Original Research
Nutrafoods (2016) 15:179-188
DOI 10.17470/NF-016-1014-3

The role of lutein in brain health and function

Samanta Maci*, Brenda Fonseca, Yong Zhu

Keywords:
Lutein,
Macular pigment optical density,
Brain,
Cognition

Correspondence to:
Samanta Maci
samanta.maci@kemin.com

Abstract

Lutein selectively accumulates in the macula lutea and is a key component of the macular pigment. Recent research has indicated that lutein is also the predominant carotenoid in both the adult and the infant brain, and studies conducted in primates and humans have shown that lutein concentration in the retina is related to its concentrations in specific regions of the brain. A carotenoid-rich diet and high plasma levels of lutein are positively associated with cognitive status or function in healthy subjects, those with mild cognitive impairment, and subjects with Alzheimer's disease.

Current research indicates that macular pigment optical density, a measure of dietary lutein (and zeaxanthin) deposited in the macula lutea, is positively associated with cognitive function. Additionally, interventional studies provide support that supplementation with lutein and/or zeaxanthin may enhance cognitive function and help maintain cognitive health. The beneficial effect of lutein is most likely linked to its antioxidant and anti-inflammatory properties, and its ability to integrate into cellular membranes, thereby influencing the structural properties and/or stability of those membranes, and possibly enhance gap junction communications. The aim of this review is to present the scientific evidence available to date.

Introduction

Lutein is well known for its role in eye health [1–4]. Three characteristics of lutein are reported to contribute to these health benefits, namely its antioxidant properties, anti-inflammatory benefits, and the nature of its interaction with lipid membranes [5–9]. New research shows that lutein crosses the blood–brain barrier and is the predominant carotenoid in the brain [5, 10], further suggesting that lutein has a critical role in overall brain health and cognitive function.

The eye and brain have a common developmental origin in the neural tube. Moreover, both organs are characterized by a high content of polyunsaturated fatty acids and high metabolic activity, making them particularly susceptible to oxidative stress and free radical damage [11]. Furthermore, carotenoids have been shown to enhance gap junction communication, which is proposed to be important for light processing in the retina and proper functioning of neural circuits in the visual system [5, 12], pointing to a joint role of lutein in both eye and brain health and function [13].

Cognition refers to the mental processes used to acquire knowledge and understanding. It is a multi-

*Kemin Human Nutrition and Health, a division of Kemin Foods L.C., Campo Grande 35- 8ºD, 1700-087 Lisbon, Portugal.
tel: +35 1214157500; fax: +35 1211412172

Received: April 22, 2016 / Accepted: July 03, 2016

dimensional concept divided into domains of memory, attention, language, information processing, and executive function [14]. Each of these cognitive domains can be influenced by factors such as sleep, mood, stress and diet. As the brain ages, declines are observed in specific domains of cognition such as processing speed, episodic and working memory, and executive function. These changes are believed to be caused by physiological damage due to oxidative stress and inflammation, among other factors [15]. Molecules such as lutein with strong antioxidant and anti-inflammatory properties have great potential to play a beneficial role in cognitive health.

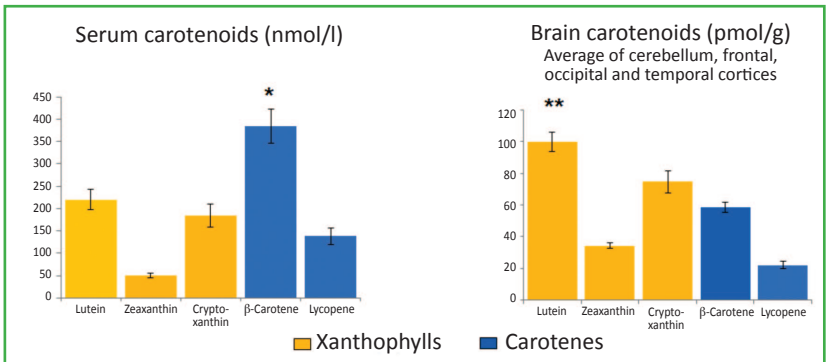

Figure 1 - Mean (± SEM) concentrations of carotenoids (trans isomers) in the serum and brain (average of cerebellum, frontal, occipital and temporal cortices) of decedents from the Georgia Centenarian Study (n=42). Cryptoxanthin is the sum of α- and β-cryptoxanthin.
*Significantly greater than all other carotenoids (p<0.02); **significantly greater than all other carotenoids (p<0.0001). Adapted from Johnson *et al*. [5]

Lutein is the predominant carotenoid in the brain

In 2004, Craft *et al.* published a study that identified and measured a broad range of antioxidants in the adult brain [16]. Sixteen carotenoids, three tocopherols and retinol were identified in brain tissue. They found that xanthophylls (lutein, zeaxanthin and cryptoxanthin) account for 66–77% of the carotenoids in the brain regions studied, while data from previously published research reported that xanthophylls only account for about 40% of the total carotenoids in human blood [17, 18], prompting Craft *et al.* to suggest that there may be a 'preferential accumulation of xanthophylls' in the brain. Johnson *et al.* confirmed and extended these results in a 2013 study that measured carotenoid levels in both the serum and brain tissue of 42 centenarian decedents [5]. Carotenes (α-carotene, β-carotene and lycopene) were the predominant carotenoids in the serum, accounting for over half (57%) of total serum carotenoids. However, the ratio was reversed in the brain, with xanthophylls (lutein, zeaxanthin and cryptoxanthin) making up 72% of total carotenoids in the brain with lutein alone accounting for over one third (34%) of all brain carotenoids, a significantly greater proportion compared to other carotenoids (p<0.02), once again suggesting a selective uptake of lutein into the human brain. Data for carotene and xanthophyll concentrations in the serum and brain are given in Fig. 1 (data for α-carotene are not presented because it was detected in serum but not in brain tissue). The authors additionally assessed the relationship between brain carotenoid levels and 6-month premortem measures of cognitive function and found significant and positive correlations between several cognitive measures and lutein and zeaxanthin concentrations in the cortex. The mean concentration of all carotenoids progressively decreased with increased Global Deterioration Rating Scale (GDRS) scores from 1 (normal cognitive function) to 3 (mild cognitive impairment, MCI). Among all carotenoids, only the difference in brain lutein content between MCI and cognitively unimpaired subjects remained statistically significant (p<0.05) after adjusting for age, sex, education, diabetes and hypertension.

A similar result confirming the preferential uptake of lutein in the brain was observed in a study on infant brains published in 2014 by Vishwanathan *et al.* [10]. Lutein comprised almost two-thirds (58%) of the carotenoids in infant brains, while zeaxanthin made up 16% of the brain carotenoids, resulting in lutein and zeaxanthin together representing 74% of the total carotenoids (Fig. 2) (data for lycopene, detected in some of the tissue in only three infants, are not reported). This high concentration of lutein relative to other dietary carotenoids is noteworthy if we consider a study of dietary intake of carotenoids in infants aged 2–11

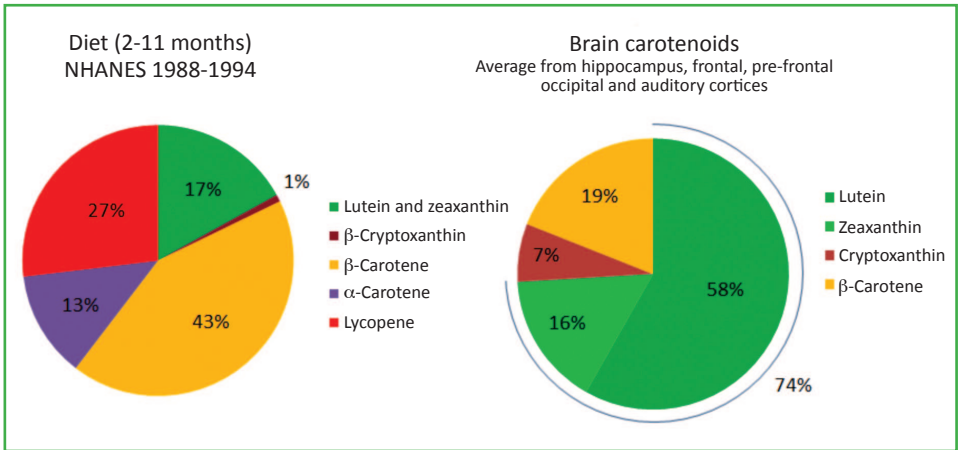

Figure 2 - Comparison of relative concentration of carotenoid in the diet of a male population 2–11 months old (data for lutein and zeaxanthin are combined in the referenced report) [19] and in 0–11-month-old infant brain (70% male) [10]

months (NHANES 1988-94) [19] which showed β-carotene as the major dietary carotenoid and lutein (assessed together with its dietary isomer zeaxanthin) representing only 17% of the total carotenoid intake (Fig. 2).

Scientific evidence

The importance of an adequate diet for maintaining general health and for sustaining optimal brain structure and function throughout life is well known [20]. Healthy subjects with high fruit and vegetable intake have higher blood antioxidant levels and better cognitive scores than healthy subjects with low fruit and vegetable intake [21]. Green and cruciferous vegetables are associated with a slower cognitive decline in ageing women [22]. These beneficial effects have been at least in part attributed to the nutritional compounds contained in these foods, including carotenoids [23]. For example, carotenoid-rich dietary patterns were positively associated with cognitive performance measured 13 years later [24]. Dietary intakes of lutein and zeaxanthin were found to be significantly lower in Alzheimer's disease (AD) subjects compared to healthy controls [25]. However, other papers assessing the relationship between diet and brain health have provided confounding results [26, 27].

A search of third party literature was conducted on PubMed through August 2015 to identify articles that evaluated the effect of lutein (and its isomer zeaxanthin, commonly discussed together with lutein) on cognitive health and function or their relationship in healthy adult subjects, those with MCI or those with AD. The search terms were "lutein" OR "zeaxanthin" AND "cognition" OR "brain" OR "dementia". Only observational studies addressing the relationship between plasma lutein (and zeaxanthin) levels and/or their concentration in the macula expressed as macular pigment optical density (MPOD) and cognitive status/function, and interventional trials involving adult participants and published in English were selected. A total of 24 studies were identified that met the search criteria. So that the selection would be as comprehensive as possible, three known published papers not retrieved by the search [21, 28, 29] were additionally included for a total of 27 papers.

Observational studies

Twenty-three papers discussed the results of observational studies conducted to assess the relationship between plasma levels of lutein and zeaxanthin and/or MPOD levels and cognitive status/function (see flowchart in Fig. 3).

Thirteen of the 16 observational studies retrieved in the literature search assessing plasma lutein and zeaxanthin levels and cognitive status/function indicate that higher plasma levels of lutein and, to some extent zeaxanthin, are positively associated with cognitive status/function [5, 7, 23, 25, 30–38], while three papers reported no or a negative association [21, 39, 40].

Plasma levels of lutein and/or zeaxanthin were found to be significantly lower in subjects with MCI, AD or vascular dementia when compared to age-matched healthy control subjects [7, 25, 30–33, 35, 36]. Studies assessing levels of oxidative stress show that AD subjects have higher plasma levels of 8-hydroxyl-2'-deoxyguanosine

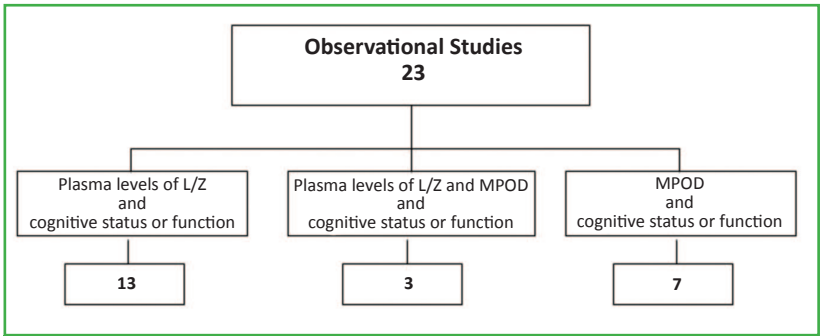

Figure 3 - Observational studies retrieved by the literature search addressing the relationship between plasma lutein/zeaxanthin (L/Z) and/or macular pigment optical density (MPOD) and cognitive status/function

(8-OHdG), a well-established biomarker of oxidative stress in DNA [30], or higher levels of phospholipid hydroperoxide (PLOOH) in red blood cells (RBC) [7] when compared to healthy subjects. Furthermore, lower plasma lutein levels were significantly correlated with higher plasma levels of 8-OHdG in AD subjects ($p<0.05$). A similar inverse correlation was observed with levels of PLOOH in RBC of both AD subjects and healthy controls ($p<0.05$ and $p<0.01$, respectively). Finally, in 2015 Feart *et al.* reported that in a population of 1,092 elderly subjects without dementia, higher plasma lutein levels were significantly associated with a decreased risk of dementia and AD over a 10-year follow-up period [23]. In the EVA ('Etude du Vieillissement Artériel') study [34] which included 589 participants, Akbaraly *et al.* showed that participants with the lowest cognitive performance, defined as a score below the 25th percentile in the neuropsychological tests, had a higher probability of having plasma zeaxanthin levels also below the 25th percentile. Data for the oldest old from the Georgia Centenarian Study [5] including 78 octogenarians (age between 80 and 89 years) and 220 centenarians (98 years or older) showed that serum lutein and zeaxanthin concentrations were more consistently associated with better performance in the different cognitive tests conducted than α-tocopherol, retinol or the majority of the other carotenoids assessed. In the octogenarian group, only serum lutein was significantly related to better cognition and executive function and lower dementia severity.

Additional support has been provided by the research conducted in the last decade and consolidated in the last 2 years that indicates that MPOD, a measure of lutein and zeaxanthin deposited in the macula lutea, is positively associated with cognitive function. All 10 observational studies measuring MPOD identified in the literature search confirmed this positive correlation [25, 28, 38, 40–46].

Studies conducted in healthy subjects across different age ranges have shown that MPOD is positively correlated with temporal processing speed and reaction time [28, 41, 43–45]. This indicates that subjects with higher MPOD have faster processing speeds and reaction times. It also supports the connection between eye and brain functionality.

In a study conducted in Ireland and enrolling 4,453 subjects 50 years of age or older [42], MPOD was found to be significantly and positively associated with two tests assessing global cognition – the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) – as well as other tests assessing specific cognitive domains. Subjects with lower MPOD had lower MMSE and MoCA scores and poorer performance in tests of prospective memory, executive function, mental processing speed and sustained attention. MMSE scores ranged on average from 28.6 to 28.2 by MPOD quintiles, while MoCA scores ranged from 25.2 to 24.6. The relationship between MPOD and different measures of cognitive performance in healthy subjects observed in this large study were additionally supported by two smaller studies published in 2014 [40] and 2015 [38] which were conducted in older and younger populations, respectively.

Research conducted in participants with MCI [46] has shown that MPOD is correlated with the composite MMSE score, the total score of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and index scores of visuospatial and constructional abilities, language ability and attention. Finally, a study comparing AD patients and healthy controls [25] indicates that MPOD is significantly lower in AD subjects.

A summary of all the observational studies addressing the relationship between MPOD and cognitive function is reported in Table 1.

Study	Participants	Key findings
Hammond *et al*, 2005 [28]	134 healthy subjects, 17–92 years old (average age 43.8 years)	Significant positive relationship between MPOD and temporal processing speed (CFF) threshold
Renzi *et al*, 2010 [41]	70 healthy subjects 15–84 years old (mean age 33 years)	Significant relationship between MPOD and temporal vision (tCSF) MPOD was also significantly related to CFF values
Feeney *et al*, 2013 [42]	4,453 community-dwelling subjects ≥50 years old (mean age 62.4 years)	MPOD was significantly associated with the two measures of global cognition: the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) Subjects with lower MPOD showed poorer prospective memory, executive function, mental processing speed and sustained attention after adjusting for age, sex and education
Renzi *et al*, 2013 [43]	49 healthy subjects (mean age 54.8 years) and 106 healthy younger subjects (mean age 20.3 years)	MPOD was significantly correlated with simple reaction time and balance ability in older healthy subjects In young subjects, MPOD was significantly related to fixed and variable reaction time, and coincidence anticipation ability at high speed
Bovier *et al*, 2014 [44]	92 healthy younger subjects 18–32 years old (average age 21.7 years)	Significant correlation was found between MPOD and CFF threshold or coincidence anticipation performance at some speeds indicating that subjects with higher MP had faster processing speed and better coincidence anticipation performance
Bovier *et al*, 2015 [45]	102 healthy younger subjects 18–32 years old	Significant correlation was found between MPOD and foveal and parafoveal tCSF at all frequencies tested
Nolan *et al*, 2014 [25]	36 subjects with mild to moderate AD (80 years old) and 33 controls (76 years old)	Central MP and MP volume were significantly lower in AD subjects compared to controls
Renzi *et al*, 2014 [46]	53 older subjects aged 65–95 years, with MCI (n=24; mean age 74.5 years) or age-matched healthy controls (n=29, mean age 73.7 years)	In healthy participants, MPOD was correlated with visuospatial and constructional abilities In MCI participants, MPOD was correlated with composite MMSE score, visuospatial and constructional abilities, language ability, attention, and total scale of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).
Vishwanathan *et al*, 2014 [40]	108 healthy subjects (mean age 77.6 years)	MPOD was significantly correlated with 6 out of the 8 measures of cognitive performance including measures of global cognition, verbal learning and fluency, verbal recall, processing speed and perceptual speed
Kelly *et al*, 2015 [38]	105 subjects free of retinal diseases (mean age 47 years) and 121 subjects with AMD (mean age 65 years)	Macular pigment was significantly and beneficially correlated with various measures of cognitive function in both groups

AD Alzheimer's disease, *AMD* age-related macular degeneration, *CFF* critical flicker fusion, *MCI* mild cognitive impairment, *MP* macular pigment, *MPOD* macular pigment optical density, *tCSF* temporal contrast sensitivity function

Table 1 - Summary of observational studies assessing the relationships between MPOD and cognitive function in healthy subjects and patients with age-related macular degeneration or Alzheimer's disease

The relationship between MPOD and cognitive function is further supported by studies conducted in primates [47] and humans [48]. These studies have confirmed that lutein concentration in the retinal region is consistently related to its concentrations in the occipital cortex (the primary visual processing area of the brain). Additional macular–brain associations were found in primates for lutein and zeaxanthin and the cerebellum, lutein and pons, as well as for zeaxanthin and the frontal cortex. These findings suggest that MPOD has the potential to be used as a non-invasive biomarker for lutein and zeaxanthin concentration in the brain and potentially explain the observed relationship between MPOD and cognition.

Interventional studies

Interventional studies also provide support that supplementation with lutein and/or zeaxanthin may enhance cognitive function and help maintain cognitive health. A total of six randomized, double-blind, controlled interventional studies have been conducted to date to investigate the role of lutein and zeaxanthin in cognitive functions [29, 44, 45, 49–51]; five of these studies used FloraGLO® Lutein as the source of lutein at a dose ranging from 8 to 12 mg. A study by Johnson *et al.* [49] provided 4 months of supplementation with lutein, DHA or a combination of both to a group of healthy 60–80-year-old women.

The research found a statistically significant improvement in verbal fluency scores for both the lutein and the DHA groups as well as significant improvements in three other measures of cognition for the lutein plus DHA combination group. Serum lutein and DHA levels also increased significantly. This study represents the first of its kind conducted to determine the role of lutein on cognitive measures in older adults. It showed that lutein supplementation significantly improved verbal memory, a measure of executive function and frontal lobe capabilities.

In addition, Bovier *et al.* [44] conducted a 4-month supplementation regimen in healthy 18–32-year-old men and women. Subjects were supplemented with high-dose zeaxanthin, lutein plus high-dose zeaxanthin and omega-3 fatty acids, or placebo. Neural processing speed was assessed at the end of the supplementation period. The researchers found that critical flicker fusion thresholds and missed coincidence anticipation time, two measures of neural processing speed, were improved upon supplementation. A second publication by the same group in 2015 using the same formulations assessed the effects of supplementation on visual processing speed [45]. Significant improvements were seen in temporal processing speeds via increased temporal contrast sensitivity function scores after 4 months of supplementation. The researchers observed a 20% increase in visual processing speed in the young healthy subjects. The baseline data in these two studies were also considered in the observational studies pool discussed above.

Three interventional studies have observed mixed effects on cognition after supplementation with lutein or zeaxanthin [29, 50, 51]. These studies are similar in that they were all conducted in non-healthy subject populations diagnosed with either age-related macular degeneration (AMD) or AD, so it may not be appropriate to translate the results to a general healthy population. Only one of the studies used a true placebo-controlled design and all studies were conducted in an older subject demographic.

In 2015, Chew *et al.* [50] conducted a secondary analysis on the AREDS2 trial data and failed to find a statistically significant difference on a composite cognitive score between a lutein/zeaxanthin group and a non-lutein/zeaxanthin group following 5 years of supplementation. The study only included subjects with medically diagnosed AMD, a neurodegenerative disease with unknown consequences on cognition in a population with an average age of 72 years. In addition, as an ancillary evaluation, the authors state that this portion of the study was not sufficiently powered to assess the cognitive benefits of supplementation. In order to control for multiple comparisons, the researchers set the α level for the study at $p<0.001$. With those limitations, the researchers still observed trends in recall ($p=0.06$) and Wechsler logical memory ($p=0.02$) test scores in the lutein and zeaxanthin treated group.

A 1-year supplementation study with zeaxanthin, lutein and zeaxanthin, or lutein by itself by Hoffman *et al.* [29] was also conducted in an older population diagnosed with mild AMD. The researchers found a significant improvement from baseline in delayed memory in the zeaxanthin only group but failed to find any other statistically significant changes in cognitive performance among the other two groups. Also, a study by Nolan *et al.* [51] with AD subjects (MMSE scores between 14 and 24) and healthy controls utilized 6-month supplementation with meso-zeaxanthin, lutein and zeaxanthin or placebo. The researchers observed significant improvements in serum concentrations, macular pigment and contrast sensitivity but failed to find a significant change in the cognitive measures assessed. The lack of cognitive findings could be due to the start of treatment after the onset of AD. The authors concluded that the results were not surprising given the fact that for lutein to have a beneficial effect, the optimal conditions are to start treatment with lutein prior to the onset of a neurodegenerative disease state. In addition, the small samples sizes (average of n=13 per group) resulted in some of the cognitive tests not being evaluated due to statistical assumption violations.

A summary of the interventional studies is shown in Table 2. In order to keep the table concise, only lutein or zeaxanthin outcomes in the listed papers have been summarized.

Study	Cohort	Study design	Key findings
Johnson *et al*, 2008 [49]	49 healthy women aged 60–80 years	R, DB, PC study 4-month supplementation with: • 12 mg FloraGLO® Lutein • 800 mg docosahexanoic acid (DHA) • 12 mg FloraGLO Lutein + 800 mg DHA • Placebo	Significant improvement in verbal fluency in the FloraGLO® Lutein and DHA groups from baseline Significant improvement in shopping list, word list and delayed recall memory tests in the FloraGLO Lutein+DHA group from baseline
Bovier *et al*, 2014 [44]	64 healthy young subjects aged 18–32 years	R, DB, PC study 4-month supplementation with: • 20 mg zeaxanthin • 8 mg FloraGLO Lutein + 26 mg zeaxanthin + 190 mg omega-3 fatty acids • Placebo	Significant improvements in neural processing speed (critical flicker fusion thresholds and missed coincidence anticipation time) for both treatment groups combined from baseline
Bovier *et al*, 2015 [45]	69 healthy young subjects 18–32 years old	R, DB, PC study 4-month supplementation with: • 20 mg zeaxanthin • 8 mg FloraGLO Lutein + 26 mg zeaxanthin + 190 mg omega-3 fatty acids • Placebo	Significant improvements in visual processing speed (temporal contrast sensitivity function) for both treatment groups from baseline
Chew *et al*, 2015 [50]	3073 AMD patients (mean age 72.7 years)	R, DB, standard of care controlled study 4-year supplementation with: • 10 mg FloraGLO Lutein + 2 mg zeaxanthin • 1 g omega-3 fatty acids • 10 mg FloraGLO Lutein + 2 mg zeaxanthin + 1 g omega-3 • Standard of care placebo*	Secondary analysis did not find a significant difference on a composite cognitive score between the lutein/zeaxanthin group and a non-lutein/zeaxanthin group Recall and memory test scores showed trends towards improvement in the FloraGLO Lutein and zeaxanthin group
Hoffmann *et al*, 2015 [29]	60 male subjects with early AMD (mean age 75.1 years)	R, DB, lutein controlled study 1-year supplementation with: • 8 mg zeaxanthin • 9 mg FloraGLO Lutein + 8 mg zeaxanthin • 10 mg FloraGLO Lutein	Significant improvements in delayed memory test scores in the zeaxanthin only group compared to baseline
Nolan *et al*, 2015 [51]	31 AD subjects (mean age 80 years), and 31 healthy controls (mean age 76 years)	R, DB, PC study 6-month supplementation with: • 10 mg lutein + 2 mg zeaxanthin + 10 mg meso-zeaxanthin • Placebo	No significant change in any cognitive functions examined in either AD subjects or controls

*All subjects (including those assigned to the placebo group received high doses of vitamin C and vitamin E, and zinc, copper and β-carotene (AREDS1 formula or a modification of it)
AD Alzheimer's disease, *DB* double-blind, *PC* placebo-controlled, *R* randomized

Table 2 - Summary of interventional studies assessing the effects of lutein and/or zeaxanthin supplementation and cognitive function in healthy subjects, individuals with age-related macular degeneration (AMD), or individuals with Alzheimer's disease (AD)

Conclusions

The body of literature presented demonstrates that lutein crosses the blood–brain barrier and is the predominant carotenoid in the adult and infant human brain. This supports lutein's role as an important nutrient for brain health and function throughout the lifespan. Observational data are consistent in suggesting that plasma lutein (and zeaxanthin) levels and MPOD are positively associated with cognitive function. Studies conducted in primates and humans indicate that macular pigment carotenoids in the retina are significantly correlated with lutein and zeaxanthin concentrations in the brain, further indicating that MPOD may serve as a non-invasive biomarker for lutein and zeaxanthin concentration in the brain and potentially for cognitive health. Furthermore, interventional studies investigating the effects of lutein and possibly zeaxanthin on cognitive function provide initial support that supplementation with these xanthophylls may enhance cognitive function and help maintain cognitive health. Although most of the data discussed were on older adults,

there is evidence from observational and intervention studies in support of the benefit of lutein and zeaxanthin on processing speed and reaction time in a young adult population. Additional studies aiming to further elucidate these benefits are now being conducted. Little is currently known about the role of lutein in early life. Lutein is present in cord blood and is the predominant carotenoid in human colostrum and breast milk. Cheatham and co-authors [52] explored the relationship between lutein, choline and DHA levels in human milk and recognition memory in 5-month-old infants and showed that high levels of lutein and choline are associated with better recognition memory. The neuroprotective effect of lutein and zeaxanthin is most likely linked to its antioxidant and anti-inflammatory properties, its ability to integrate into cellular membranes thereby influencing the structural properties and/or stability of those membranes, and possibly to enhance gap junction communications. In an exploratory metabolomics analysis conducted on postmortem infant brain tissues, Lieblein-Boff and co-authors [53] indicated that lutein is concentrated in neural tissues important for learning and memory and is correlated with fatty acids, phospholipids, antioxidants and amino acid neurotransmitters in the brain. Additional work demonstrated significant correlations across the lifespan for brain concentrations of lutein and StARD3, a specific binding protein for lutein previously identified in retinal tissues, suggesting a possible mechanism for the selective accumulation of lutein in the brain [54]. As both lutein and StARD3 are found in membranes, future studies investigating lutein's role in modulation of the functional properties of synaptic membranes could help to elucidate the specific mechanisms of action underlying the beneficial role of lutein in brain health and function.

Conflict of Interest

Samanta Maci, Brenda Fonseca and Yong Zhu are employees of Kemin Food L.C.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Hammond B, Fletcher LM, Roos F, Wittwer J, Schalch W (2014) A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. Invest Ophthalmol Vis Sci 55:8583–8589
2. Ma L, Dou HL, Wu YQ, Huang YM, Huang YB, Xu XR, Zou ZY, Lin X (2012) Lutein and zeaxanthin intake and the risk of age-related macular degeneration: a systematic review and meta-analysis. Br J Nutr 107:350–359
3. Age-Related Eye Disease Study 2 (AREDS2) Research Group (2014) Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression. AREDS2 Report No. 3. JAMA Ophthalmol 132:142–149
4. Dawczynski J, *et al.* (2013) Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study. Graefes Arch Clin Exp Ophthalmol 251:2711–2723
5. Johnson E, Vishwanathan R, Johnson MA, Hausman DB, Davey A, Scott TM, Green RC, Miller LS, Gearing M, Woodard J, Nelson PT, Chung HY, Schalch W, Wittwer J, Poon L (2013) Relationship between serum and brain carotenoids, α-tocopherol, and retinol concentrations and cognitive performance in the oldest old from the Georgia Centenarian Study. J Aging Res. doi: 10.1155/2013/951786. Epub 2013 Jun 9
6. Kritchevsky SB, *et al.* (2000) Serum carotenoids and markers of inflammation in nonsmokers. Am J Epidemiol 152:1065–1071
7. Kiko T, Nakagawa K, Tsuduki T, Suzuki T, Arai H, Miyazawa T (2012) Significance of lutein in red blood cells of Alzheimer's disease patients. J Alzheimers Dis 28:593–600
8. Gruszecki WI, Strzalka K (2005) Carotenoids as modulators of lipid membrane physical properties. Biochim Biophys Acta 1740:108–115
9. Stahl W, Nicolai S, Briviba K, Hanusch M, Broszeit G, Peters M, Martin HD, Sies H (1997) Biological activities of natural and synthetic carotenoids: induction of gap junctional communication and singlet oxygen quenching. Carcinogenesis 18:89–92
10. Vishwanathan R, Kuchan MJ, Sen S, Johnson E (2014) Lutein and preterm infants with decreased concentrations of brain carotenoids. J Pediatr Gastroenterol Nutr 59:659–665
11. Johnson E (2012) A possible role for lutein and zeaxanthin in cognitive function in the elderly. Am J Clin Nutr 96:1161S–1165S
12. Stahl W, Sies H (1998) The role of carotenoids and retinoids in gap junctional communication. Int J Vitam Nutr Res

68:354–359

13. Ohno-Matsui K (2011) Parallel findings in age-related macular degeneration and Alzheimer's disease. Prog Retin Eye Res 30:217–238
14. Blazer D, Yaffe K, Liverman CT (2015) Cognitive aging: progress in understanding and opportunities for action. The National Academies Press, Washington, D.C.
15. Riddle D (2007) Brain aging: models, methods, and mechanisms. CRC Press, Boca Raton, FL
16. Craft N, Haitema TB, Garnett KM, Fitch KA, Dorey CK (2004) Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J Nutr Health Aging 8:156–162
17. Kaplan LA, Lau JM, Stein EA (1990) Carotenoid composition, concentrations, and relationships in various human organs. Clin Physiol Biochem 8:1–10
18. Nierenberg DW, Nann SL (1992) A method for determining concentrations of retinol, tocopherol, and five carotenoids in human plasma and tissue samples. Am J Clin Nutr 56:417–426
19. Department of Health and Human Services, Center for Disease Control and Prevention, and National Center for Health Statistics (2002) Dietary intake of macronutrients, micronutrients, and other dietary constituents: United States, 1988–94. Vital and Health Statistics, Series 11, Number 245
20. Hamer M, Dye L, Mitchel ES, Laye S, Saunders C, Boyle N, Schuermans J, Sijben J (2016) Examining techniques for measuring the effects of nutrients on mental performance and mood state. Eur J Nutr. Published online 7 Jan
21. Polidori M, Praticó D, Mangialasche F, Mariani E, Aust O, Anlasik T, Mang N, Pientka L, Stahl W, Sies H, Mecocci P, Nelles G (2009) High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. J Alzheimers Dis 17:921–927
22. Kang J, Ascherio A, Grodstein F (2005) Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol 57:713–720
23. Feart C, Letenneur L, Helmer C, Samieri C, Schalch W, Etheve S, Delcourt C, Dartigues JF, Barberger-Gateau P (2015) Plasma carotenoids are inversely associated with dementia risk in an elderly French cohort. J Gerontol A Biol Sci Med Sci 71:683–688
24. Kesse-Guyot E, Andreeva VA, Ducros V, Jeandel C, Julia C, Hercberg S, Galan P (2014) Carotenoid-rich dietary patterns during midlife and subsequent cognitive function. Br J Nutr 111:915–923
25. Nolan J, Loskutova E, Howard AN, Moran R, Mulcahy R, Stack J, Bolger M, Dennison J, Akuffo KO, Owens N, Thurnham ID, Beatty S (2014) Macular pigment, visual function, and macular disease among subjects with Alzheimer's disease: an exploratory study. J Alzheimers Dis 42:1191–1202
26. Nooyens A, Milder E, van Gelder BM, Bueno-de-Mesquita HB, van Boxtel MP, Verschuren W (2015) Diet and cognitive decline at middle age: the role of antioxidants. Br J Nutr 113:1410–1417
27. Takeda A, Nyssen OP, Syed A, Jansen E, Bueno-de-Mesquita B, Gallo V (2014) Vitamin A and carotenoids and the risk of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 42:25–38
28. Hammond B, Wooten BR (2005) CFF thresholds: relation to macular pigment optical density. Ophthalmic Physiol Opt 25:315–319
29. Hoffmann K, Richer SP, Wrobel JS, Chen E, Podella C (2015) A prospective study of neuro-cognitive enhancement with carotenoids in elderly adult males with early age related macular degeneration. Ophthalmol Res 4:1–8
30. Mecocci P, Polidori MC, Cherubini A, Ingegni T, Mattioli P, Catani M, Rinaldi P, Cecchetti R, Stahl W, Senin U, Beal MF (2002) Lymphocyte oxidative DNA damage and plasma antioxidants in Alzheimer disease. Arch Neurol 59:794–798
31. Polidori M, Mecocci P (2002) Plasma susceptibility to free radical-induced antioxidant consumption and lipid peroxidation is increased in very old subjects with Alzheimer disease. J Alzheimers Dis 4:517–522
32. Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, Cherubini A, Catani M, Cecchetti R, Senin U, Mecocci P (2003) Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol Aging 24:915–919
33. Polidori M, Mattioli P, Aldred S, Cecchetti R, Stahl W, Griffiths H, Senin U, Sies H, Mecocci P (2004) Plasma antioxidant status, immunoglobulin g oxidation and lipid peroxidation in demented patients: relevance to Alzheimer disease and vascular dementia. Dement Geriatr Cogn Disord 18:265–270
34. Akbaraly NT, *et al.* (2007) Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA study. J Gerontol A Biol Sci Med Sci 62:308–316
35. Wang W, Shinto L, Connor WE, Quinn JF (2008) Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity. J Alzheimers Dis 13:31–38
36. Dias I, Polidori MC, Li L, Weber D, Stahl W, Nelles G, Grune T, Griffiths HR (2014) Plasma levels of HDL and carotenoids are lower in dementia patients with vascular comorbidities. J Alzheimers Dis 40:399–408
37. Min J, Min KB (2014) Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults. Dement Geriatr Cogn Disord 37:246–256

38. Kelly D, Coen RF, Akuffo KO, Beatty S, Dennison J, Moran R, Stack J, Howard AN, Mulcahy R, Nolan J (2015) Cognitive function and its relationship with macular pigment optical density and serum concentrations of its constituent carotenoids. J Alzheimers Dis 48:261–277
39. Schmidt R, Hayn M, Reinhart B, Roob G, Schmidt H, Schumacher M, Watzinger N, Launer LJ (1998) Plasma antioxidants and cognitive performance in middle-aged and older adults: results of the Austrian Stroke Prevention Study. J Am Geriatr Soc 46:1407–1410
40. Vishwanathan R, Iannaccone A, Scott TM, Kritchevsky SB, Jennings BJ, Carboni G, Forma G, Satterfield S, Harris T, Johnson KC, Schalch W, Renzi LM, Rosano C, Johnson E (2014) Macular pigment optical density is related to cognitive function in older people. Age Ageing 43:271–275
41. Renzi L, Hammond B (2010) The relation between the macular carotenoids, lutein and zeaxanthin, and temporal vision. Opthalmic Physiol Opt 30:351–357
42. Feeney J, Finucane C, Savva GM, Cronin H, Beatty S, Nolan JM, Kenny RA (2013) Low macular pigment optical density is associated with lower cognitive performance in a large, population-based sample of older adults. Neurobiol Aging 34:2449–2456
43. Renzi L, Bovier ER, Hammond BR (2013) A role for the macular carotenoids in visual motor response. Nutr Neurosci 16:262–268
44. Bovier E, Renzi LM, Hammond B (2014) A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency. PLoS One 9:e108178
45. Bovier E, Hammond B (2015) A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. Arch Biochem Biophys 572:54–57
46. Renzi L, Dengler MJ, Puente A, Miller LS, Hammond B (2014) Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults. Neurobiol Aging 35:1695–1699
47. Vishwanathan R, Neuringer M, Snodderly DM, Schalch W, Johnson E (2013) Macular lutein and zeaxanthin are related to brain lutein and zeaxanthin in primates. Nutr Neurosci 16:21–29
48. Vishwanathan R, Schalch W, Johnson EJ (2016) Macular pigment carotenoids in the retina and occipital cortex are related in humans. Nutr Neurosci 19:95–101
49. Johnson EJ, *et al.* (2008) Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci 11:75–83
50. Chew E, Clemons TE, Agrón E, Launer LJ, Grodstein F, Bernstein PS; Age-Related Eye Disease Study 2 (AREDS2) Research Group (2015) Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 Randomized Clinical Trial. JAMA 314:791–801
51. Nolan J, Loskutova E, Howard A, Mulcahy R, Moran R, Stack J, Bolger M, Coen RF, Dennison J, Akuffo KO, Owens N, Power R, Thurnham D, Beatty S (2015) The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. J Alzheimers Dis 44:1157–1169
52. Cheatham CL, Sheppard KW (2015) Synergistic effects of human milk nutrients in the support of infant recognition memory: an observational study. Nutrients 7:9079–9095
53. Lieblein-Boff JC, Johnson EJ, Kennedy AD, Lai CS, Kuchan MJ (2015) Exploratory metabolomic analyses reveal compounds correlated with lutein concentration in frontal cortex, hippocampus, and occipital cortex of human infant brain. PLoS One 10:e0136904
54. Tanprasertsuk J, Li B, Bernstein PS, Vishwanathan R, Johnson MA, Poon L, Johnson EJ (2016) Relationship between concentrations of lutein and StARD3 among pediatric and geriatric human brain tissue. PloS One 11:e0155488