Carotenoids, Colors and Cannabis

Jeffrey Anshel, OD
Carotenoids, Colors & Cannabis
Weeding Through Current Trends in Ocular Nutrition

Jeffrey Anshel, OD, FAAO
Corporate Vision Consulting

Introduction to Carotenoids

Yellow, orange, red lipophilic pigments
~ 600 known carotenoids
40-50 in typical human diet
14 found in serum
Lutein, β-Carotene, Lycopene, α-Carotene, Zeaxanthin, β-Cryptoxanthin

Analysis of Lutein and Zeaxanthin in Retina

Snodderly DM, Auran JD, Delori FC (1984) IOVS 25, 674-685
Lutein and Zeaxanthin

Putative Role of Macular Pigment

- ↓ glare by absorbing blue light
- ↑ VA & CSF
- ↓ chromatic aberrations
- ↓ photophobic discomfort
- Scavenges free radicals (and associated with ↓ AMD)
- Stabilizes cellular membranes

Antioxidant protection

©2002 by American Society for Nutrition
Meso-zeaxanthin

- Not a naturally occurring nutrient in traditional diets
- Is generated from the metabolism of lutein
- Does not convert from zeaxanthin

Conversion of Lutein to Mesozeaxanthin

Macaques raised on a diet depleted in xanthophylls lack macular pigment. When these animals were fed:

- Lutein and Meso-Zeaxanthin are present in the MP
- Only Zeaxanthin is present in the MP


Future Research with Meso

- Control for diet
- Consume the supplement with a fat transport mechanism
- Control for genetic markers-DNA testing
- Control for smoking and ideal weight
- Control for mal-absorption syndromes
- Address co-existent inflammatory disease...CRP levels
- Use mesozeaxanthin as a stand-alone supplement
- Address quality control of all products to improve bioavailability


**AMD and Epidemiology**

The Prevalence of AMD: In the US will increase to 2.95 million in 2020.

**Diet influences risk of advanced AMD**

Antioxidants and zinc can reduce the risk of developing advanced age-related macular degeneration (AMD) by about 25 percent.

*Arch Ophthalmol.* 2004; 122:564-572

Dietary lutein/zeaxanthin intake at baseline was inversely associated with neovascular AMD.

*Arch Ophthalmol.* 2007;125:1225-1232

**Three Human Macular Pigments**

Lutein, Zeaxanthin & Mesozeaxanthin

<table>
<thead>
<tr>
<th>Carotenoid ratios</th>
<th>L:Z:M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>3:1:0</td>
</tr>
<tr>
<td>Whole retina</td>
<td>2:1:0.5</td>
</tr>
<tr>
<td>Fovea</td>
<td>1:2:1</td>
</tr>
</tbody>
</table>

Lutein is 5x more common in the US diet.

**Beta Carotene**

- Beta carotene is an effective antioxidant
- It is not an appropriate source of Vitamin A
- Does not readily convert to pre-formed Vitamin A (retinol) in the older population as it does in younger people
- Does not convert to vitamin A if there are sufficient stores of Vitamin A in the system
- Increased risk of cancer in smokers and SECOND-HAND smokers!
- Interferes with the absorption of lutein and zeaxanthin

**Beta Carotene**

“Higher beta-carotene intake was associated with an increased risk of AMD.”

*Dietary Antioxidants and the Long-term Incidence of Age-Related Macular Degeneration (The Blue Mountain Eye Study)*


**Lutein and Zeaxanthin found in dark green leafy and yellow-orange fruits and vegetables**

<table>
<thead>
<tr>
<th>FOOD</th>
<th>SERVING</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale (cooked)</td>
<td>1 cup</td>
<td>23.0</td>
</tr>
<tr>
<td>Spinach (cooked)</td>
<td>1 cup</td>
<td>38.0</td>
</tr>
<tr>
<td>Collard (cooked)</td>
<td>1 cup</td>
<td>14.6</td>
</tr>
<tr>
<td>Turnip greens (cooked)</td>
<td>1 cup</td>
<td>12.2</td>
</tr>
<tr>
<td>Broccoli (raw)</td>
<td>1 cup</td>
<td>3.9</td>
</tr>
<tr>
<td>Carrot (raw or cooked)</td>
<td>1 cup</td>
<td>2.3</td>
</tr>
<tr>
<td>Green peas (cooked)</td>
<td>1 cup</td>
<td>2.0</td>
</tr>
<tr>
<td>Broccoli (cooked)</td>
<td>1 cup</td>
<td>1.0</td>
</tr>
<tr>
<td>Orange juice (16 oz)</td>
<td>1 cup</td>
<td>1.3</td>
</tr>
<tr>
<td>Green beans (cooked)</td>
<td>1 cup</td>
<td>0.8</td>
</tr>
<tr>
<td>Eggs</td>
<td>2 (large)</td>
<td>0.9</td>
</tr>
<tr>
<td>Orange</td>
<td>1 medium</td>
<td>0.2</td>
</tr>
</tbody>
</table>
The Lutein Gap


L & Z in the retina: AMD vs. Controls

Day 0 40 80 120 160 200
Lutein concentration, µg/ml 0.0 0.2 0.4 0.6 0.8 1.0 1.2
Subject A
End of supplementation

Effect of 30 mg/day of lutein on the serum

Subject A
End of supplementation

Effect of 30 mg/day of lutein on the macular pigment

Subject A
Left Right

End of supplementation

Pre-supplementation values are not significantly different \( P = 0.66 \)

Dose in mg \( / \) day

Increase \( 2.6 \times \)

Increase \( 6 \times \)

Increase \( 3.4 \times \)

\( P < 0.0001 \)

Pre-supp. values not significantly different \( P = 0.66 \)
**Obesity and MPOD**

- Note for patients with BMI over 30: Lutein is sequestered in adipose tissue and therefore is less available to ocular tissue.
- It is not beyond our scope to discuss weight issues with our patients.

---

**Lutein Absorption**

“Olive and coconut oils improve the intestinal absorption of lutein in mice.”

Dietary fatty acid determines the intestinal absorption of lutein in lutein-deficient mice

*Food Research International Volume 64, October 2014, Pages 256-263*

---

**Statins and Carotenoids**

After 6 weeks, the crude plasma levels of oxygenated (lutein-zeaxanthin and β-cryptoxanthin) and hydrocarbon carotenoids (lycopene, α-carotene and β-carotene) were reduced in the simvastatin group by 21%.

*Mireille Ryden, Per Leanderson, K-G Karlstrom and Lena Jonasson, Effects of simvastatin on carotenoid status in plasma Nutrition Metabolism and Cardiovascular Diseases, (22) 2012, 1, 66-71.*

---

**In Vivo Measurement of Macular Pigment**

- Heterochromatic Flicker Photometry-subjective
- Reflectance Photometry*
- Scanning Ophthalmoscopic*
- Autofluorescence Spectrometry*
- Resonance Raman Spectrometry*

*Laboratory only

---

**MPOD Testing**

<table>
<thead>
<tr>
<th>Device/Manufacturer</th>
<th>QuantifEye (ZeaVision)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterochromatic flicker photometry</td>
<td>Heterochromatic flicker photometry</td>
</tr>
<tr>
<td>Self-contained unit</td>
<td>MPOD unit plus laptop</td>
</tr>
<tr>
<td>3-5 minutes per patient</td>
<td>2-3 minutes per patient</td>
</tr>
<tr>
<td>Alternate wavelength stimulus presented</td>
<td>Alternate wavelength stimulus presented</td>
</tr>
<tr>
<td>$23,000.00</td>
<td>Purchase Cost</td>
</tr>
<tr>
<td>$17,999.00</td>
<td>Lease Option 90 day free trial</td>
</tr>
</tbody>
</table>

Nutrition: MacuHealth Nutrition: EyePromise

---

**MPOD measurement is not a scam**

- Any patient with high risk AREDS signs
- Any patient with a strong AMD risk factor (over 50 – smoker – obese – poor diet)
- Any patient with a family history of AMD
- Any patient with diabetes
- Any patient with photophobia
- Any patient with a non-refractive reading / driving issue
- Anyone in the transportation industry (3%)
- Athletes i.e. Skiers (glare); Baseball (fine acuity)
Glare Recovery & Macular Pigment

Photostress recovery time is directly related to the amount of macular pigment. Subjects with very high MP density recover about twice as fast as subjects with very low MP density.

Epidemiological evidence that lutein and zeaxanthin lower the risk cataract development

High dietary levels of lutein and zeaxanthin had a 23% lower prevalence of nuclear cataract

Astaxanthin

- Xanthophyll carotenoid but not converted to vitamin A
- Has potent antioxidant activity
- Commercial astaxanthin is produced naturally and synthetically
- May be beneficial in cardiovascular, immune, inflammatory and neurodegenerative diseases
- Not found naturally in ocular tissue
- Found in microalgae, yeast, salmon, trout, krill, crayfish, etc.

The Blue Light Blues

A Solution Looking for a Problem?
Why You Need to Talk to Your Patients about Blue Light

“Recent research has PROVEN harmful blue light contributes to eye strain, macular degeneration, and sleep disruption. With many of your patients spending more than half their waking hours exposed to blue light emitted by smartphones, tablets, computer monitors, televisions, LED and CFL lighting, it’s never been more crucial to discuss the importance of protection.”

Blue Light Exposure

Even though the amount of blue light emitted from sunlight and digital devices is roughly the same (25% to 35%), our daily exposure to blue light from indoor sources (i.e., digital and lighting) is significantly greater because we are spending more time indoors.


Primary Sources of Blue Light

- Sunlight
- Digital Devices (e.g., computer screens, smartphones, television)
- Artificial lighting - specifically LED (light-emitting diode) and CFL (compact fluorescent lighting)

Sleep Disruption

- The light blue peak from LEDs pales in comparison to the blue peak from the blue sky
- Most "research" uses energy levels 1,000,000 times brighter than the blue peak from an LCD screen in order to elicit a significant difference in tissue
- Modern LEDs employ yellow phosphors which give a much more even spectrum. The peak is shifted to 465nm with almost zero at 420nm.
- Most “blue light lenses” only block 20%-25% at 420nm.
Blue Is Not Bad

Blue-turquoise light ranges from 465-495nm essential for:
- Sleep/wake cycles
- Memory
- Mood
- Cognitive performance
- Pupillary constriction
- Blue-turquoise light is also needed for visual acuity and color perception.

Five human photoreceptor types

- They convey different information to our brain about vision
- They have different spectral sensitivities

James Sheedy, OD, PhD
Professor
Pacific University

The 5 human photoreceptors are:
- Newer and foveal
  - 1. L cones
  - 2. M cones
- Older and only non-foveal
  - 3. S cones
  - 4. Rods
  - 5. Intrinsically photosensitive retinal ganglion cells (iPRGC)

“Light”
- It is conscious perception of light (vision)
- Its magnitude is brightness.
- We have classically quantified human vision (i.e. “light”) with “brightness.”
- The luminosity function describes “light” so that it can now be measured
- Our quantification of “light” is based upon comparative brightness

The S cone does not contribute to brightness
Two vision categories

- Conscious - "light"
  - L cones
  - M cones
  - Unconscious
  - S cones
  - Rods (at daytime operating levels)
  - iPRGC

The five human photoreceptors

- Conscious light
- Blue light


"Blue light"

is herein defined as electromagnetic radiation that collectively stimulates the more primitive iPRGC, rods, and S cones.

Blue light

- Is not light
- Is unconscious
- Serves fundamental aspects of vision
- Affects primarily the earlier and basic functions of vision
  - Circadian rhythm entrainment
  - Movement detection
  - "Awareness" of objects in the environment
  - Location of objects with respect to self
  - Directionalization
  - Potentially affects emmetropization

Damage of photoreceptor-derived cells in culture induced by light emitting diode-derived blue light

- While blue LED light damaged the primary retinal cells and the damage was photoreceptor specific.
- N-Acetylcysteine (NAC), an antioxidant, protected against the cellular damage induced by blue LED light.

Science Reports 2014; 4: 5223. Published online 2014 Jun 9.
Do blue-light filtering intraocular lenses affect visual function?

- This study showed no significant effects of a blue-light filtering IOL on visual acuity and no influence on color perception and CS.
- After more than 2 years, there were no significant differences in macular changes between the IOL groups.
- Clinical evidence of the effect of a blue-light filtering IOL on macular protection is still lacking.

Optom Vis Sci. 2014 Nov;91(11):1348-54

Cannabis Quiz

- Cannabis is a gateway drug.
- Marijuana is worse for your lungs than tobacco.
- Cannabis use leads to crime.
- Cannabis is addictive.
- We all know what stoners look like.
Cannabis is a gateway drug

“Many people mistakenly believe that marijuana use precedes rather than follows initiation of other illicit drug use. In fact, most drug use begins with alcohol and nicotine before marijuana, making nicotine and alcohol the two most common drugs of abuse.”

Constance Scharff, Ph.D
Psychology Today, Aug 2014

Marijuana is worse for your lungs than tobacco.

- Study tested the lung function of over 5,000 young adults between 18 and 30 to determine marijuana’s effect on lungs.
- In fact, researchers were surprised to find marijuana smokers performed slightly better than both smokers and non-smokers on the lung performance test.
- Why? The most likely explanation seems to be that the act of inhaling marijuana—holding each puff in for as long as possible—is a lot like a pulmonary function test, giving marijuana smokers an edge over their cigarette smoking counterparts.

JAMA published study in 2012

Cannabis use leads to crime

- The total number of marijuana court cases fell from 39,027 in 2011 to 2,036 cases in 2014.
- Those 37,000 fewer cases represent a savings of untold millions of dollars in court costs and law enforcement fees.
- They represent 37,000 fewer people who have to deal with the stigma and financial burden of an arrest and possible conviction.”

Cannabis is addictive

Frequent marijuana users often report irritability, mood and sleep difficulties, decreased appetite, cravings, restlessness, and/or various forms of physical discomfort that peak within the first week after quitting and last up to 2 weeks.

National Institute on Drug Abuse

We all know what stoners look like
Schedule 1 drugs
- Heroin (diacetylmorphine)
- LSD (lysergic acid diethylamide)
- Marijuana (cannabis, THC)
- Mescaline (Peyote)
- MDMA (3,4-methylenedioxymethamphetamine or “ecstasy”)
- GHB (gamma-hydroxybutyric acid)
- Psilocybin
- Methaqualone (Quaalude)
- Khat (Cathinone)
- Bath Salts (3,4-methylenedioxyxymethamphetamine or MDPV)

Forms of Cannabis
- There are over 480 chemicals in marijuana, but only 66 of them are unique to the Cannabis plant -- these are called cannabinoids.
- Dronabinol (Marinol®) and Nabilone are synthetic forms of key ingredients in marijuana. Approved both drugs as treatments for nausea and vomiting associated with cancer chemotherapy.
- Dronabinol also is approved for loss of appetite associated with weight loss in patients with AIDS.

Cannabinoids
- Δ9-Tetrahydrocannabinol (THC) is the cannabinoid responsible for the main psychoactive effects.
- The compound is a mild analgesic and cellular research has shown the compound has antioxidant activity.
- THC is believed to interact with parts of the brain normally controlled by the endogenous cannabinoid neurotransmitter anandamide.

Cannabinoids
- Cannabidiol (CBD) CBD may hold the most medical potential for many serious conditions.
- CBD is a non-psychoactive cannabinoid that is believed to reduce the psychoactive effects of THC. Smokers of cannabis with a higher CBD content are less likely to experience anxiety. CBD may also inhibit cancer cell growth.
- Cannabinol (CBN) Cannabinol is a weak psychoactive cannabinoid found only in trace amounts in Cannabis Sativa and Cannabis Indica. It is mostly a metabolite of tetrahydrocannabinol. It has a higher affinity to CB2 receptors.

Cannabinoids
- Tetrahydrocannabinol (THCV) is found in largest quantities in Cannabis varieties indigenous to central Africa, like certain phenotypes from Malawi.
- It is currently being researched as a treatment for metabolic disorders including diabetes, as well as serving as a potential appetite suppressant.
- Tetrahydrocannabinolic Acid (THCA) is the main constituent in raw cannabis (prior to drying).
- THCA holds much of the anti-inflammatory, anti-proliferative, neuroprotective as well as anti-spasmodic properties.
Cannabinoids
- Cannabigerol (CBG) A non-psychoactive cannabinoid, CBG has been shown to relieve intraocular pressure.
- Cannabichromene (CBC) Research suggests that CBC includes: anti-inflammatory, analgesic, bone stimulant, and anti-cancer properties.
- Cannabidiolic Acid (CBDA) Similar to THCA, it is the main constituent in cannabis that has elevated CBD levels.
  - THCA and CBDA hold most of the anti-inflammatory properties that cannabis has to offer.

CB1 Receptors
- Found predominantly present in the nervous system, connective tissues, gonads, glands, and organs.
- Not found in the medulla oblongata (no risk on cardiovascular or respiratory systems)
- Responsible for the euphoric and anticonvulsive effects

CB2 Receptors
- Found primarily in the immune system, mostly in the spleen.
- Only found in the peripheral nervous system
- Recently, discovered to be present in a specific perivascular microglial cell type of the cerebellum.
- Appear to be responsible for the anti-inflammatory and possibly other therapeutic effects.

Endocannabinoid System
- The first endocannabinoid discovered was named anandamide.
- 2-arachidonoyl glycerol was isolated from canine gut and identified as a second endocannabinoid.
- Both of these chemicals are ultimately made from essential fatty acids such as are found in fish and seed oils. They are analogues of arachidonic acid.
- Anandamide is critical to “forgetting”.
Cannabis and Glaucoma

- In 1971 it was reported that a 25 to 30% IOP lowering effect of smoking marijuana occurred in a small group.
- The proposal for action of the cannabinoids in the ocular tissue is that the effect occurs in both production and outflow of aqueous.
- This was a dose-response relationship lasting only 3-4 hours.

Ocular Cannabinoid Receptors

- Ciliary epithelium
- Trabecular meshwork
- Schlemm’s canal
- Ciliary muscle
- Ciliary body vessels
- Retina
- NONE: choroid; corneal stroma

IOP Lowering Effects

- Dexanabinol, administered IV, is an effective IOP-lowering agent, devoid of any significant side effects (blood pressure, heart rate or pupil diameter, all of which have been reported previously for cannabinoids).
- Involvement of the adrenergic system is indicated in mediating the IOP-lowering effects of Dexanabinol that appear to reflect a change in fluid outflow from the eye.

Cannabigerol and Glaucoma

- (THC and Cannabigerol) produced a two-to three-fold increase in aqueous outflow facility. Cannabigerol and related cannabinoids may have therapeutic potential for the treatment of glaucoma.

Cannabinol or Cannabigerol

- Cannabinol produced both ocular toxicity and neurotoxicity. As cannabigerol lacked these toxicities, it appears that the ocular hypotensive effect of this cannabinoid is somewhat dissociable from both the adverse central and ocular effects accompanying marijuana intake.

Possible IOP Reduction Mechanisms

- A direct role of ocular CB1 receptors in the IOP reduction induced by cannabinoids.
- A direct effect on the ciliary processes, and specifically a reduction in capillary pressure, leading to changes in aqueous humor dynamics.
- Δ9-THC decreased the secretion of ciliary processes and led to a dilatation of the ocular blood vessels through a possible β-adrenergic action.
- Cannabinoids may inhibit calcium influx through presynaptic channels and in this way reduce the noradrenaline release in the ciliary body, leading to a decrease in the production of aqueous humor.
- Cannabinoids might be acting as vasoconstrictors on blood vessels of the anterior uvea, thus improving the aqueous humor uveoscleral outflow.
- Cannabinoids may influence the IOP through a prostaglandin mediated mechanism.
Cannabis Side Effects (Ocular-Related)
- Dry Mouth; Dry Eyes
- Conjunctival Injection
- Increased heart rate
- Decrease in blood pressure

Glaucoma Medications- Side Effects
- Prostaglandin Analogs: possible changes in eye color and eyelid skin, stinging, blurred vision, eye redness, itching, burning. Exacerbation of Crohn's Disease.
- Beta Blockers: low blood pressure, reduced pulse rate, fatigue, shortness of breath; rarely: reduced libido, depression.
- Alpha Agonists: burning or stinging, fatigue, headache, drowsiness, dry mouth and nose, relatively higher likelihood of allergic reaction.
- Carbonic Anhydrase Inhibitors: in eye drop form: stinging, burning, eye discomfort; in pill form: tingling hands and feet, stomach upset, memory problems, depression, frequent urination.

Glaucoma Summary
- It does appear that marijuana can lower IOP for the management of glaucoma but the effects appear to last only about three to four hours.
- To equal the sustainability of a typical topical prostaglandin the patient would have to consume or inhale the drug 6 to 8 times per day.
- The effects of Marinol (synthetic) on glaucoma are not impressive.
- There is evidence that there may be characteristics of the cannabinoid components of marijuana that are neuroprotective in nature.

Cannabis and Neuroprotection
“Our results indicate that cannabidiol exerts a combination of neuroprotective, anti-oxidative and anti-apoptotic effects against β-amyloid peptide toxicity, and ... cannabidiol is involved in the signaling pathway for this neuroprotection.”

Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on β-amyloid-induced toxicity in PC12 cells.
Teresa Iuvone, Giuseppe Esposito, Ramona Esposito, et al
Journal of Neurochemistry
Volume 89, Issue 1, pp. 134-141, April 2004
Cannabis and Neovascularization

- "Cannabinoids restrict the sprouting of blood vessels to brain tumors by inhibiting the expression of genes needed for the production of vascular endothelial growth factor (VEGF)".
- Cannabinoids lowered the expression of several genes related to the VEGF pathway, critical for angiogenesis.

Marijuana Ingredient Inhibits VEGF Pathway Required For Brain Tumor Blood Vessels
Journal Cancer Research, August 15, 2004

Cannabis and Parkinson’s Disease

- "... score on the motor Unified Parkinson Disease Rating Scale score improved significantly.
- There was also significant improvement of sleep and pain scores. No significant adverse effects of the drug were observed.
- The study suggests that cannabis might have a place in the therapeutic armamentarium of Parkinson’s Disease."

Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study.
Lotan I, Treves T, Rapitz S, Dyckstein R.
Cannabis Legalization - May 2015

Most Would Be Hithered by Public, Not Private, Marijuana Use

Survey conducted Feb. 24-28, 2014
PERSPECTIVE CENTER

How is Colorado Doing?
- 77 percent decrease in state court marijuana cases
- $2 Million in new tax revenue in the first month on sales of $14 million.
- 58 percent support for legalization
- 10 percent monthly usage rate (same as before legalization)
- 6.3 percent increase in airline flight searches
- Since marijuana was legalized in Colorado, marijuana arrests are way down, tax revenue is up and support for reform continues to grow.
(as of February 25, 2014)
Synthetic Marijuana

No ‘Kid’ding...

Hemp

- Regulatory limits require the use of strains of the plant which are bred for low (1%) content of THC.
- Hemp products are already legal in the US, but only if it is imported from the more than 30 countries that legally grow it.

<table>
<thead>
<tr>
<th>Hemp seed foods</th>
<th>hemp oil</th>
<th>textiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>wax resin</td>
<td>rope</td>
<td>clothing</td>
</tr>
<tr>
<td>pulp</td>
<td>biodegradable plastics</td>
<td>paper</td>
</tr>
<tr>
<td>bio-fuel</td>
<td>cereals</td>
<td>ice cream</td>
</tr>
<tr>
<td>Frozen meals</td>
<td>hemp milk</td>
<td>hemp tofu</td>
</tr>
<tr>
<td>nut butters</td>
<td>paints</td>
<td>cosmetics</td>
</tr>
<tr>
<td>insulation</td>
<td>animal feed</td>
<td></td>
</tr>
</tbody>
</table>

HEMP

About 44% of the weight of hemp seed is edible oils, containing about 80% essential fatty acids.

One of the highest concentrations of polyunsaturated fats and an ideal balance of the omega-6 and omega-3 (3.75:1) for dry eye.

Contains phytosterols which are anti-carcinogenic

A source of complete protein offering 17 different amino acids (including 9 essential), including cysteine and methionine

Hemp Seed Oil

Carotenoids, Colors & Cannabis

Weeding Through Current Trends in Ocular Nutrition

Thank You

Jeffrey Anshel, OD, FAAO
Corporate Vision Consulting