($p=0.04$). (23)
Stringham <i>et al.</i> (2008) <i>n</i> = 40	Healthy adults	10 mg/d lutein +2 mg zeaxanthin; interventional	6 months	Significant MPOD increase ($p=0.032$) and glare disability decrease ($p=0.002$) at 4 mo of lutein intake; MPOD significantly correlated with glare disability and photostress recovery. (26)
Parisi <i>et al.</i> (2008) <i>n</i> = 27	Non-advanced AMD vs. healthy controls (CARMIS)	10mg/d <i>all-trans</i> lutein in antioxidant formula; randomized, controlled	12 months	Significantly increased central retina responses at 6 and 12 months with lutein treatment ($p<0.01$). (17)
Chew <i>et al.</i> (2007) <i>n</i> = 4000	AMD patients (AREDS2)	10 mg/d <i>all-trans</i> lutein; randomized, controlled	60 months	5 year study of lutein + zeaxanthin, and omega 3 fatty acid effects on AMD, cataract, visual function, cognitive function, and genetic risk factors. (5)
Kvansakul <i>et al.</i> (2006) <i>n</i> = 32	Healthy adults (LUXEA)	10mg/d [followed by 20mg/d] <i>all-trans</i> lutein; randomized, controlled	6-12 months	Improved visual performance; significantly improved contrast acuity vs. placebo with lutein treatment ($p=0.001$); trends of decreased light scattering and wave front aberration. (14)
Rodriguez-Carmona <i>et al.</i> (2006) <i>n</i> = 92	Healthy adults (LUXEA)	10mg/d [followed by 20mg/d] <i>all-trans</i> lutein; randomized, controlled	6-12 months	Significant increase in central MPOD among supplemented vs. controls ($p<0.05$); predicted improvement in Red-Green sensitivity with increased MP density. (20)
Rosenthal <i>et al.</i> (2006) <i>n</i> = 45	Healthy adults	2.5, 5, or 10mg/d <i>all-trans</i> lutein; randomized, controlled	6 months + observed 6 months	Serum lutein increased at 1 mo, peaked at 3 mo, in significant dose-responsive manner (2x, 3x, 4x respectively, $p<0.001$); no toxicity observed. (21)
Khachik <i>et al.</i> (2006) <i>n</i> = 45	Healthy adults	2.5, 5, or 10mg/d <i>all-trans</i> lutein; randomized, controlled	6 months + observed 6 months	Significant ($p<0.0001$) increase in serum lutein and lutein metabolites previously found in ocular tissues. Supplemental lutein had no effect on mean serum concentration of other dietary carotenoids. (12)
Bahrami <i>et al.</i> (2006) <i>n</i> = 34	Retinitis pigmentosa patients	10mg/d [followed by 30mg/d] <i>all-trans</i> lutein; randomized, controlled	3 months [3months]	Statistically significant effect of lutein on visual field and some improved visual acuity. (2)
van het Hof <i>et al.</i> (1999) <i>n</i> = 54	Healthy adults	11 mg/day <i>all-trans</i> lutein	4 weeks	Serum lutein increased most in lutein supplement group, more than 50% higher than the high-vegetable group. (27)



The LUXEA Study

Over the past three years, several researchers have published results from the Lutein Zeaxanthin Eye Accumulation (LUXEA) Study, a randomized, double blind, placebo-controlled, 6-12 month supplementation trial (14,20,22,23). In this study, 92 healthy participants (aged 22-39 years) were supplemented with 10 mg/day FloraGLO Lutein for 6 months, zeaxanthin for 6 months, or a combination of the two (10 mg each/day) for one year. In an extension of the study, 14 participants received double doses of lutein or zeaxanthin (20 mg/day) for a second 6 month period. MPOD responses, plasma carotenoid levels, blue light sensitivity, and the visual function parameters of contrast acuity, light scattering, and wave front aberration were measured.

Results: Daily supplementation with 10 mg FloraGLO Lutein and zeaxanthin, alone or combined, resulted in increased lutein and zeaxanthin plasma concentrations as well as increased retinal MPOD. Schalch *et al.* reported that plasma lutein level increased 7-fold after one month and the peak concentration of plasma lutein was sustained over the six months of supplementation (23). Supplementation with 10 mg/day FloraGLO Lutein caused significant increases in MPOD of 15% at the fovea relative to placebo ($p=0.04$). No significant change in MPOD was observed with zeaxanthin supplementation (2.7%, $p>0.1$). There were no adverse effects related to treatment over the course of the study.

Kvansakul *et al.* investigated lutein supplementation and visual performance in 34 subjects from the LUXEA study group (14).

Results: A trend of improved contrast acuity thresholds (CAT) observed in subjects from all treatment groups was only significant in subjects supplemented with 10 mg/day FloraGLO Lutein ($p=0.001$). Decreasing trends of light scattering and wave front aberration were detected but not significant. These findings indicate that supplementation with 10 mg/day of FloraGLO Lutein may improve visual performance under low light conditions.

As part of the LUXEA investigation, Rodriguez-Carmona examined the extent to which MPOD affects color discrimination and color sensitivity (20). The objective was to assess whether yellow-blue (YB) color discrimination thresholds are attributed to differences in MPOD, both in the central and peripheral regions of the retina, as well as whether high MPOD contributes any benefits in other visual functions such as red-green (RG) color discrimination sensitivity.

Results: The data revealed a statistically significant ($p<0.05$) increase in MPOD among supplemented subjects relative to controls that was uniform within the central region of the fovea, over $\pm 8^\circ$ of eccentricity around the macula, a much larger area than previously described. While YB color thresholds were not associated with high MPOD in this evaluation, the authors suggest that MPOD may affect YB color discrimination differently under low light conditions. When cone photoreceptor change at detection thresholds was examined, their model unexpectedly predicted a marginal improvement on RG color threshold with increased MPOD. The authors conclude that increasing MPOD is more likely to improve contrast sensitivity when low light conditions prevail.

LUTEIN AND OTHER VISUAL FUNCTION STUDIES

Glare Recovery and MPOD

In a 2008 published study in the Journal of Optometry and Vision Science, Stringham and Hammond assessed the relationship between increasing MPOD and changes in visual performance under glaring light conditions by supplementing forty healthy subjects with 10 mg FloraGLO Lutein and 2 mg zeaxanthin for 6 months (26). Changes from baseline in MPOD, xenon light induced glare disability, and photostress recovery time were measured.

Results: Significant correlations between MPOD and glare disability ($r=0.76$) and photostress recovery ($r=0.80$) were established from subjects' baseline data. Significant increases in MPOD from baseline were observed at 4 mo ($p=0.032$) and 6 mo ($p=0.003$). Lutein and zeaxanthin supplementation provided significantly less glare disability at 4 mo ($p=0.002$) and 6 mo ($p=0.0001$) relative to baseline. This reduction in glare disability meant that subjects could tolerate a significantly greater amount of veiling glare and still detect a central target. After 6 months of lutein and zeaxanthin supplementation, average MPOD increased 39% and significantly reduced the deleterious effects of glare in terms of both disability threshold and recovery time.



Central Retinal Function

In this randomized controlled trial, Parisi *et al.* enrolled 27 non-advanced AMD patients (AREDS category 3) who consumed either an antioxidant treatment including 10 mg of FloraGLO Lutein or a placebo for 12 months (17). Components of the antioxidant treatment were vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), lutein (10 mg), astaxanthin (4 mg), zeaxanthin (1 mg) and copper (1 mg). The study measured response amplitude densities (RAD) in 5 retinal areas (fovea – midperiphery) using multifocal electroretinograms (mfERG). By averaging the bioelectrical responses, mfERG represents a method of evaluating the function of localized retinal and macular areas that can selectively detect a dysfunction in the central retina commonly observed in early AMD.

Results: Researchers found dysfunction in the central retina of these AMD patients compared to healthy controls at baseline. AMD patients treated with the antioxidant combination had highly significant increased central responses (RAD 0°-5°) at 6 and 12 months ($p < 0.01$). The findings suggest that in non-advanced AMD, the selective dysfunction in central retina may be improved by supplementation with antioxidants including 10 mg lutein daily.

Visual Acuity, Contrast Sensitivity, and Central Visual Field

Bahrami and colleagues at Johns Hopkins University School of Medicine investigated the effects of lutein supplementation on visual acuity, contrast sensitivity, and central visual field in 34 subjects diagnosed with retinitis pigmentosa. This randomized, double blind, cross-over, placebo controlled study supplemented subjects with placebo or 10 mg/day FloraGLO Lutein for 12 weeks followed by 30 mg FloraGLO Lutein/day for an additional 12 weeks (2).

Results: Although no significant difference in visual acuity or contrast sensitivity was detected in this population, there was a significant reduction in the natural decline of vision due to retinitis pigmentosa ($p < 0.05$) in subjects supplemented with FloraGLO Lutein. Significant improvements were also detected ($p = 0.038$) for visual field. No significant adverse events were documented while subjects consumed the FloraGLO Lutein supplements.

INCREASED LUTEIN LEVELS ARE SAFE

The safety of consuming lutein at dosages 10 mg per day and greater has been well documented. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) for the World Health organization (WHO) evaluated the safety of lutein and established an acceptable daily intake (ADI) level for lutein of up to two mg per day per kg body weight (8,9). This is equivalent to a daily intake of about 140 mg of lutein for a 70 kg person. Beyond the 10 mg supplementation trials described in the present technical literature, Shao and Hathcock provided evidence for the safe use of lutein up to 20 mg/day in their recent review of clinical research conducted between 1998 and 2006 (25). They reported on eight clinical studies in which 12 to 20 mg/d all-trans lutein was supplemented for periods ranging from 8 weeks to 2 years with no adverse effects.

CONCLUSION

Lutein is believed to offer optical and/or metabolic protection with its blue light filtering and antioxidant properties (23). Blue light and reactive oxygen species contribute to natural reductions in both macular pigment and visual acuity associated with aging and ocular impairments such as AMD. As the most recent clinical studies have shown, a daily intake of 10 mg FloraGLO Lutein may attenuate cumulative damage from chronic visible and UV light exposure and may reduce the risk of age-related eye disease. The efficacy demonstrated with a 10 mg daily dose of lutein provides good support e.g., for useful structure function claims made in the US related to improvements in visual acuity and function, and in the EU, for claims such as the registered opinion of France's food safety agency (AFFSA) that "lutein has proven antioxidant performance in the eye" (1).

Based on the available evidence, 10 mg of FloraGLO Lutein can be safely recommended by manufacturers for inclusion in their eye health supplements and multi-vitamin formulations and by medical professionals to patients for maintaining good eye health and promoting optimal eye function.

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