




Nourish Your Eye and Brain: Focus on Lutein & Zeaxanthin

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KEMIN® INSPIRED MOLECULAR SOLUTIONS™

FloraGLO® LUTEIN

Outline

- Lutein and Zeaxanthin
  - Diet
  - Intake
  - Function
- Lutein and Zeaxanthin and the Eye
- Lutein and Zeaxanthin and the Brain

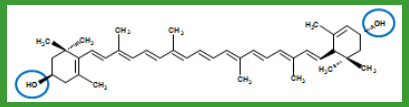
Lutein & Zeaxanthin are Carotenoids

Carotenoids

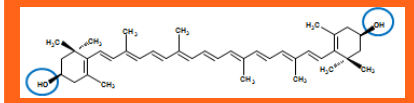
- Natural pigments
  - Powerful antioxidants
  - Cannot be synthesized by humans and have to be obtained from the diet (or supplements)
    - Over 600 known carotenoids in nature
    - 40-50 typically consumed in the diet
    - 14 have been detected in serum
- Lutein and zeaxanthin are two of the 6 major carotenoids detected in serum

Murray IJ et al. IOVS 2013; 54(3):1781-8
Ong and Tee. Methods Enzymol 1992; 213:142-167
Khachik F, et al Methods Enzymol 1992; 213:347-359

Lutein & Zeaxanthin – Food Sources



Food	Lutein Content (µg/100g serving)
Spinach, cooked	12,640
Kale, cooked	8884
Spinach, raw	6603
Zucchini, cooked (with skin)	1355
Romaine Lettuce	3824
Asparagus, cooked	991
Broccoli, cooked	772
Egg (yolk and white), cooked	645
Green beans, cooked (from frozen)	306
Corn, (cooked from frozen)	202
Orange Juice	33



Food	Zeaxanthin Content (µg/100g serving)
Goji berry	43835
Pepper, orange	1665
Corn meal, yellow	531
Corn tortilla	255
Egg (yolk and white), cooked	216
Corn, cooked (from frozen)	202
Orange juice	26
Artichoke heart	18
Iceberg lettuce	12
Grapes, green	6

Perry A., et al. Journal of Food Composition and Analysis 2009;22:9-15

Lutein & Zeaxanthin - Intakes

- Daily consumption is generally well below the levels of intake found to be beneficial for eye health (10 mg L + 2 mg Z)

Region / Country	Average Daily L+Z consumption (mg)
USA[1]	0,8 - 1,1
Europe[2-4]	0,45 - 4
Brasil[5,6]	0,61-1,11 Daily intake of fruit and vegetables is below the recommended levels (400g) in 90% of the population (POF 2008-2009)
Japan[7]	0,35
China[8]	2,9

1. Johnson *et al. Journal of the America Dietetic Association* 2010; 110:1357-1362
2. Granado et al. Public Health Nutrition 2007; 10(10):1018-1023
3. O´Neill *et al. British Journal of Nutrition* 2001; 85:499-507
4. Lucarini et al. *Int. J Vitam Nutr Res*. 2006; 76(3):03-9
5. Dantas Amancio and Vieira da Silva. Segrança Alimentar e Nutricional.2012; 19(2):130-141
6. Instituto Brasileiro de Geografia e Estatística 2011– Pesquisa dos orçamentos familiars (POF) 2008-2009
7. Hosotani and Kitagawa. *J Nutr Sci Vitaminol* 2007; 53:207-212
8. Song et al. *China J. Public Health* 2007; 23(11):1378-1380

Lutein and Zeaxanthin – Functional Properties

- Decreasing oxidative stress through their antioxidant properties[1]
- Decreasing inflammation by reducing inflammatory markers[2]
- Act as antioxidant molecules in erythrocytes (red blood cells (RBCs)), by decreasing markers of lipid oxidation in cellular membranes[3,4]
  - RBCs with lipid oxidation may have a decreased ability to transport oxygen
  - Supplementation with 10 mg lutein in healthy subjects has been shown to induce lutein accumulation and to decrease lipid oxidation in RBCs
- Lutein and zeaxanthin are filters of high energy blue-light[5]. This effect can be beneficial for eye and skin.
- Lutein can integrate into cellular membranes in multiple directions[6], where it likely influences the functional properties of membranes
- Evidence shows that carotenoids enhances gap junction communication[7]

1. Johnson EJ. et al. J. Aging Res. 2013; 2013:951786
2. Kritchevsky et al. Am J Epidemiol. 2000; 152(11):1065-71
3. Kiko T et al. J Alzheimers Disease. 2012; 28(3):593-600
4. Nakagawa K. et al. Br J Nutr. 2009; 102(9):1280-1284
5. Bernstein, PS. et al. Vision Res. 2010; 50:716-728
6. Gruszecki WI, Carotenoids in Health and Disease. New York: Marcel Dekker, Inc..2004 pp 151-163, 2004
7. Stahl and Sies. Biofactors, 2001; 15:95-98

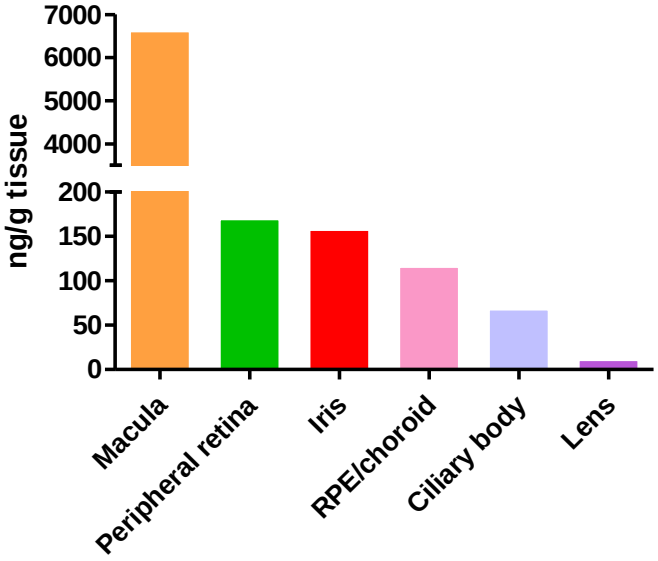
Brain and Eye Connection

- Common origin: neural tube[1]
  - The retina is an integral part of the central nervous system
- Susceptible to oxidative stress[1,2]
  - High oxygen consumption
  - Presence of significant amounts of unsaturated fatty acids
- Adversely affected by elevated blood sugar levels (diabetes) at least partially via oxidative stress[3]
- Contain measurable amounts of lutein and zeaxanthin[4,5]
  - Preferential accumulation relative to other dietary carotenoids

1 Ohno-Matsui K. Prog Retin Eye Res. 2011; 3(4):217-238
2 Kaarniranta K. et al. J Alzheimers Dis. 2011; 24:615-631
3 Muriarch M. et al. Free Radic Biol Med. 2006; 41(6):979-84
4 Nolan JM. et al. J. Alzheimers Dis. 2014; 42(4):1191-1202
5 Johnson EJ. et al. J. Aging Res. 2013:951786

Lutein & Zeaxanthin in the Eye

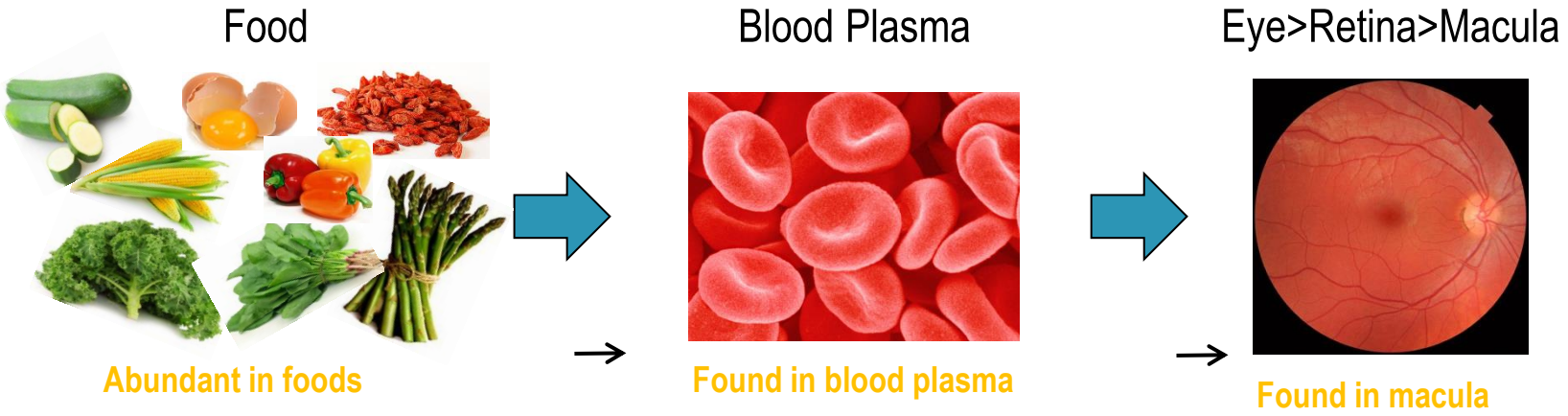
- Deposited in the eye[1-3]
  - Presence of L & Z during visual development
    - L&Z are present in the fetus retina as early as 17 to 22 weeks of gestation
    - Lutein is the dominant carotenoid in infant retina



- Among all the carotenoids only **dietary lutein and zeaxanthin** and their metabolites are selectively deposited in the macula lutea and in the lens

1. Bernstein et al. Exp Eye Res. 2001; 72:215-223
2. Yakovleva M.A. et al. Russian Journal of Developmental Biology. 2007; 38(5):317-321
3. Bone R.A. et al., Invest.Ophthallmol. Vis. Sci.1993; 29(6):843-849

Lutein & Zeaxanthin in the Macula



- Key component of the Macular Pigment[1]
  - Macular pigment is exclusively of dietary origin[2]
- 10.000-fold higher concentration in the macula as compared to serum[3,4]
  - Likely due to an active transport mechanism
- Macular Pigment Optical Density (MPOD): a measure of lutein and zeaxanthin in the macula[5]

1. Krinsky et al. Annu Rev Nutr 2003; 23:171-201
2. Johnson et al. Inves Ophthalmol Vis Sci 2005; 3(2):692-702
3. Bhosale et al. Biochemistry. 2009; 48(22):4798-807
4. Bhosale et al. J Biol Chem. 2004; 279(47):49447-54
5. Bernstein et al. Vision Res. 2010; 50:716-728

The Macular Pigment is of Dietary Origin

- Monkeys are the only animals that have a macula lutea, similar to humans[1]
  - The Oregon National Primate Research Center
    - Colony of adult rhesus monkeys fed xanthophyll-free diets since birth
    - Control animals available for comparison

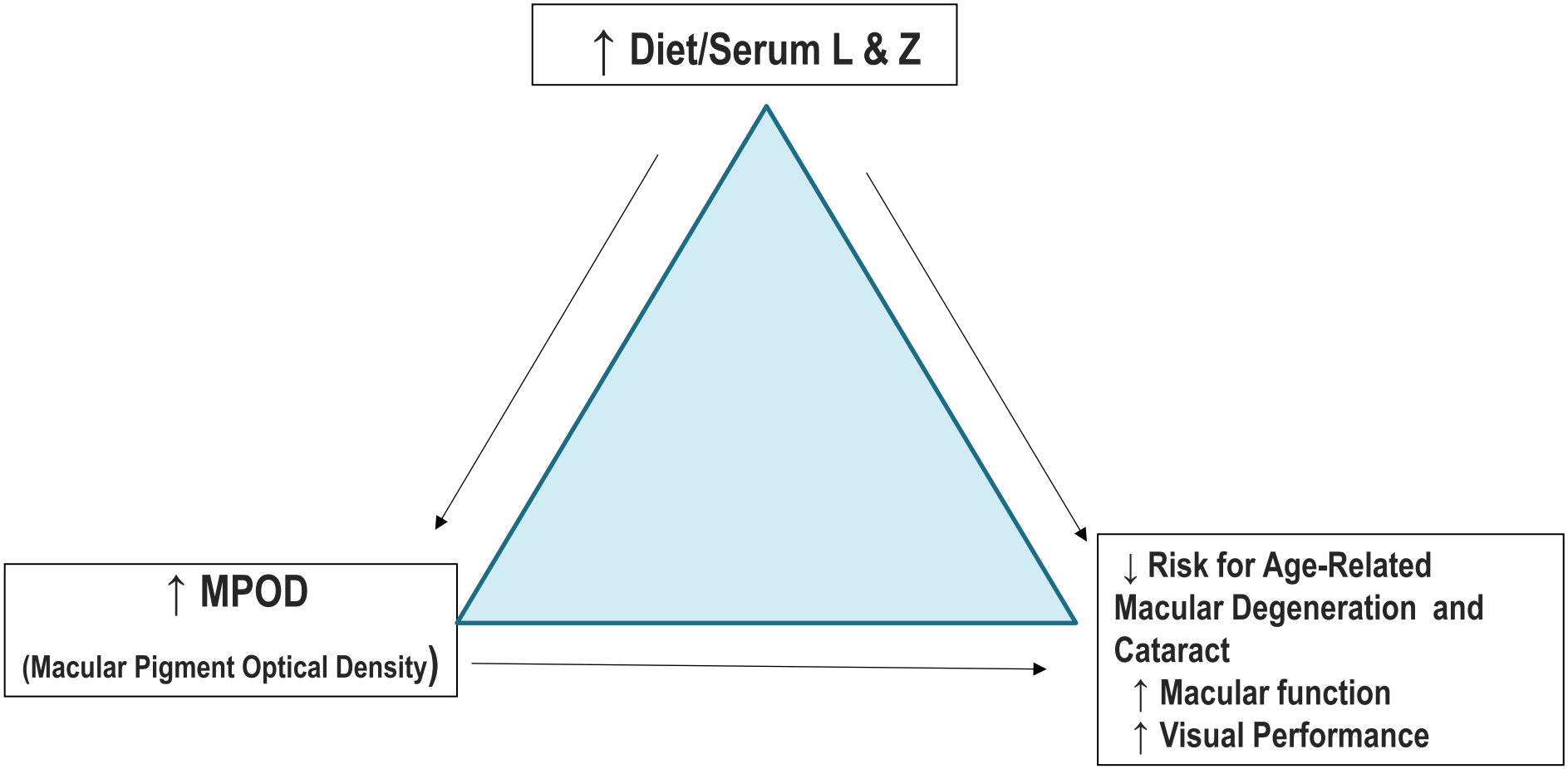
- Xanthophyll-free animals have no macular pigment or xanthophylls in their plasma[1]
  - Structural changes in their eyes compared to monkeys fed diets containing lutein[2]
  - When retina was exposed to blue-light these animals where more vulnerable to blue-light induced damage than the control animal[3]

- Lutein or zeaxanthin supplementation increases serum xanthophylls and macular pigment[1]

- Lutein supplementation decreases blue-light induced damage to the retina[3]

1. Neuringer M. et al. IOVS 2004; 45(9):3234-3243
2. Leung et al. Invest Ophthalmol Vis Sci 2004; 45:3244-56
3. Barker F.M. et al. IOVS 2011; 52(7):3934-3942

L & Z and MPOD - Eye Protection & Visual Performance



Bone et al. Exp Eye Res. 2000; 71:239-245; Ciulla et al. Ophthalmol. 1999; 128:75-80; Bone et al. Invest Ophthalmol Vis Sci. 2001; 34:2033-2040; Seddon et al. JAMA. 1994; 272:1413-1420; Delcourt et al. Invest Ophthalmol Vis Sci. 2006; 47(6):2329-35; Schalch et al. Arch.Biochem. Biophys. 2007; 458(2):128-35; AREDS Study Group Arch. Ophthalmol. 2007; 125:1225-1232: Stringham and Hammond. Optometry and Vision Science 2007; 84: 859-864; Stringham et al. Invest Ophthalmol Vis Sci. 2011 52(10):7406-15; Richer et al. Optometry 2004; 75(4):216-230; Richer et al. Optometry 2007; 78:213-219; Wenzel et al. Vis Res. 2006; 46:4615-22; Loughman et al. J. Optom. 2010; 3(2):73-89; Hammond et al. IOVS. 2013; 54(1):476-481; Hammond et al. Invest Ophthalmol Vis Sci 2014; 55(12):8583-9

Benefits of Lutein and Zeaxanthin Supplementation

- Supplementation with lutein & zeaxanthin alone or in combination with other nutrients (vitamins and minerals, other carotenoids or omega-3 Fatty Acids):
  - Increases serum levels of L&Z and MPOD
  - Improves macular function
  - Improves visual functions
    - Visual Acuity
    - Contrast sensitivity
    - Glare Recovery

Richer S. et al. Optometry 2004; 75(4):216-230; Richer S. et al. Optometry 2007; 78:213-219; Cangemi F. BMC Ophthalmology 2007; 7:3; Parisi V. et al. Ophthalmology 2008; 115(2):324-333; Richer S. et al. Optometry 2011; 82:667-680; Ma L. et al Ophthalmology 2012; 119(11):2290-7; Murray IJ. et al. IOVS 2013; 11:54(3):1781-8; Arnold et al. JAMA Ophthalmol. Published online March 21, 2013; Dawczynski et al. Graefes Arch clin Exp Ophthalmol. Published online on May 22, 2013; AREDS2 research Group. JAMA Published online May 5, 2013. Presented by Dr Emly Chew at ARVO Special section on May 5, 2013; AREDS2 Research Group et al. Ophthalmology 2012; 119(11):2282-9. Stringam and Hammond. Optometry and Vision Science. 2008; 85(2):82-88; Ma et al. Br. J. Nutr. 2009;102(2):186-90; Yao et al., Nutrition 2013; 29(7-8):958-64; Hammond et al. Invest Ophthalmol Vis Sci 2014; 55(12):8583-9

Dietary Antioxidants and Brain Health

- Healthy subjects with high fruit and vegetable intake (5 daily portions) have higher blood antioxidant levels and better cognitive scores than healthy subjects with low fruit and vegetable intake (1 daily portion)[1]
- Green and cruciferous vegetables are associated with a slower cognitive decline in ageing women[2]
- Elderly subjects with mild cognitive impairment (MCI) and patients with AD or vascular dementia have reduced plasma levels of non-enzymatic antioxidants (vitamin A, C, E, lutein, zeaxanthin, β-cryptoxanthin, lycopene and α-carotene) compared to healthy controls[3,4]
- In the Rotterdam study, high serum carotenoids were associated with less severe periventricular cerebral white matter lesions (WML)[5] and in Japanese males lower L/Z serum levels were associated with the presence of deep WML[6]

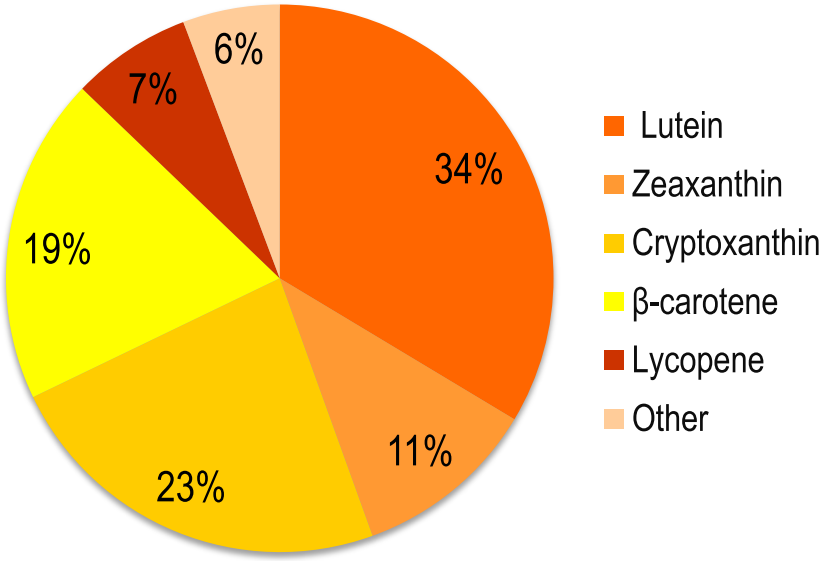
Low levels of serum carotenoids could play a role in cognitive impairment[7]

1. Polidori MC.et al. J Alzheimers Dis. 2009;17:921-927
2. Kang JH. et al. Ann Neurol. 2005; 57:713-720
3. Rinaldi P. et al. Neurobiol Aging. 2003; 24(7):915-9
4. Polidori MC. et al. Dement Geriatr Cogn Disord. 2004; 18:265-270
5. dem Heijer T. et al. J Am Geriatr Soc. 2001; 49(5):642-6
6. Ohshima Y. et al. J Nutr Health Aging. 2013; 17(5):456-60
7. Akbaraly NT. et al. J Gerentol A Biol Sci Med Sci. 2007; 62(3):308-316

Lutein is the Predominant Carotenoid in the Infant and Centenarian Brain

Centenarian Brain[1] (n=47)

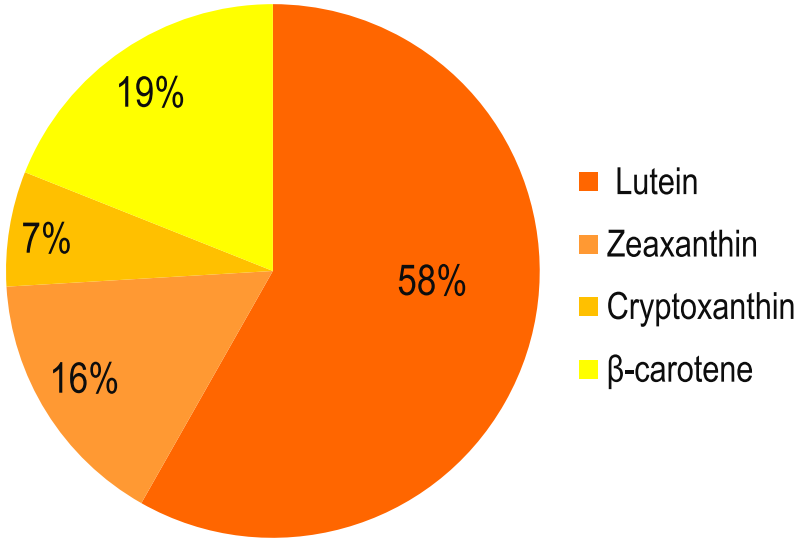
(% of total concentrations in cerebellum, frontal, occipital and temporal cortices)



Others: cis lutein isomers, 9 cis beta-carotene

Infant Brain[2] (n=30)

(% of total concentrations in hippocampus, prefrontal, frontal, occipital and auditory cortices)

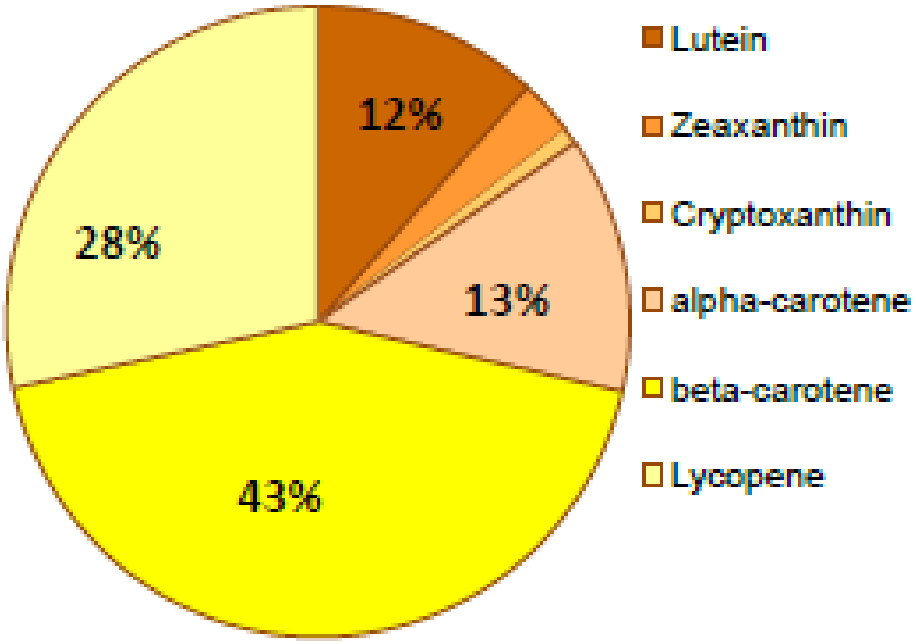


Lycopene detected only in 3 decedents,
No α-carotene was detected in any tissue

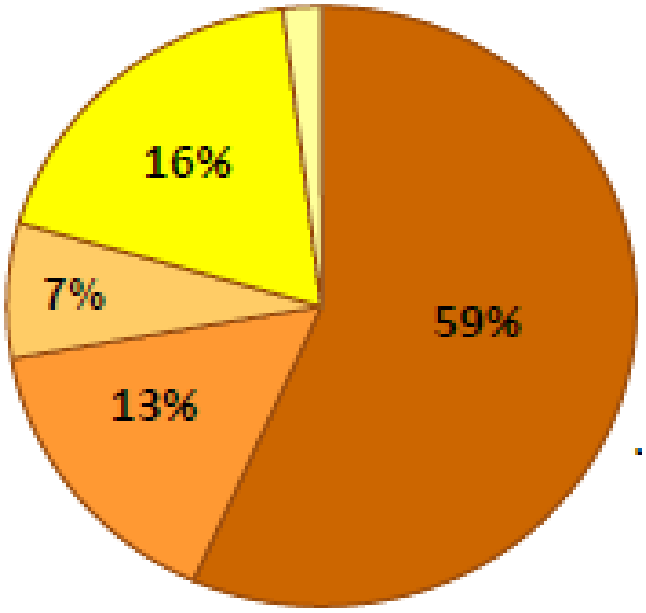
1. Johnson EJ. etal. J Aging Res. 2013; 2013:951786
2. Vishwanathan R et al.J Pedriatr Gastrenterol Nutr. 2014; 59(5):659-65

Preferential Uptake of Lutein into the Infant Brain

Diet[1]
(NHANES 1988-1994, 2-11 months)



Infant Brain Carotenoids[2]
(0-11 months)



Slide Courtesy of Dr. Elizabeth Johnson

[1]Food and Nutrition Board, Institute of Medicine (2000) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington (D.C.): National Academies Press. Available: http://www.nap.edu/books/0309072794/html/.
[2]Vishwanathan R et al. 2014, J Pedriatr Gastrenterol Nutr. 59(5):659-65

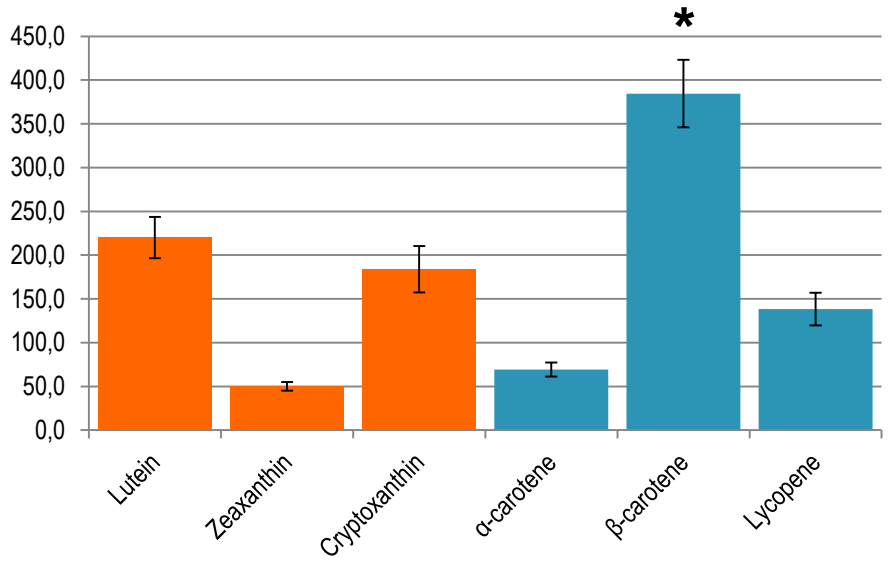
Preferential Uptake of Lutein into the Elderly Brain

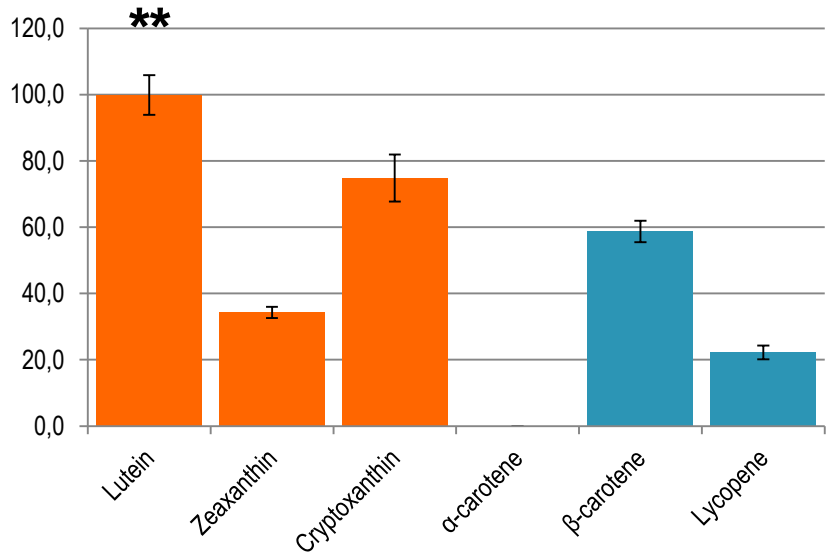
Serum carotenoids (nmol/L)

Brain Carotenoids (pmol/g)

Average of cerebellum, frontal, occipital and temporal cortices)

(Mean ± SEM, n=42)





Xanthophylls Carotenes

* Significantly greater than all other carotenoids ($p<0.02$)

** Significant greater than all other carotenoids ($p<0.0001$)

Cryptoxanthin is the sum of α- and β-cryptoxanthin

Johnson EJ. etal. J Aging Res. 2013; 2013:951786

Macular L & Z is related to Brain L & Z in Humans

Study population and design:

- Decedents aged >50 y with either normal cognitive function or Alzheimer's Disease (AD)
- Brain and Retina samples (analyzed by HPLC)
  - Retina: Whole retina
  - Brain: Occipital cortex (OC) (primarily responsible for visual processing) and Hippocampus (Hipp) (primarily associate with memory)

Aim: To examine the relationship between retinal and brain lutein and zeaxanthin; To explore the occurrence of meso-zeaxanthin (MZ) in human brain tissue

Results:

- No statistical difference in concentration of individual carotenoids in the retina and the brain between normal and AD decedents (data were combined)
- Lutein and cryptoxanthin concentration was significant higher in OC compared to Hipp
  - No difference for other carotenoids
- No MZ was detected in any of the brain tissues analyzed
- MP carotenoids were significanthy related to their level in the OC but not in the Hipp
  - Retinal L+MZ was significantly related to brain L concentration in the OC
  - Retinal Z not related to brain Z

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Vishwanathan R. et al. Nutr Neurosci. 2015 [Epub ahead of print]

Brain Lutein is Associated with Cognitive Performance
Georgia Centenarian Study

Study Population and Design

- Octogenarians (80-89years) and centenarians (age ≥ 98years), community- dwelling or institutionalized
  - Participants agreed to donate their brain after death
- Conducted from 2001 to 2009
- Brain tissues collected from 4 regions: right cerebellum, right temporal cortex, right and left frontal and occipital cortices
- Serum and brain concentration measured
- Cognitive function evaluated with a battery of tests to assess global cognitive function, dementia, depression as well as specific cognitive domanis such as memory, processing speed, attention and executive functioning
- Data analyzed for all participants together and separately based on the pre-mortem Global Deterioration Rating Scale (GDRS)

Objectives: To evaluate the relationship between serum cartenoids and cognitive function (all : n=298);
To evaluate the cross-sectional relationship between brain carotenoids and pre-mortem measures of cognitive function (Centenarian: n=47)

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Johnson EJ. et al. J Aging Res. 2013; 2013:951786

Brain Lutein is Associated with Cognitive Performance
Georgia Centenarian Study

Brain Carotenoids and Cognition:

- Brain carotenoids were significantly related to their concentration in serum
  - Xanthophylls account for 72% of the total carotenoids
- Lutein was the dominant carotenoid in all the brain tissues analyzed
  - **34% of the total** and significantly greater than all the other carotenoids
  - Greater concentration of L and Z in the cerebellum compared to occipital, temporal and frontal cortices
- Mean carotenoids concentration (pmol/g) decreases progressively with increasing GDRS scores from 1 (no memory deficits) to 3 (MCI)
  - Differences for L were statistically significant after adjusting for age, sex, education diabetes and hypertension

Global Deterioration Scale			
Group	1	2	3
Lutein (trans)	133±21	124±17	67±14*
(*p<0.05 compared to group 1)			

- Positive and significant correlations were observed between L and MMSE (cognitive function) and Boston Naming Test (language) and negative association with Geriatic Depression Scale
- Positive and significant association between Z and verbal fluency

Johnson EJ. et al. J Aging Res. 2013; 2013:951786

MPOD is Positively Associated with Cognitive Performance

- **Health Aging and Body Composition (ABC) Study[1]**
  - Cross-sectional study, 108 healthy older adults (77.6 y)
  - Aim: To assess whether cognitive measures are related to serum L /Z or MPOD
  - **Results:** Association with serum L+Z not consistent

    MPOD significantly and positively correlated to 6 out of 8 measures of cognitive function (global cognition, verbal learning, memory, executive function, speed and associative learning, perceptual speed)
- **TILDA Study[2]**
  - Cross-sectional study, 4453 Irish participants >50 y old
  - Aim: To nvestigate the relationship between MPOD and cognitive performance
    - Global Cognition, Memory, Executive function, Processing speed and Attention
  - **Results:** Subjects with lower MPOD showed significantly poorer performance on-

    Global Cognition Function, Executive Function, Prospective Memory and Processing Speed
- **Renzi 2014[3]**
  - 24 individuals with MCI (74.54 y old) compared to 24 age matched controls (73.69 y old)
  - Aim: To assess whether MPOD was related to cognitive function when comparing healthy older adults with adults with and without mild cognitive impaiment (MCI)
  - **Results:** In older adults without MCI MPOD was related to visual-spatial and constructional ability

    In older adults with MCI , MPOD was related to a more broad range of cognitive assessments

1 Vishwanathan R et al., Age and Ageing. 2014; 43:271-275
2 Feeney J et al. Neurobiol Aging. 2013; 34(11): 2449-56
3 Renzi L et al. Neurobiol Aging. 2014; 34: 1695-1699

Lutein Supports Cognitive Function

Study population and design:

- Randomized, double-blind, placebo-controlled trial
- 49 healthy older women (60-80 y old)
- Four month supplementation
  - Placebo (n=11),
  - Lutein (12 mg per day) (n=12),
  - DHA (800 mg/day) (n=14)
  - Lutein + DHA (n=14)

Aim: To assess the effect of supplementation with lutein and DHA on cognitive function (verbal fluency, memory, processing speed and accuracy in older adults

Results:

- Significant increase in serum lutein and in MPOD
- Significant improvements in verbal fluency in Lutein, DHA and Lutein+DHA groups compared to baseline
- Significant improvements in memory, rate of learning and learning efficiency in the Lutein+DHA group compared to baseline

This data suggests that supplementation with L alone and/or L with DHA has cognitive benefits in healthy older adults

Johnson EJ. et al. Am J Clin. Nutr. 2008; 87(5):1521-9
Johnson EJ. et al. Nutr Neurosci. 2008; 11(2):75-83

Summary on Lutein and Zeaxanthin

- Cannot be synthesized by humans and have to be obtained through the diet (or supplements)
  - Average intake of lutein/zeaxanthin is generally low
- Are key components of the macular pigment
  - High L & Z intake is associated with higher MPOD
- Supplementation with L & Z alone or in combination with other antioxidants or omega-3 FA has been shown to increase L & Z serum levels and MPOD and to benefit visual function
- L is the predominant carotenoid in adult and infant brains
- Macular L & Z are related to brain concentrations in primates and humans
- MPOD and brain L & Z have been shown to be significantly related to cognitive function in healthy adults including centenarians and subjects with MCI
- Lutein supplementation has been shown to significantly improve cognitive function in healthy older women compared to baseline

THANK YOU