



Astaxanthin & Key Carotenoids: Creating Leading Edge Eye Healthcare Formulations

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Today's Presentation: Astaxanthin and Eye Healthcare

- Valensa is fully integrated on all key carotenoids for eye health care through it's partnership with Parry Nutraceuticals
 - Astaxanthin
 - Zeaxanthin
 - Lutein
- Valensa is the Astaxanthin Expert for:
 - Custom Formulations to meet all client needs
 - Supercritical CO2 Extraction
 - Omega-3 /Astaxanthin products with Krill and plant based Oils
 - Carotenoid Stabilization
 - Eye health / ARMD Patent Holder
 - Chain of custody from biomass through formulation



Carotenoids: Astaxanthin and Eye Health

Important Carotenoids Supplement(s) for Eye Health:

- Natural Zanthin® brand Astaxanthin uniquely protects the eye's fovea and cones. Astaxanthin is not found in vegetables. Found in algae and seafood. For eye health benefit: Supplementation necessary
- Zeaxanthin found in cone cells and fovea (common carotenoid found in nature, it is found in peppers, maize, kiwi, grapes, oranges, squash). Supplementation is optional but recommended



Lutein Supplementation optional

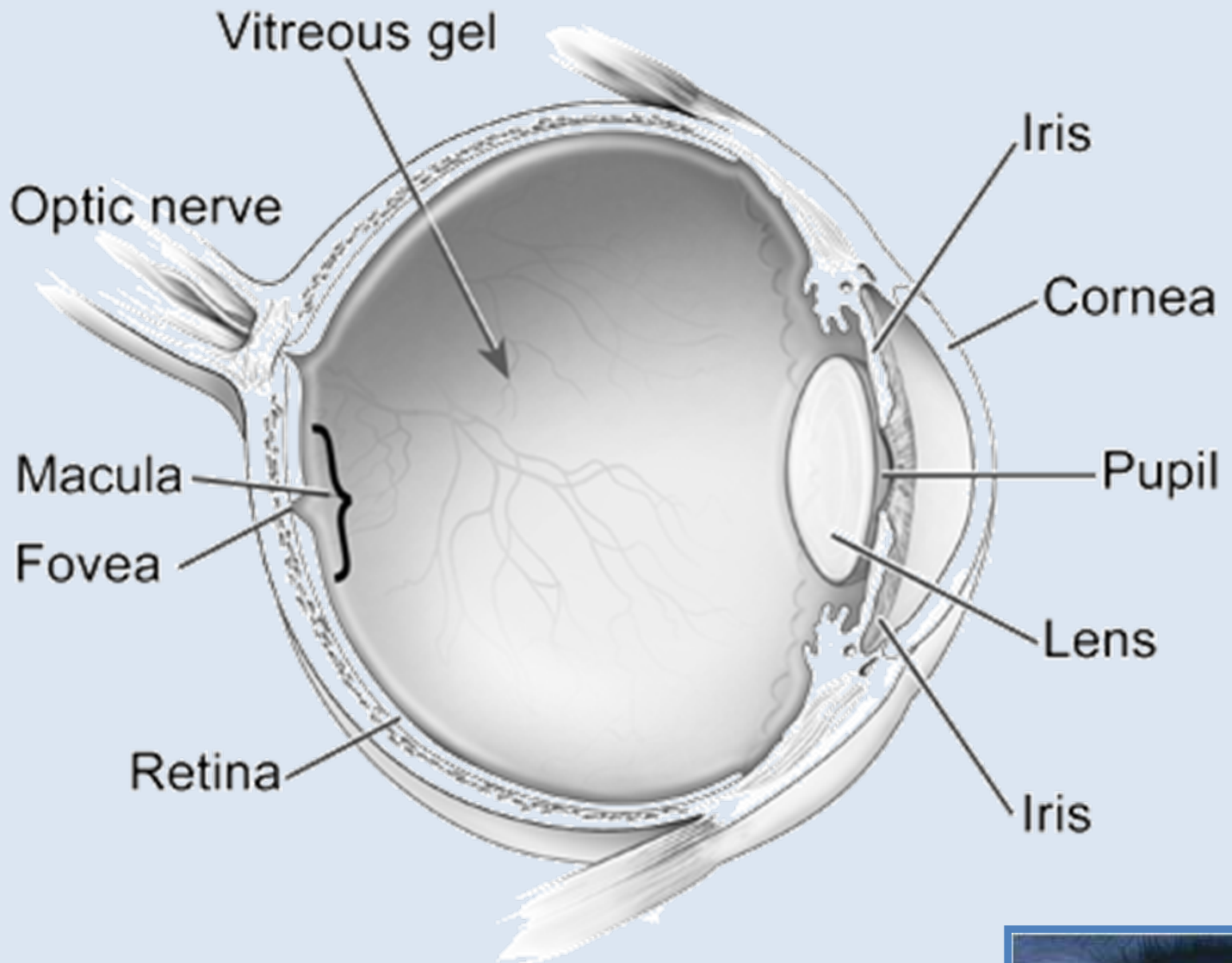
- Lutein: Very abundant in most vegetables, protective of rods
- Protects rods of the eye
- Marketing driven inclusion in formulas



Carotenoids Are Essential for Eye Health

- Protect against oxidative and free radical damage
 - Protects rods, cones and DHA containing membranes
 - Astaxanthin is a potent inhibitor of DHA oxidation. DHA content of the eye is 30% of dry mass.
- Must be able to cross blood eye barrier
 - Astaxanthin Lutein and Zeaxanthin
 - Cryptoxanthin benefits unknown
- Canthaxanthin –
 - Leads to canthaxanthin retinopathy (inclusions in the eye) – Not recommended





Macular degeneration: The leading cause of blindness for people over 50



Lutein is located in the outer peripheral macula rod cells

Density of Rods

Density of Cones

Macula

Macula

Retina

Fovea

Blood Vessels

Astaxanthin and Zeaxanthin are concentrated in the cone cells of the Fovea, the center of macula

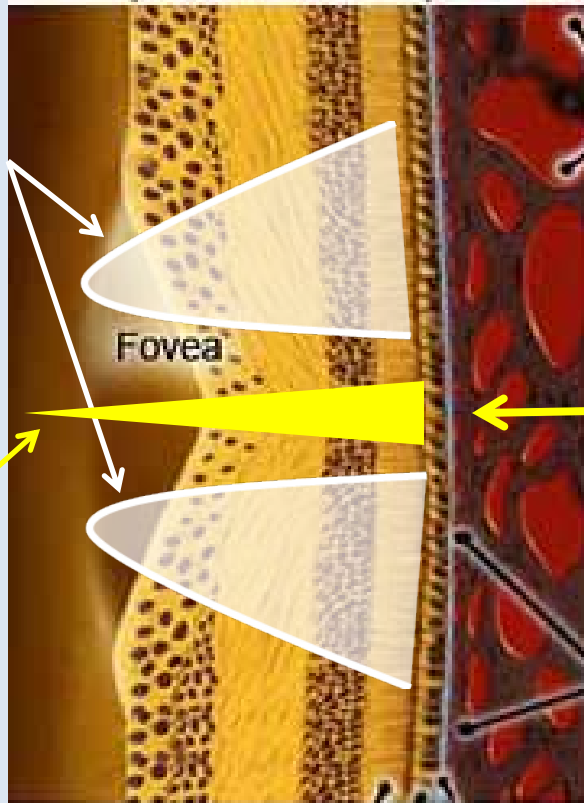
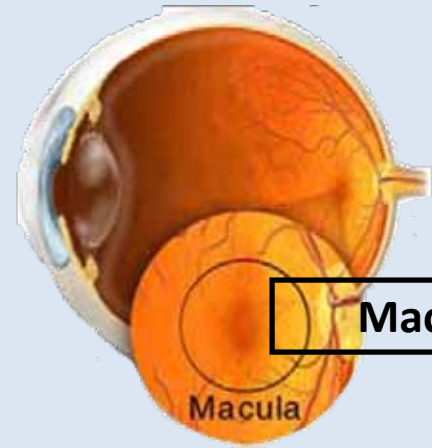
Capillarie

Rods and Cones

Bruch's Membra

DHA is found in the RPE.
DHA content of the eye is 30% of dry mass

Retinal Pigmented Epithelium (RPE)





The Major Causes of Blindness

- Age Related Macular Degeneration (ARMD)
- Cataracts



ARMD/Cataract Symptoms

- Loss of vision
- Drusen formation
- Blurred vision
- Loss of visual acuity
- Loss of dark vision
- Scotoma (black area in visual field)
- Visual distortion Micropsia & Macropsia

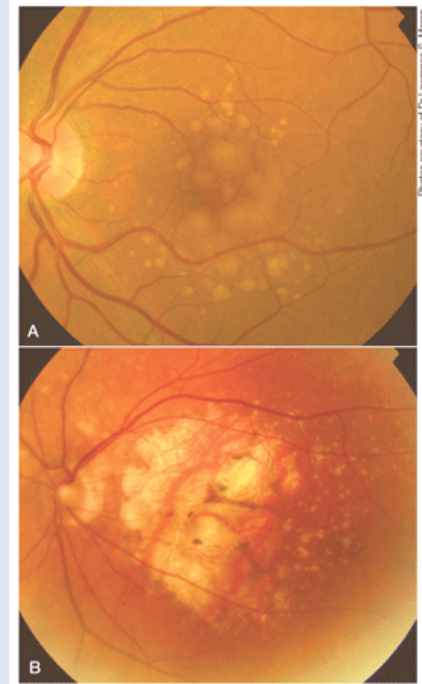


Figure 2—Macular changes in dry AMD. (A) Multiple large, soft drusen in early dry AMD. (B) Geographic atrophy with adjacent soft drusen in advanced dry AMD.

These can be arrested with natural Astaxanthin
Lutein and zeaxanthin

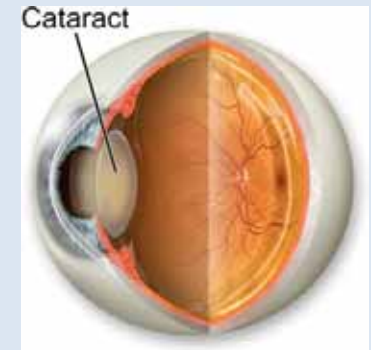


Age Related Macular Degeneration (AMRD)

- **Age Related Macular Degeneration (ARMD)**
 - Severe, irreversible vision loss in the elderly (effects 30% over age 55)
 - 60 Million suffer from ARMD Worldwide
 - 10 Million suffer blindness
 - 90% of these are Dry ARMD
 - Characterized by tiny yellow deposits in the macula and,
 - Death of the nerve cells in the macula area
 - Macula loses its yellow color turning white
 - Caused by cellular damage by free radicals and reactive oxygen species

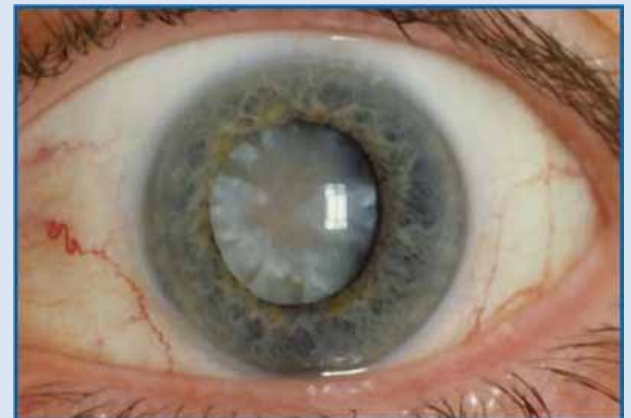


Cataracts



- Caused by lipid per-oxidation of the epithelial layer of the lens. A major lipid in the eye is DHA
- Worldwide over 10 Million procedures annually, estimate 19 million have cataracts
- 3 Million procedures annually, 20 million have cataracts in the US alone

Astaxanthin and natural Zeaxanthin
Are prophylactic agents





Zanthin[®]

The Super Carotenoid For Eye Health





Astaxanthin: Patent Protected for Eye Health

- US Patent 5,527,533, Patented in the EU and Germany
- Professor Mark Tso, University of Illinois, USA was first to prove that Astaxanthin crossed the Blood-Brain-Retina Barrier by direct measurement of retinal astaxanthin concentrations he demonstrated protection from photon induced damage of photo-receptors, ganglion and neuronal cell damage
- Valensa owns the rights to the Tso patent



Astaxanthin: Key Characteristics

- The most powerful carotenoid antioxidant
- No pro-vitamin A activity
- Soluble in Lipids, incorporates in cell membranes
- Crosses the Blood-Retina & Blood-Brain Barriers
- Singlet Oxygen Quenching
- Free Radical Scavenging
- Potent UVB Absorber
- Reduces DNA Damage
- Suppresses Inflammatory Markers



Astaxanthin: Suppresses Inflammatory Markers

- In induced uveitis (induced eye irritation), astaxanthin showed a dose dependent ocular anti-inflammatory effect by suppression of:
 - Nitrous Oxide Synthase
 - PGE-2
 - Tumor Necrosis Factor Alpha
 - C-Reactive Protein





Singlet Oxygen & Light Induced Free Radicals

The Major Causes of Eye & CNS Related Diseases such as:

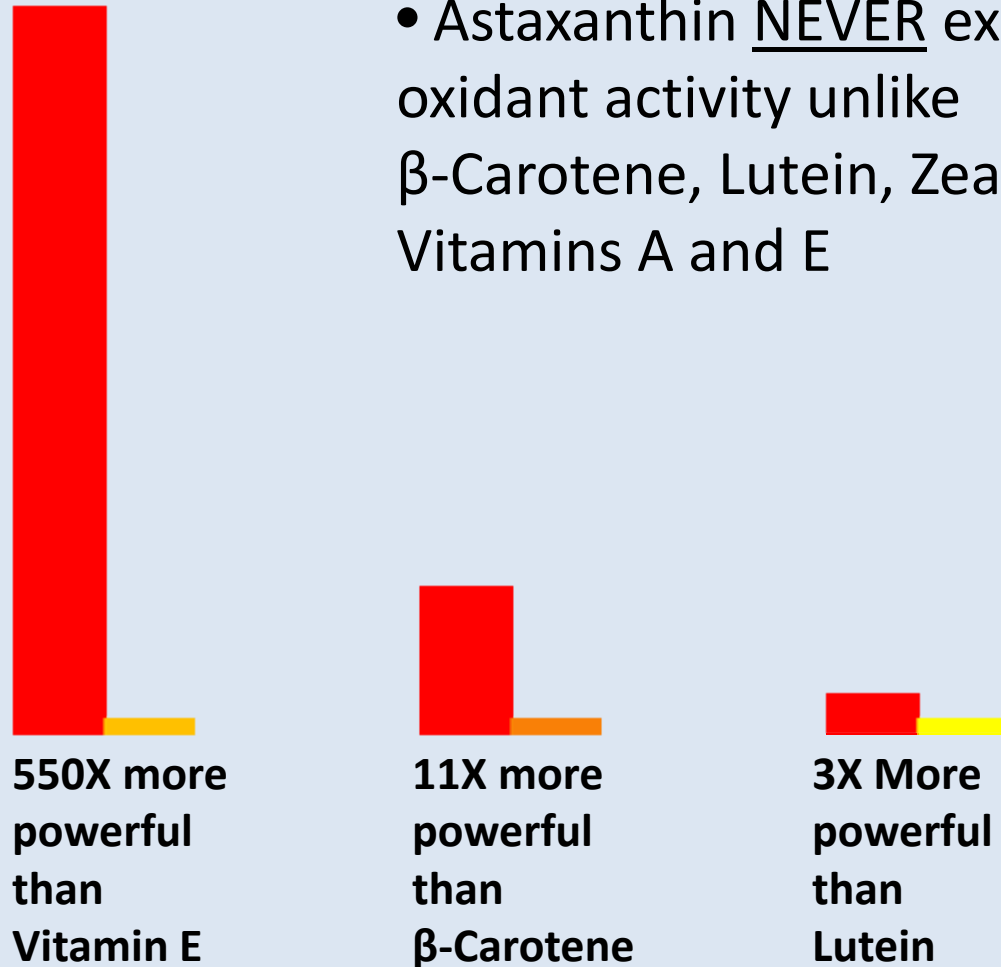
- Age Related Macular Degeneration (ARMD)
- Cataracts
- Retinal Arterial & Venous Occlusion
- Eye: Fatigue, Strain, Blurring, Diplopia
- Diabetic Retinopathy
- Trauma & Inflammation
- Depth Perception Issues

**Astaxanthin mitigates all of these issues
at doses between 2 – 4mg/day**



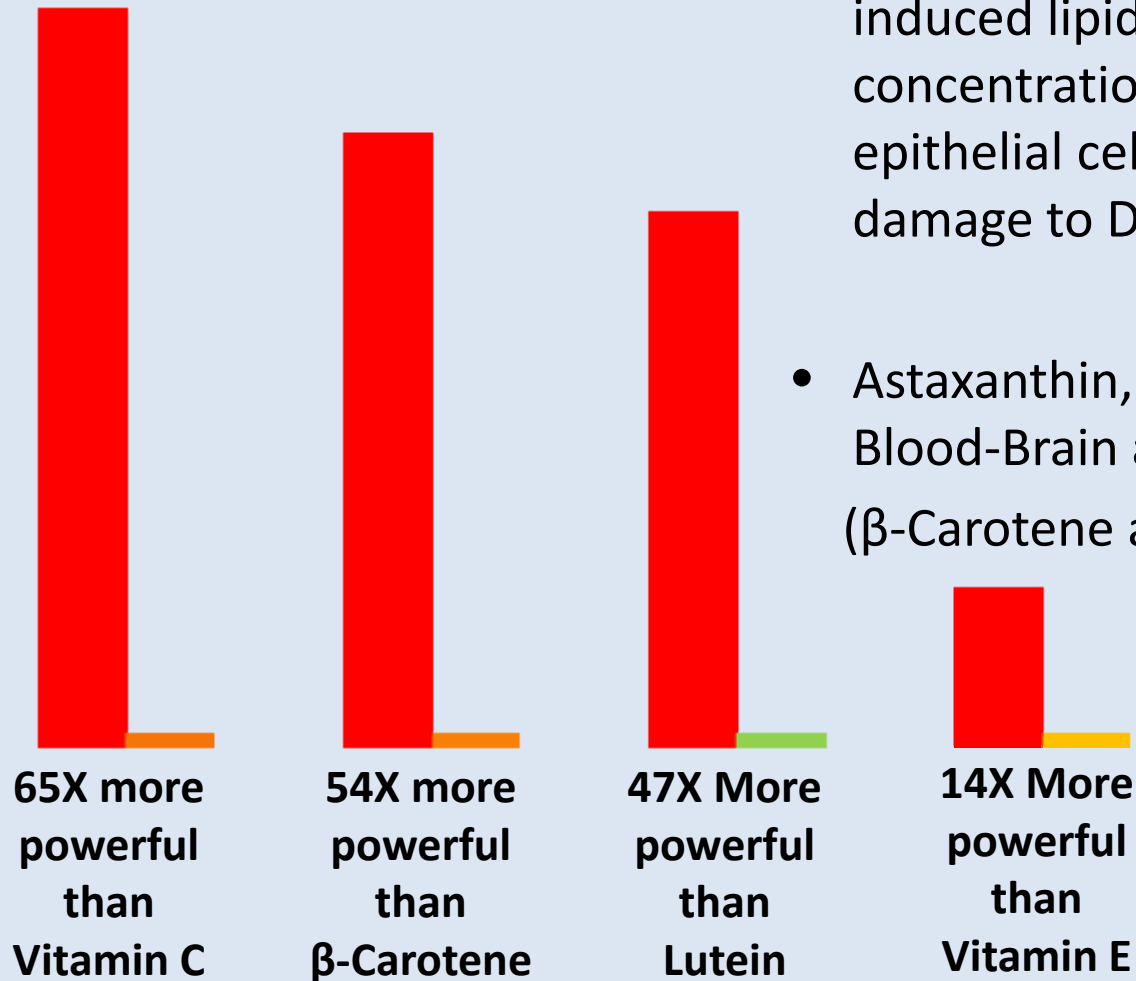
Astaxanthin: Singlet Oxygen Quenching

- Astaxanthin NEVER exhibits pro-oxidant activity unlike β -Carotene, Lutein, Zeaxanthin & Vitamins A and E



Astaxanthin: Free Radical Scavenging

- Astaxanthin is a potent inhibitor of UVB induced lipid peroxidation at $\mu\text{mol/L}$ concentrations on *in vitro* human lens epithelial cells Asta inhibits free radical damage to DHA.
- Astaxanthin, Lutein & Zeaxanthin cross the Blood-Brain and Blood-Retinal Barriers (β -Carotene and Lycopene do not)



Valensa Zanthin® Brand Astaxanthin: Purity, Stability and Integrated Supply

- Zanthin® is the only brand of astaxanthin that is stabilized with a proprietary O2B™ Peroxidation blocker system
 - No other astaxanthin brand is as stable as Zanthin
 - Protects the product and protects people
 - Prevents free radicals and singlet oxygen, chelates metals.
 - Provides additional zeaxanthin, beta carotene and lutein components
- Valensa Zanthin® is the only fully integrated “Extractor” marketing Novel Foods approved astaxanthin
 - Flavex, Rehlingen, Germany (extraction only)
 - Extract Solutions, New Zealand (extraction, allergen issues)



Astaxanthin: Excellent Safety

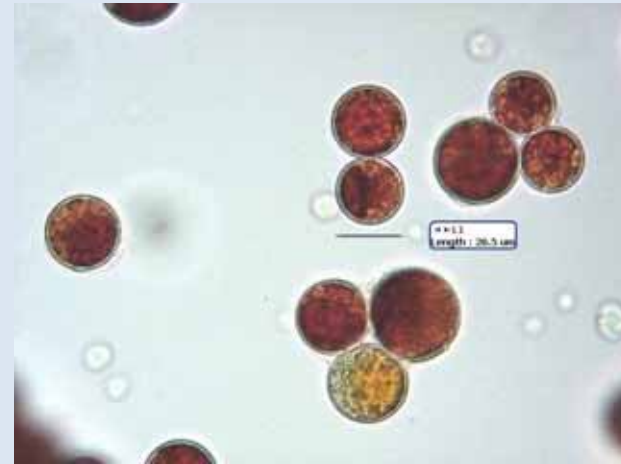
- Oral LD₅₀: 600 mg/kg (rats)
- NOAEL: 465 mg/kg (rats)
- Serum Pharmacokinetics: Stewart et al. 2008
 - T_½: 16 hrs
 - T_{max}: 8 hrs
 - C_{max}: 65 µg/L
- 8 weeks of supplementation @ 6 mg/day: No negative effect in health adults. Spiller et al. 2003
- Since astaxanthin is fat soluble, there is intermediate term bioaccumulation. Valensa can recommend the proper dosage



Astaxanthin: Two Prime Sources



3 mg astaxanthin per 240 g serving



1% to 7% astaxanthin in microalgae

Valensa with its biomass suppliers is the only fully integrated producer of astaxanthin. Growth of microalgae, extraction and standardization in a GMP allergen free, organic certified facility





Recommended Eye Health Formulas*

(For persons with low risk factors for ARMD or cataracts)

- **Softgels (Vegetarian, small size)**
 - 1-2 mg Zanthin® astaxanthin oleoresin
 - 5 mg lutein as ester
 - 0.25 to 1 mg zeaxanthin
 - 100 mg krill oil
- **Tablets (coated)**
 - 2 mg Zanthin astaxanthin as 2.5% beadlet
 - 5 mg lutein powder
 - 1 mg zeaxanthin powder
 - 50 mg DHA (encapsulated)
- **Gummy Bears**
 - 1-2 mg Zanthin oleoresin
 - 5 mg lutein
 - 0.25 to 1 mg zeaxanthin
 - Black Currant extract (optional)
- **Hard Shell Capsules**
 - Same as tablets, minus excipients





Recommended Eye Health Formulas*

(For persons with high risk factors for ARMD or cataracts)

- Softgels (Vegetarian, small size)

- 2-4 mg Zanthin® oleoresin
- 8 mg lutein (optional)
- 1 mg zeaxanthin
- 100 mg krill oil

- Tablets (coated)

- 2-4 mg Zanthin as 2.5% beadlet
- 8 mg lutein powder
- 2 mg zeaxanthin powder
- 50 mg DHA or krill oil(encapsulated)

- Hard Shell Capsules

- Same as tablets, minus excipients

New Patented Valensa Eye Health Formulas



Astaxanthin Based Gummy Bears Eye Formula

(Prototype for adults)

- Pectin Base
- Astaxanthin at 1-2 mg per serving
- Lutein 5 mg as ester
- Zeaxanthin 0.25 to 1 mg
- Natural Black Current extract
- Natural flavor
- Natural sugar



Important: Gummy bear products are often consumed in excess due to the “candy effect”. Therefore it is recommended that the daily serving amount be positioned somewhat lower than in softgels

Available for licensing





Eye Health Formulations: Introducing SpiruZan™ Eye



SPIRUZAN™ EYE



- Eye Health
- Immunity Support
- Antioxidant Support

Spirulina + Astaxanthin

SPIRUZAN™ EYE Spirulina + Astaxanthin

Proprietary Patented Astaxanthin
Eye Health Complex US 5,527,533

SPIRUZAN™ EYE is made with certified organic Spirulina and Astaxanthin to support the health of eyes which are particularly affected by free radicals.

Astaxanthin has been shown to reach vulnerable cells in the eye and protect against the damage caused by free radicals and oxidative stress.

Superfood Spirulina, is a source of B₁₂, potassium, iron, calcium, as well as carotenoids which support eye health, like beta-carotene.

A Product of Valensa International
www.valensa.com (352) 357-2004
2751 Nutra Lane Eustis, FL 32726

2 x 500 mg Tablet Serving

Spirulina	800 mg
Astaxanthin	2 mg
Lutein	2 mg
Phycocyanins	150 mg





Zanthin® Astaxanthin Serving Recommendations

- For persons with high risk factors for ARMD and Cataracts 2-4 mg/day Zanthin
- For persons with ARMD or Cataracts 4 mg/day Zanthin
- For adult gummy bear candy 1-2 mg/day
- For children over 6 years old 1 mg Zanthin/day
- For dogs over 20 kg 1-2 mg/day Zanthin
- For cats over 6 months of age 0.5 to 1 mg/day Zanthin





Valensa: The Astaxanthin Expert

- Do not formulate metal salts with astaxanthin
 - Causes decomposition
 - Formulate salts in tablet formulas, two compartment hard shells or separate dosage*
- Do not formulate krill oil with metals
- Potential issues with Cu, Zn and Se metals
 - Recent Polo horse tragedy in US – Selenium overdose
 - Zn without Cu causes copper anemia
 - Multivalent metal ions are known carcinogens – select with care
 - Manufacturing errors with metal salts common and dangerous

*Valensa does not recommend using metal ions in any supplements





Conclusions

- Eye Formulations Containing Astaxanthin as well as Zeaxanthin and Lutein Create the Most Effective ARMD Eye Healthcare Products. Valensa encourages incorporation of krill oil in the formulas.
- Astaxanthin in combination with our proprietary O2B package, is compatible with all Omega-3 sources, especially krill.
- Valensa's Eye Patent for use of Astaxanthin for Eye Healthcare Offers IP Product Protection Until Q4 2014

Valensa is a Key Manufacturer for World Class, Science-Based, Stable Eye Healthcare Formulations





Astaxanthin

The Super Carotenoid For Eye Health

Thank You!



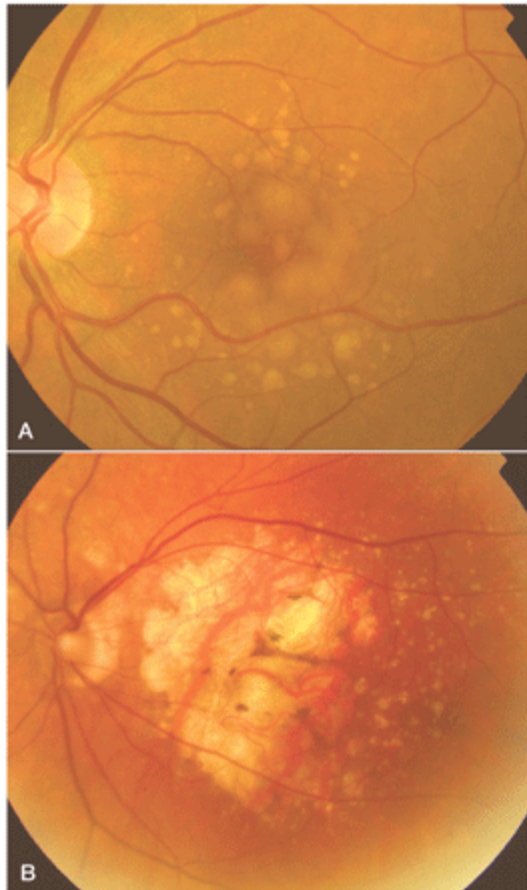
Appendix

- Astaxanthin crosses the blood-brain barrier and is the most effective free radical and singlet oxygen quencher in the carotenoid series & is safe in humans.
- Oral treatment in mammals was shown that astaxanthin deposits on the macula.
- Astaxanthin is absorbed by *in vitro* lens epithelial cells where it dramatically suppresses UVB induced lipid peroxidative mediated cell damage at $\mu\text{mol/L}$ concentrations
- Sifi's Azyr, containing lutein, zeaxanthin and astaxanthin, is the leading eye healthcare product in Italy. Recently Azyr Mega was also launched adding omega-3 oils based on AREDS II study.
- American diet is poor in carotenoids and omega-3's but rich in pro-inflammatory omega-6's
- ALA is not only efficiently converted to EPA but also is a powerful down regulator of the LA to AA cascade
- Omega-3 therapy including ALA, EPA and DHA are all important to maintenance of eye healthcare

ARMD Science Chronology

- **Seddon et al. 1994:** JAMA Article describes use of Vitamins A, C, E & Carotenoids in ARMD & direct relationship between low carotenoid levels and ARMD
- **2001 AREDS I:** Established Vitamins- A, C, & E Zn and Cu as important Eye Healthcare supplements
- **2002 Beaver Dam Eye Study:** Established correlation between dietary intake of carotenoids and ARMD
- **2006 AREDS II:** Exploring Lutein/Zeaxanthin with Omega-3's for use in Eye Healthcare
- **2004 LAST:** Established that Lutein improved visual acuity
- **2006 CARMIS:** Established Sifi's Azyr as an effective eye healthcare formula (contains lutein (10mgs), zeaxanthin (1mg) and astaxanthin (4mgs)) improved function of the central retina only (0-5 Degs). Measured by multifocal electroretinogram Response Amplitude Densities
- **Mark Tso: US 5,527,533** established that Astaxanthin deposits in the macula of mammals with extraordinary benefits.
- **Miljanovic 2005:** Established relationship between Omega-3's with clinically diagnosed dry eye syndrome (68% reduction in dry eye risk)

We can conclude from these science based studies(and many more not cited here) that Carotenoids know to pass the blood brain barrier, Vitamin C, E, Zn in conjunction with Cu, as well as Omega-3's are important components of good eye healthcare formulations for the mitigation of ARMD progression in man and help ameliorate dry eye syndrome.



Photos courtesy of Dr. Lawrence S. Morse.

Early stage dry AMD

Advanced stage dry AMD

Figure 2—Macular changes in dry AMD. (A) Multiple large, soft drusen in early dry AMD. (B) Geographic atrophy with adjacent soft drusen in advanced dry AMD.

Both feature soft drusen

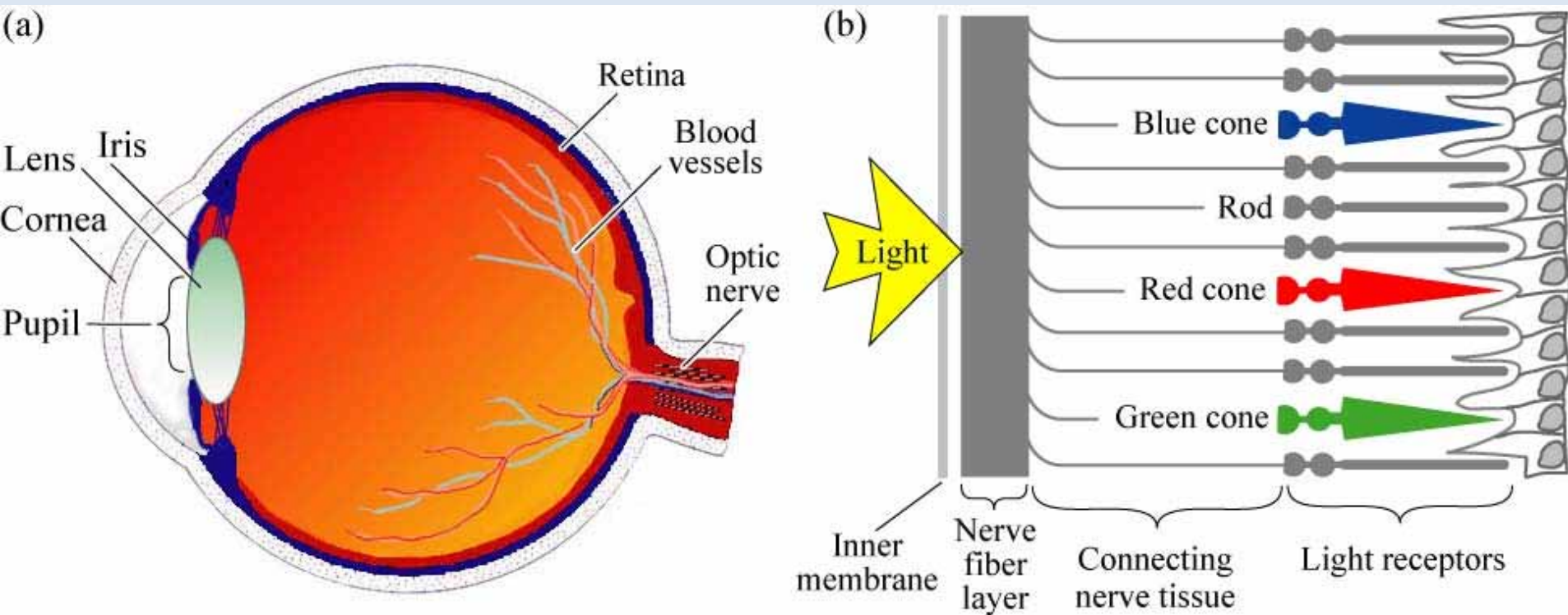
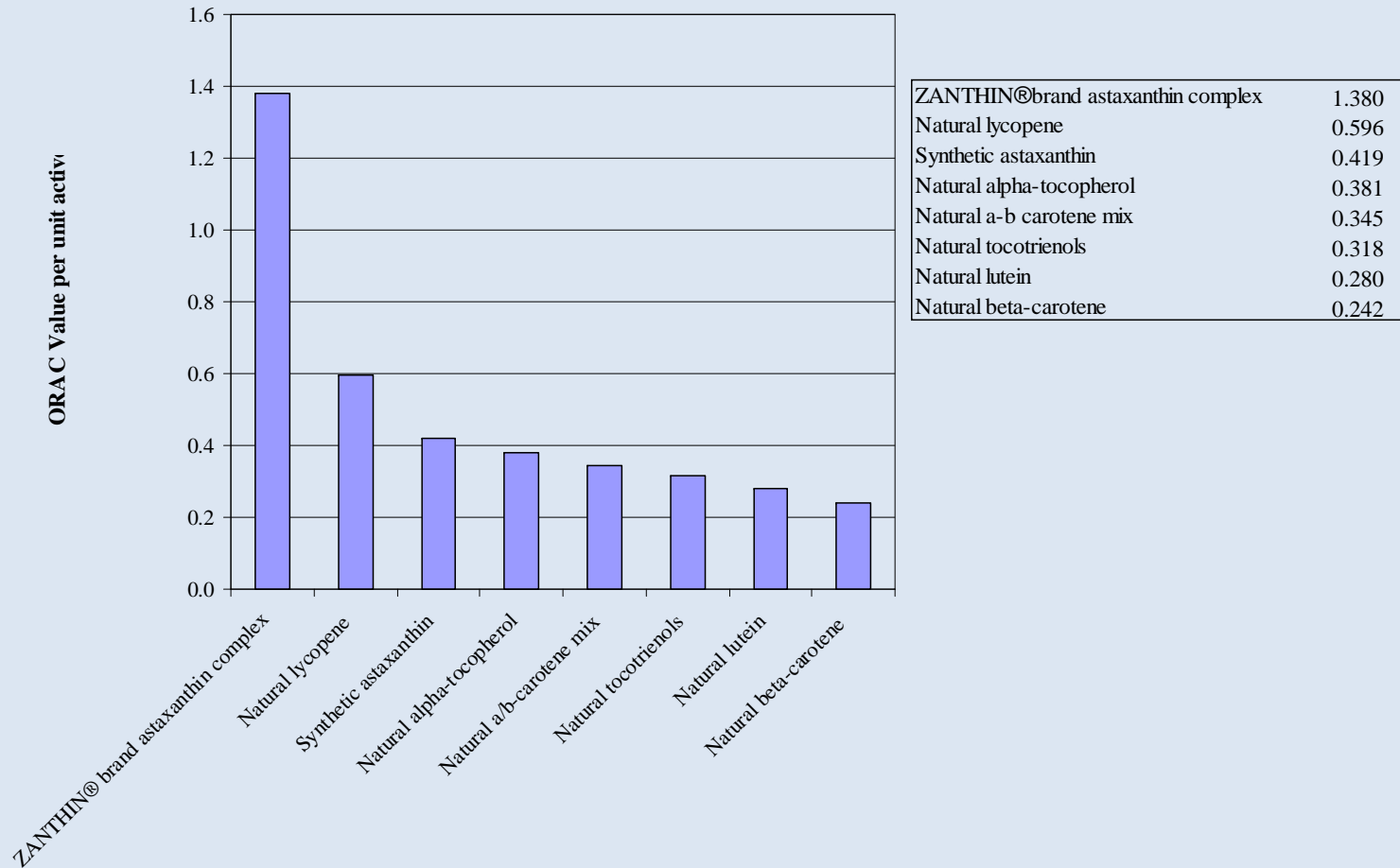


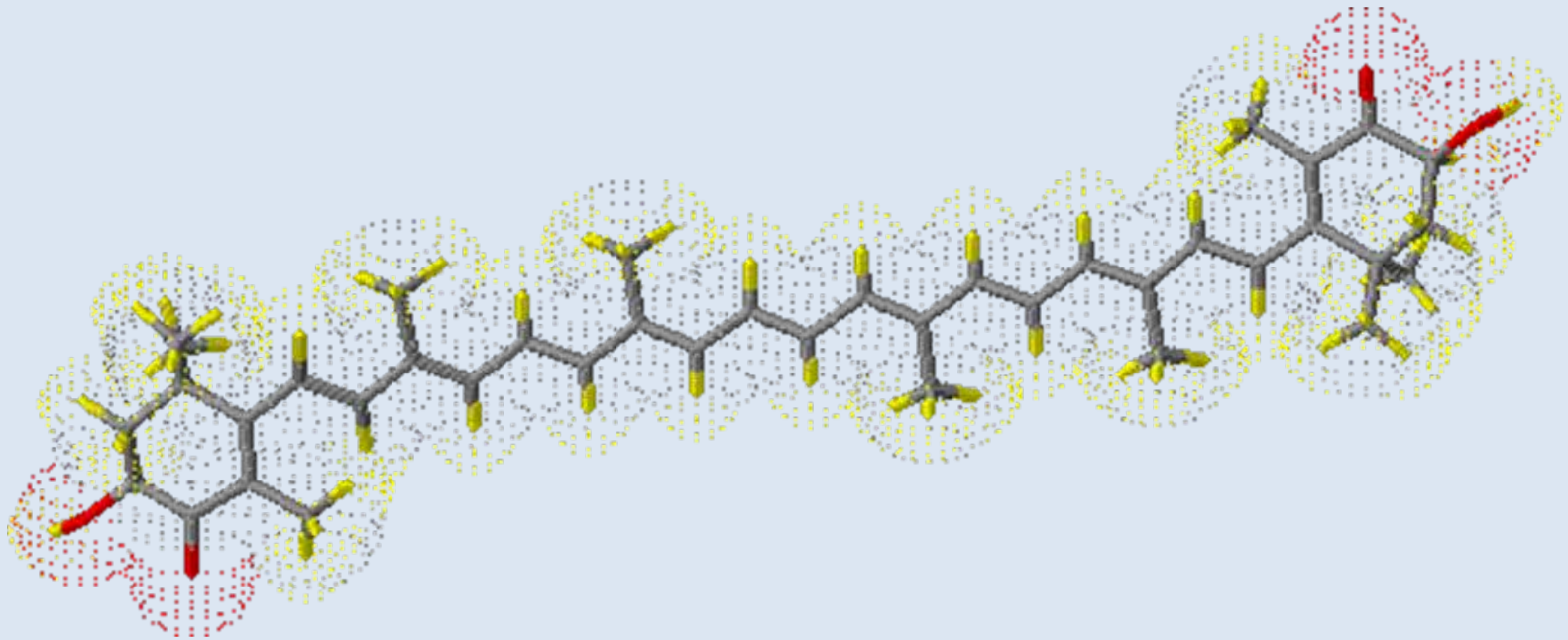
Fig. 16.1. (a) Cross section through a human eye. (b) Schematic view of the retina including rod and cone light receptors (adapted from Encyclopedia Britannica, 1994).

ORAC (Oxygen Radical Absorbance Capacity) Values

ORAC Values of Antioxidants

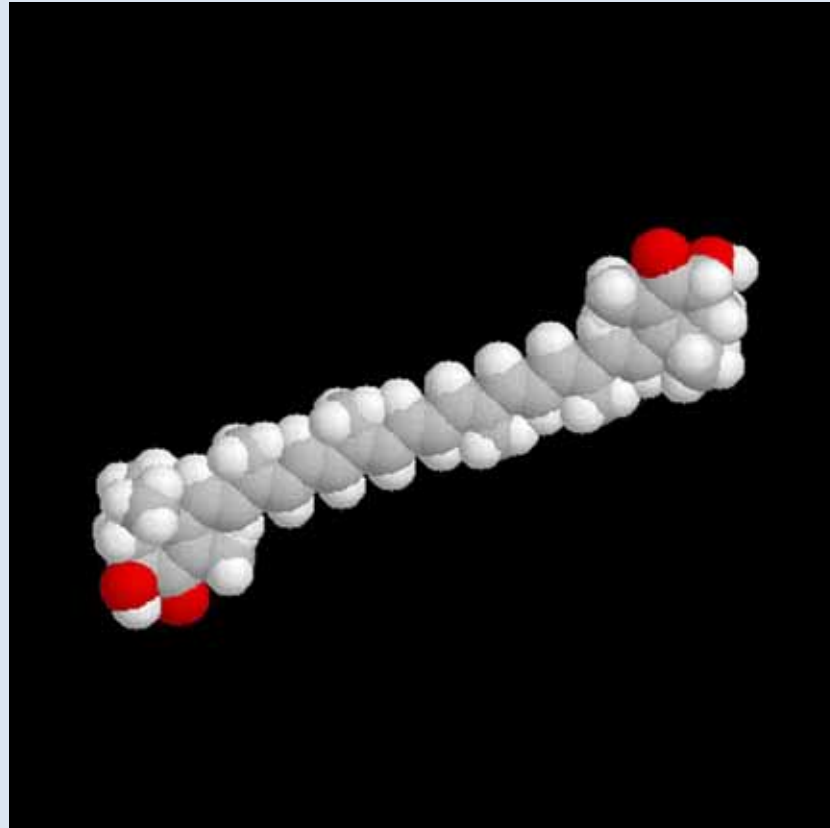


Astaxanthin 3-D



Highly active polar oxygen atoms

Astaxanthin 3-D



Highly active polar oxygen atoms