SuperiorAntioxidant™

Goal

To supply a NSF Certified for Sport (NSFCS) product containing corrective amounts, when combined with diet, of the natural bio-active compounds: lycopene, lutein, zeaxanthin, astaxanthin, Co-enzyme Q10 (CoQ_{10}) and alpha lipoic acid, to achieve daily levels associated with better overall health and recovery outcomes at all life stages. The goals of achieving proper levels of these combined ingredients are to 1) supply structural and functional components limited by diet, allergies or age; 2) offer unique non-vitamin/mineral antioxidant protection to help manage free radical production caused by normal biological processes and exacerbated by stress, aging, exercise, and the environment; 3) help control obligatory inflammation – i.e. free radical and antioxidant/inflammation balance; and 4) cumulatively support daily energy and recovery.

Desired outcomes after 30 days of continuous daily use compared to a non-supplemented state and especially when combined with a complete daily multivitamin and mineral formula (MVM) containing at least the known under-consumed vitamins and minerals, include enhanced energy, improved and reduced recovery time, and unique structural and functional support for the maintenance of eye, cardiovascular, immune, skin and brain health. Further, this product contains the individual ingredients (carotenoids, alpha-lipoic acid and CoQ-10) in amounts and forms shown to be consistent with what is needed to raise the food content of these bio-actives to match levels associated with the above goals contributing to healthy aging and the prolonged ability to perform desired activities at the highest level.

Practitioners should be mindful that dietary supplements designed to support health are formulated around the "prevention before cure" approach, meaning correcting food intake nutrition levels through filling nutrition gaps (i.e., supplementing the diet) to meet recommended levels over a lifetime, thus allowing the necessary nutrient/bioactive synergy in the creation, development and maintenance of human tissues leading to a superior human entity than otherwise.

Rationale

The bio-active compounds: lycopene,[1] lutein,[2] zeaxanthin,[3] astaxanthin,[4] CoQ_{10},[5] and alpha lipoic acid[6] are naturally present in the human body, primarily from specific foods we may or may not regularly consume, and make significant and indispensable contributions to human health and performance.[1,2,3,4,5,6,7,8]

Humans and other animals cannot synthesize carotenoids in meaningful quantities and therefore they must be supplied through diet.[9,10] Carotenoids (e.g., lycopene, zeaxanthin, lutein, astaxanthin, etc.) are health promoting bio-actives which are synthesized in plants/algae, bacteria, yeast and fungi, and are acquired by humans by consuming these organisms as foods.[11,12]

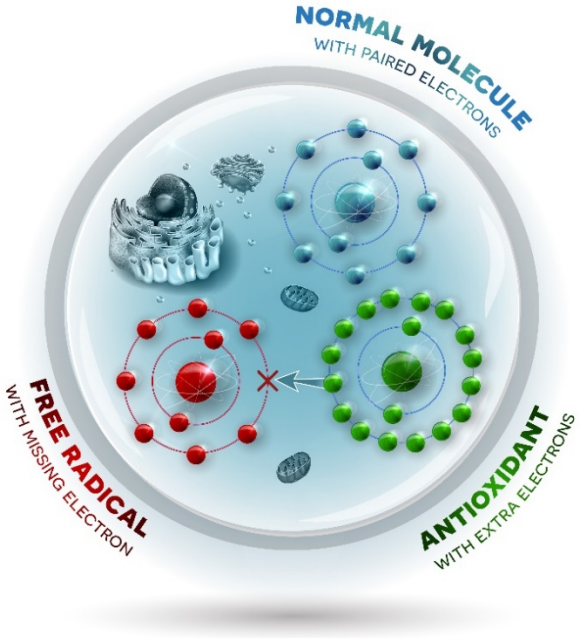
Although there are no formal recommendations for daily individual carotenoid consumption, compared to expert findings on carotenoid intakes, (founded on carotenoid blood/tissue levels associated with health benefits[327]),[13,14] the specific carotenoids named above are found to be commonly low throughout the human body due to: under-consumption/food preferences or availability,[7,15,16,17] limited bio-availability,[18,19,20] allergies,[21,22] or aging,[23] but demonstrated to be structurally and functionally critical to human health including, along with alpha-lipoic acid and CoQ_{10}, supporting energy, daily recovery, immunity, and healthier aging giving rise for supplementation to bridge the food gap.[1,2,3,4,5,6,7,8,16,24] Although alpha-lipoic acid and CoQ_{10} also have strong antioxidant qualities, they are intrinsically connected to cellular energy production and can be supplied by diet and synthesized by humans.[5,6] However, diet choices and aging compromise substrate availability and the natural biosynthesis of both molecules often justifies supplementation.[5,6,25,26] Additionally, excessive mental and physical stress (also a major cause of immune suppression), dieting, and environmental insults to the human metabolism/organism may increase the need for these active substances thus adding to the above known under-consumption and aging rationale for supplementation.[27,28,29,30,31,32,33,34]

The Carotenoids, Lycopene, Lutein, Zeaxanthin and Astaxanthin

Besides dividing carotenoids into pro-vitamin A and non-pro-vitamin A classes, depending on the identification of an oxygen molecule in the carotenoid, they are often separated into two basic categories, 1) oxygen containing xanthophylls or 2) unoxygenated carotenes. Lycopene is a carotene and astaxanthin, lutein and zeaxanthin are xanthophylls.[35]

Carotenoids which are unable to be synthesized by humans, are naturally occurring lipophilic pigments found in most vegetables and fruits and when consumed in adequate quantities, are associated with significant reductions in health risks and improved cardiovascular, ocular, brain, muscular skeletal, skin and aging health overall.[8,10,34] Unfortunately most persons in the US and other developed nations are woefully low on fruit and vegetable intake[17,36,37] and therefore missing the carotenoids' full health contributions including positive effects on gene expression, the structural integrity of tissue/organ components, protection from free radical damage (antioxidant properties, see Figure 1) and inflammation, both conditions that lead to compromised immunity, poor overall health outcomes and early aging.[7,8,10,34,38,39,40]

Figure 1 – How Antioxidants Work



Free radicals are part of normal biological processes, but damage becomes excessive from underperforming antioxidant systems due to physical and environmental insults from stress, poor diet and intense exercise, leading to poor health outcomes, inadequate daily recovery and accelerated aging.

Although there are over 750 carotenoids identified in nature, less than 100 have been found to be present in the human diet and ~30 have been found in human blood with only six making up 95% of all carotenoids found in the blood/tissues.[34] Lycopene, lutein, zeaxanthin and astaxanthin are among these primary carotenoids in humans that positively effect human structure, function and health but are also among the most under-consumed.[8,10] Additionally, the bio-accessibility, thus availability/absorption, of these molecules from plant foods is strikingly low because their chemical structures tightly bind them to the plant matrix,[18,41] furthering the already significant variability in their bioavailability[42,43] based on other factors such as the recipient's age (older persons have lower carotenoid digestion/absorption),[23] degree of plant food processing (heat/canning/pasteurizing and mechanical processing improves bioavailability),[44,45] consumption in the presence of dietary fats (once extracted from the food carrier, it requires dietary fat to incorporate the carotenoids into micelles for absorption through the enterocytes) since it has been demonstrated that an intake of approximately three to five grams of fat is critical for maximum absorption.[46,47]

Under-consumption of fruits and vegetables combined with the bio-accessibility/availability of the important carotenoids, especially lycopene, lutein, zeaxanthin and astaxanthin has encouraged the use of properly formulated dietary supplements to bridge the food delivery gap to achieve daily desired levels, i.e., lipid soluble ingredients in diet corrective amounts. Moreover, although dietary supplements (DS) do not replace foods but are used to supplement the diet with isolated compounds to work synergistically with foods, because carotenoids as DS do not need to be released from the plant matrix, properly formulated supplements can be more efficiently absorbed than specific carotenoids in foods to help overcome the variances in bioavailability from foods or gastrointestinal tract limitations.[48,49,50]

The majority of populations in developed nations are considered low in lycopene and total carotenoid blood concentrations, which translates to greater health risks as described above, although carotenoids have not yet been named to be essential micronutrients such as the vitamins and essential minerals that do have essential/nutrient status. However, experts in the field have proposed an advantageous plasma concentration for best health outcomes.[51] Taking results from meta-analyses, experts declared five cut-off levels of plasma carotenoid concentrations. A level <1μM (<1000 nmol/L) designates a very high risk of negative health consequences. High to moderate health risk with carotenoid concentration in the range 1.5–2.5 μM. Concentration from 2.5–4 μM being a moderate risk and concentrations over 4 μM are proposed as having the lowest risk of poor health consequences (>2500 nmol/L is categorized as best health protection). These experts also report that over 95% of the US population falls into the moderate or high-risk category of the proposed carotenoid health index described here.[51,52]

Lastly, the carotenoids (lycopene, lutein, zeaxanthin and astaxanthin) and their dosages found in this product are commonly used as supplements both topically and orally to support skin health since a primary cause of poor skin health, including early signs of aging and immune suppression, is caused by photo-oxidative damage and these ingested carotenoids exist in human skin to protect humans from the harmful effects of ultraviolet radiation (UVR).[3,4,28,29] The photo protective effects of these carotenoids are not solely from their direct light-absorbing and antioxidant properties but also connected to their regulation of ultraviolet light induced gene expression, making them potentially helpful in mitigating environmental insults to human skin, including photo-aging. Therefore lycopene, lutein, zeaxanthin and astaxanthin, together contribute to supporting overall skin appearance and health throughout aging.[3,4,28,29]

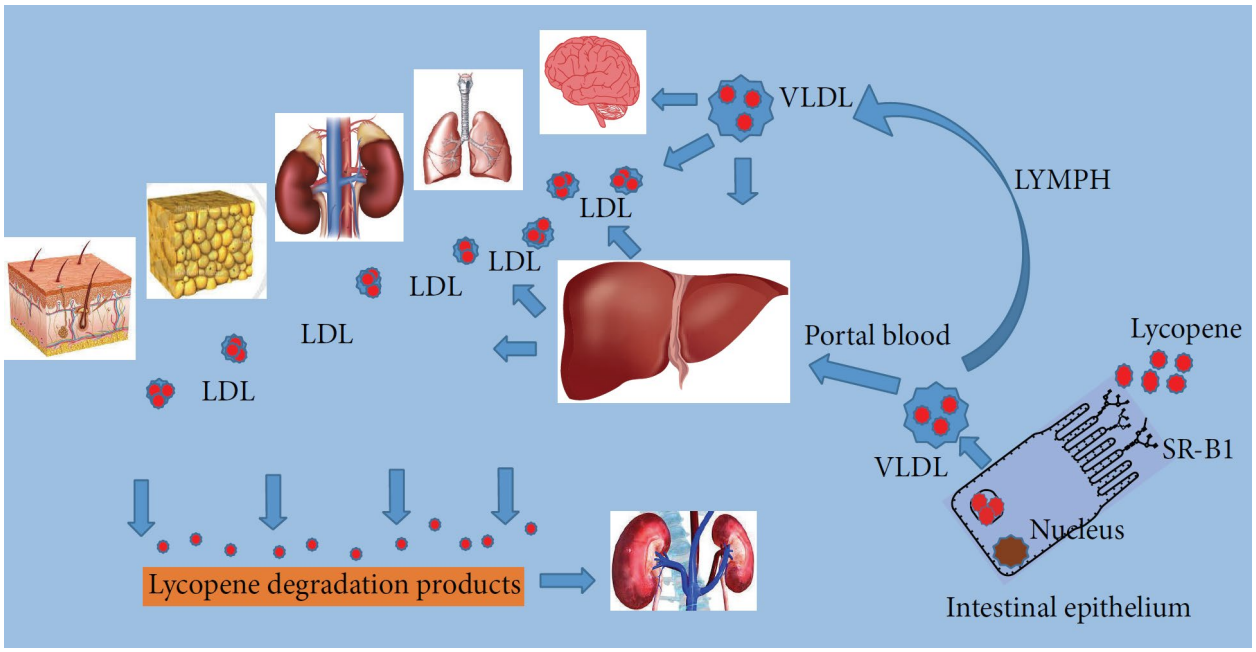
Lycopene in Health and Risk Reduction/Protection

Lycopene is a lipophilic, multi-hydrocarbon non-provitamin A unsaturated carotenoid with a chemical structure that undergoes alterations when exposed to heat, light and other chemical interactions such as food processing.[53] It is found in red-colored fruits and vegetables, including tomatoes, papaya, red grapefruits, guava and watermelon.[54] As with DS sources, processed tomato products (which supply ~85% of lycopene in the North American diet[55]), such as tomato paste, juice, ketchup, puree, sauce or soups are lycopene sources with improved bioavailability primarily due to the processing releasing lycopene from the fibrous cell structure matrix or heat alteration.[56] The average/mean daily intake of lycopene in the United States is 4.6 mg but ranges from .28–10.5 mg/day.[52,57] How much is absorbed is wildly variable as described above. In humans, lycopene absorption from foods is in the range of 10%–30% with the remainder being excreted.[41,42,43,44,45,46,47,50]

Figure 2 from Petyaev et al. depicts lycopene metabolism including primary tissue distribution.[52] Lycopene has many properties that contribute to human health including functioning as a powerful antioxidant (11 conjugated double bonds make lycopene a superior carotenoid antioxidant) in quenching reactive oxygen species (ROS) in specific cell types and subsequently reducing/controlling damage to DNA,[58,59,60,61] acting as an anti-inflammatory[62,63,64] and anti-proliferative agent.[64,65] Although these are generally noted as dietary lycopene's primary functions associated with better health outcomes, undoubtably, the actions of the lycopene molecule in human structure and function are interrelated as they metabolize and extend their activities in specific regions of the body in making their final contributions to overall health.[1,14,24,27,38,56,66] (See Figure 2). Further, beyond these mechanisms, findings have shown

lycopene to positively interact within intercellular communications and metabolic and immune system pathways.[59,67,68]

Figure 2: Lycopene Metabolism and Distribution[52]



Ingested lycopene released from the food source is solubilized and emulsified inside the intestinal lumen, then transported with scavenger receptor class B type 1 protein (SR-B1) via the epithelium of small intestine. Plasma lipoproteins are the primary delivery systems of carotenoids including lycopene in humans. Lycopene distribution is highly selective with the adrenals, testes, prostate, and liver, having the highest concentration, but also found in skin and other organs. Source: Petyaev, Ivan. (2016). Lycopene Deficiency in Ageing and Cardiovascular Disease. Oxidative Medicine and Cellular Longevity. 2016. 1-6. 10.1155/2016/3218605.

Lycopene and Vascular/Cardiovascular Health

Meta-analysis confirms that people in the highest quartile of lycopene intake compared with the three lower levels have better vascular/cardiovascular health.[1,66,69,70] The mechanisms of action are proposed to be multiple: 1) effective antioxidant in quenching singlet oxygen and modulating the production of antioxidant enzymes (e.g. superoxide dismutase and catalase). Via reducing oxidative stress and ROS, lycopene may indirectly increase the availability of nitric oxide (oxidative stress in the vascular system leads to endothelial dysfunction) subsequently improving endothelium-dependent vasodilation and reducing DNA, lipid and mitochondria damage and inhibit platelet functions/adhesions.[71,72,73,74] Therefore as an antioxidant, lycopene increases antioxidant enzymes, arrests nitrogen species and ROS and defends endothelial cells from damage. 2) Anti-inflammatory agent to help control excessive inflammation related to cardiovascular health by, in part, suppressing lipopolysaccharide (LPS)-induced inflammation (LPS is a membrane component of Gram-negative bacteria, which is a major pathogenic activator in organ dysfunctions[75]).[34] This anti-inflammatory function may be due to lycopene's enhancement of vascular barrier integrity and inhibition of cell adhesion molecules (CAM).[76] To be sure, the anti-inflammatory actions of lycopene are modulated by the downregulation of NF-kappa B and TNF-alpha production (expression of TNF-alpha induced intercellular adhesion molecule [ICAM-1] is inhibited by lycopene).[24,77,78] 3) Inhibition of genes involved in inflammation are also mediated by lycopene.[77,79] For more on lycopene's effects beyond or related to its antioxidant and anti-inflammatory actions on overall vascular including total cardiovascular (CV) health, readers are referred to the Mozos et al. review titled "Lycopene and Vascular Health."[24]

The preponderance of evidence supports the positive effects of tomato products and/or lycopene supplementation on vascular/CV health.[27,66,80,81,82,83,84,85,86,87,88,89] Increasing the lycopene intake both through tomato products or supplementing (lycopene doses range from 4-30 mg/day incremental to normal dietary intake) has been shown in recent meta-analyses to improve blood lipids, blood pressure and endothelial function and significantly decrease cardiovascular events while reducing mortality.[66,82] For more details on the peer reviewed clinical trials including designs, dosages, and outcomes, see Table 1 in the Cheng et al. meta-analysis, "Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis,"[82] and updated Cheng et al. "Lycopene and Tomato and Risk of Cardiovascular Diseases: a Systematic Review and Meta-Analysis of Epidemiological Evidence" that includes blood level correlation to improved CV outcomes.[66]

Lycopene Cognitive Function and Health

According to the National Institute on Health (NIH), cognitive health (the ability to clearly think, learn, and remember) is an important component of brain health, along with motor function (how well you make and control movements), emotional function (how well you interpret and respond to emotions) and sensory function (how well you feel and respond to sensations of touch, including pressure, pain, and temperature).[90] Many individual carotenoids found in fruits and vegetables have been divergently associated with cognitive health, which may be due to their respective unique antioxidant properties and tissue distribution.[34,91,92] As with vitamins and essential minerals that are indispensable for brain creation, structure, function and health maintenance, lycopene and its metabolites are also found in the brain leading researchers to surmise lycopene to have a unique neuroprotective role,[93,94] and thus may offer a prophylactic effect in brain neurons supporting cognitive health through lycopene's well known antioxidant[58,59,60,61] and anti-inflammatory properties.[62,63,64,77,79,95,96] To be sure, the high energy demand of the central nervous system (CNS), especially the brain, can lead to oxidation overload and cause neuro-inflammation, particularly in aging,[52,97] and therefore, lycopene's unique antioxidant and anti-inflammatory properties may also be active in supporting brain health.[14,98] The Chen et al. review describes lycopene intervention activities and study results of human and animal trials related to cognitive health. From this data, the authors summarized the direct and indirect potential mechanisms of action of how lycopene may exert its protective effect on cognitive health, thus helping to explain the association of high lycopene intake and improved brain health.[98] Mechanisms identified ranged from attenuating oxidative stress and neuroinflammation, inhibition of neuronal apoptosis, to the restoration of mitochondrial function.[98] Further, the authors cited that the neuroprotective effects of lycopene are also mediated by other systems such as "inhibition of Jun N-terminal kinase (JNK) activation,[99] activation of the PI3K/Akt*, brain-derived neurotrophic factor (BDNF), adenosine 5'-monophosphate activated protein kinase (AMPK), and peroxisome proliferator-activated receptor γ (PPARγ) signaling[95,100,101] and restoration of intracellular Ca2+ homeostasis."[102] Lycopene intake, and more accurately measured circulating levels of lycopene, are positively associated with protecting cognitive health suggesting a steady intake of this carotenoid throughout a lifespan would be advantageous to maintaining the health of the human brain. Further, due to variances in bio-availability including plant sources, diet selection and the natural age-related decline in intake and absorption, supplementation (6-10 mgs/day based on absorption saturation[34,103,104,105]) offers a viable option in complementing diets to achieve the circulating levels associated with better cognitive structural and functional health outcomes.[14,98,106,107,108]

** The PI3K-Akt Pathway is a signal transduction corridor that promotes survival and growth in response to extracellular signals. Key proteins involved are PI3K (phosphatidylinositol 3-kinase) and Akt (Protein Kinase B).*

Lycopene in Prostate Health and Fertility

Liver, seminal vesicles and prostate tissue are the primary sites of lycopene accumulation in vivo[109] and therefore lycopene interventions are commonly considered in supporting prostate health and fertility.[1,110,111,112,113]

Interest in lycopene's potential role in prostate health, as with all of lycopene's role in health discussed so far, grew from identifying the relationship between fruit (specifically tomato products) and vegetable intake and prostate health risk, along with the fact that prostate tissue is a major site of lycopene deposition/activity. Both factors have led researchers to isolate lycopene's potential contribution. Mechanisms of action not only include lycopene's known

antioxidant,[24,58,59,60,61] anti-inflammatory[62,63,64,79] and anti-proliferative properties,[1,64,65,114] but also lycopene's inhibition of the nuclear transcriptional factor (NF-κB) signaling pathway,[115] and interactions within insulin-like growth factor 1 (IGF-1) activated signaling pathways and other areas of androgen metabolism.[114,116] The Chen et al. comprehensive meta-analysis concluded that higher lycopene consumption was linearly associated improved prostate health with a threshold between 9 and 21 mg/day. Further, higher circulating lycopene levels significantly protected prostate health. The concentration of circulating lycopene between 2.17 and 85 mg/dL was linearly inversed with health risk, but there was no linear association >85 mg/dL. In addition, greater efficacy for the circulating lycopene concentration on prevention was found for studies of high quality including a follow-up >10 years and where results were adjusted by the age or the body mass index.[110] The emerging data on lycopene intake, supplement or food form including processed tomato products, appears to lend credence to a recent finding that lycopene was the only dietary supplement found to significantly lower the risk of all-cause mortality (18%) and associated with an over 50% reduction in specific health risks.[117]

Because of lycopene's specific tissue antioxidant activities noted above, and the fact that oxidative stress is a cause of major spermatozoa damage affecting male fertility, lycopene supplementation (dose ranges from 4-30 mg/day for three to 12 months) has been used to improve the quality (the number and motility) of spermatozoa, which in turn shown to increase active sperm parameters and chances of pregnancy.[1,111,112,118,119,120]

Lycopene in Skin Health and Aging

Lycopene concentration in the skin correlates with its level in the plasma.[121] The lycopene distributed within human skin tissue acts locally to prevent skin photo-damage primarily through its antioxidant properties.[122] Individuals with the highest concentration of lycopene in the skin have significantly lesser amount of wrinkles, furrows and skin roughness than people with lower skin concentrations making lycopene supplementation a common component in supporting skin appearance and health.[28,122,123,124,125] Supplementation from 3-16 g/day has been shown to raise skin concentrations and help protect against acute and long-term negative effects of photodamage and improve skin appearance.[28,122,123,124,125,126]

Lutein & Zeaxanthin in Health and Risk Reduction/Protection

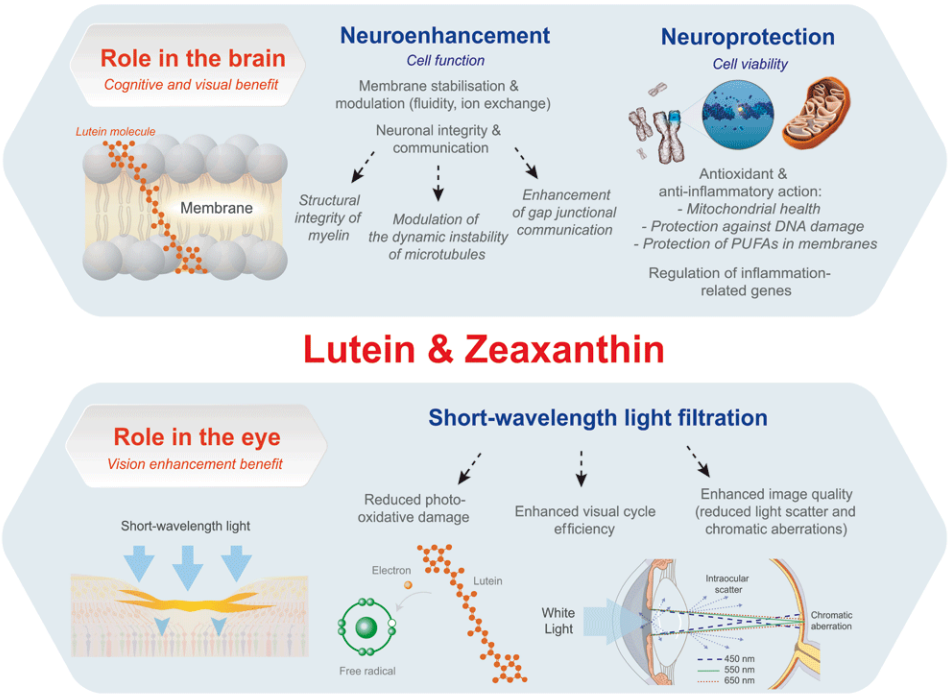
As noted within this document, and due to their identified mechanisms of actions, carotenoids found in the human body have been shown to be beneficial to health throughout the lifecycle and this may be especially true for lutein (L) and zeaxanthin (Z) because of their indispensable contribution to eye/ocular development, structure and function, [127,128,129] also making L and Z passage from mother to fetus paramount to the growing child in maximizing respective tissue development.[130,131] As referenced above, humans cannot synthesize carotenoids and dietary L and Z is notoriously low relative to potential health needs and lifespans.[7,8,10,15,16,17,51,52] Five to 10 milligrams per day of L and Z is recommended based on reported intakes and corresponding serum/tissue concentrations of persons demonstrating better eye and cognitive structure, function and long-term health,[132,133,134] whereas the average dietary intake of these two carotenoids in the US is between one and three milligrams per day (European countries range between two and five milligrams per day) with women generally consuming the higher number.[135,136] The research discoveries of L and Z mechanisms of action, tissue distribution and needs (see Figure 3), including estimated amounts, to support "womb to tomb" health, especially ocular and cognition, combined with widespread under-consumption from food sources, has led to purified isolated supplementation being used to correct the dietary deficit.

Xanthophylls are oxygen-containing carotenoids. The xanthophylls, L and Z are defined by the presence of a hydroxyl group at both ends of the molecule, which also separates them from other carotenoids. L and Z are isomers differing by the location of a double bond unsaturation in the terminal ring.[137] Further, meso-zeaxanthin (MZ) is a lutein derivative (L and Z can be interconverted in the body through an intermediate called meso-zeaxanthin, a stereoisomer and only found in ocular tissue[138]).[137] It's been demonstrated, based on lipid transport availability, that the bioavailability of L and Z is affected by the simultaneous presence in foods of other carotenoids, such as beta carotene, which can lead to a reduction in serum concentrations of L and Z compared to separated ingestion.[139,140]

Wide ranges in concentration of L (0.1–1.44 µmol/L) and Z (0.07–0.17 µmol/L) in human serum exist because of varied dietary intake,[141] with the highest levels associated with better ocular, skin and cognitive health outcomes.[28,132,133,134,142,143,144]

After intestinal absorption, L and Z enter the bloodstream as chylomicron remnants which are shuttled to the liver to be stored and/or re-secreted to circulation and transported to their destinations of needed activity such as the visual system (eye and brain) and skin.[145,146] Further, L and its isomers (Z and MZ) make up 80% to 90% of carotenoids in human eyes and the majority of carotenoids in the brain.[147,148] They are the only carotenoids in the neural retina and lens.[149] In fact, the highest levels of these xanthophylls are found in the eye macula where their concentrations range between 0.1 and 1mM.[150,151, 152]

Figure 3 - Schematic of the proposed mechanistic processes through which lutein and zeaxanthin might influence brain and ocular development and maintenance – i.e., immediate and long-term health.



Source: Loskutova E, Shah K, Flitcroft ID et al. Lutein and zeaxanthin: The possible contribution, mechanisms of action and implications of modern dietary intake for cognitive development in children. [version 1; peer review: 2 approved]. HRB Open Res 2019, 2:8. (https://doi.org/10.12688/hrbopenres.12903.1)

Lutein and Zeaxanthin in Eye Health

L and Z as structural and functional components of the vison system, are predominately active in the macula of the retina but also found in the lens of the eye along with their oxidized metabolites.[134,153] There is a 2:1 lutein: zeaxanthin ratio in the peripheral area of the retina, but zeaxanthin becomes the dominant pigment in the macular area.[154] At the center of the macula, total Z content is both zeaxanthin and meso-zeaxanthin in a 1:1 ratio.[154] The macula is responsible for central vision and acuity. Both L and Z serve as blue light and near-ultraviolet radiation filters, protecting underlying ocular tissues from damage.[134] L and Z absorb 40-90% of incident blue light, thus protecting the retina from damage related to light.[134,155,156] Like all carotenoids, L and Z function as powerful antioxidants and anti-inflammatory agents.[2,3,10,34,38,157] Specifically, (as shown in Figure 3) L and Z defend against oxidative stress naturally taking place in eye tissue (e.g. retinal pigment epithelium, iris, lens, etc.) directly through their specific localized

antioxidant properties,[149,158] and indirectly by absorbing light that would otherwise cause additional oxidative damage.[134,155,156] L and Z (especially L) also protect against inflammation, a known pathogenic mechanism in ocular health. L and Z anti-inflammatory mechanisms may be related to their inhibition of LDL oxidation and upregulating expression of inflammation related genes.[146,159,160]

As with all carotenoids with proven health contributions, there is still no recommended daily intake for lutein and zeaxanthin but based on observational data and intervention studies it is generally proposed that health benefits from L and Z including visual health and protection require a daily intake from diet and/or supplements of 7-10 mg of lutein and at least 2 mg of zeaxanthin.[161,162,163] To be sure, a large number of human clinical trials have demonstrated that L and Z supplementation significantly augments macular pigment optimal density (MPOD), and together or in combination with omega-3s and/or specific vitamins or minerals (VMs)* improves many aspects of visual performance[3,134,135,162,164,165,166,167,168,169,170] including but not limited to: visual acuity (measured as ability to distinguish smaller and smaller letters at a given distance),[131,165,166,171,172,173,174,175] contrast sensitivity (ability to detect contrasts in levels of lightness or darkness of an object or of colors, relative to the objects background),[161,163,165,166,171,174,175,176,177] glare tolerance (shorting time to recover from bright lights),[166,174,175,177,185] and visual processing speed (the amount of time needed to make a correct judgment about visual stimulus), which may be important to persons of all ages including athletes that rely on hand to eye activities such as baseball players.[161,176,178,179,180,181]

Beyond Prevention

Supplementation (although not equivocally*) to meet proposed requirements and increase MPOD, as referenced throughout this document, has also been shown to slow the progression and reduce the risk of common age-related visual disorders, assuming the disorder had not fully taken hold or progressed too far where a nutrition solution would be generally expected to be futile based on the necessity of long-term nutrient/bio-active (in proper amounts) synergy in creating and maintaining the health of tissue structures*.[162,166,182,183,184,185,186,187] However, the preponderance of evidence has led to the AREDS2 formulation with a daily dose of 10 mg of lutein and 2 mg of zeaxanthin now being the standard of care and routine recommendation by ophthalmologists for reducing the probability of advanced AMD in patients with substantial risk factors for progression to severe visual loss. Further, evidence exists that persons receiving AREDS2-type supplements may have "stabilization and improvement of best-corrected visual acuity."[185,186,188,189] Moreover, a study from Frost & Sullivan concluded that daily supplementation with L and Z could save $7.3 billion in age-related macular degeneration healthcare costs per year in Europe alone. Meaning for every $1.17 spent on supplementation, $5.88 would be saved in healthcare cost. Savings in the US would be even greater.[190]

Lutein and Zeaxanthin in Brain Health

As with eye structures/tissues (concentration levels measured as MPOD), L and Z accumulate in the brain where levels are positively associated with MPOD [148] and subsequently cognitive performance across a lifespan suggesting a protective effect.[31,142,191,192,193,194,195,196] In support of a L and Z role in protecting areas of the brain/central nervous system (CNS), Walk et al. studied the relationship between carotenoids and neuroelectric indices underlying cognitive control in subjects 25-45 years of age.[197] Results were that across all participants MPOD was related to both age and the specific measured electrical brain activity during the decision-making process called the P3 wave. Although younger adults exhibited greater P3 amplitudes than the older subjects, older adults with higher MPOD levels displayed P3 measurements like their younger adult counterparts in amplitude. Therefore, the authors stated, "the protective role of carotenoids within the CNS may be evident during early and middle adulthood, decades prior to the onset of older age."[197]

In the younger brain, lutein makes up 60% of the total brain content of carotenoids but only 12% of carotenoids from diet demonstrating a preferential destination.[194] Mechanisms of action of L and Z in protecting cognition/brain health are generally attributed to their antioxidant and anti-inflammatory properties not just locally but systemically[2,3,10,34,38,157,198] since uncontrolled oxidation and inflammation can overwhelm innate systems when dependent components are shorted of cofactors (e.g. vitamins, minerals, Z and L, etc.) and both conditions are known

to effect brain health including neuroprotection and ultimately cognitive functioning and aging.[195,199] Since lutein accumulation in neural tissue is fivefold greater than other carotenoids, L has been suggested to play a unique and potentially protective role in cognitive function and brain health.[200] Certainly the brain is a ripe target for oxidative stress because of the high metabolic activity combined with high polyunsaturated fatty acids (PUFA) content.[201,202] Moreover, lutein's structure allows it to localize in membrane structures rich in PUFA.[203] Additionally, overweight and obese individuals are at high risk for low MPOD status and excess body fat, in part due to chronic inflammation, is associated with poorer cognitive function and brain health.[204] To this point, Cannavale et al. found overweight people with the highest serum lutein had better relational memory performance.[205] The researchers suggested that since overweight people have higher levels of inflammation and inflammation is harmful to hippocampal function via inhibiting long-term potentiation (the mechanism for memory function), lutein's anti-inflammatory actions and ability to reduce oxidative stress may be the primary mechanisms of actions in protecting the brain and evolutionary reasoning for local deposition.[205] In line with this, Stringham et al. found that six months of supplementation with 13 or 27 mg/day of L, Z and MZ, to significantly improve cognitive performance (composite and verbal memory, sustained attention, processing and psychomotor speed) compared to placebo.[206] The lower dose contained 10.86 mg of L and 2.27 mg of Z and MZ combined. Results showed that both intervention groups had significant increases in antioxidant capacity and in brain derived neurotrophic factor (BDNF). An important neurotropic factor, BDNF is a protein found in the brain and spinal cord that promotes the survival of nerve cells via its role in the growth, maturation and maintenance of these neurons. In the brain, the BDNF protein functions at the connections between nerve cells (synapses), where cell-to-cell communication occurs. The synapses can change and adapt over time in response to experience, a property known as synaptic plasticity. The BDNF protein helps regulate synaptic plasticity, which is important for learning and memory.[207,208] The authors found the increase in BDNF related to significant decreases in the pro-inflammatory cytokine, IL-1β and TNF-α, and suggested that regular intake of these xanthophylls "interrupts the inflammatory cascade that can lead to reduction of BDNF."[206] This study was done on healthy young persons with improvements not trivial, and therefore suggests at least a protective role throughout a lifespan. Interestingly, the same supplement ingredients, amounts and protocol was also found to reduce stress, cortisol, and symptoms of sub-optimal emotional and physical health.[209] Finally, Lindbergh et al. found through use of functional magnetic resonance imaging (MRI) that 12 mg/day of L and Z supplementation benefited neurocognitive function by enhancing cerebral perfusion thus another potential mechanism in cognitive health.[210]

Lutein (L) and Zeaxanthin (Z) Summary

In summary, the available evidence strongly favors most adults using L and Z (including MZ) supplements in a range of 5-8 mg/day of L and 2-4 mg of Z, to support commonly low dietary intake from food selection, and overcome bioavailability factors based on age, polymorphisms, diet preferences and/or food processing to not just achieve recommended L and Z intake, but also present an adequate bio-assessable amount consistent with better health outcomes including skin, at all life stages.

**Nutrients and other bio-actives work synergistically and therefore study outcomes are often determined on other available supporting nutrition in proper/recommended amounts over a lifetime. Therefore, practitioners should encourage persons of all ages to ingest a daily complete MVM to correct the known VM deficit between food intake and the recommended dietary allowances (RDAs) for vitamins and minerals along with consuming ~500-1000 mg/day of omega-3s from fish and/or a marine-based supplement, thus supporting the potential benefits of L and Z intake/supplementation shown in varied studies using L and Z alone or in combination with vitamin and mineral and/or omega-3 supplements.*

Astaxanthin in Health, Recovery and Risk Reduction/Protection

Like the other xanthophylls (XP) astaxanthin (AXN), has unique health contributions, must be supplied by the diet and intake of this XP from food alone (0.8-2.0 mg/day if assuming the seafood consumption is all fortified though aquaculture[30]) is generally well below its associated health benefits (experts recommend ~2-4 g/day[34]) since marine food including algae is the primary source of AXN from diet and notably under-consumed in the US, thus giving

rationale for supplementation.[17,28,34,135,211] But unlike other XP (mindful AXN digestion, absorption and transport is similar to L and Z as described above), AXN has more hydroxyl groups and two terminal rings linked by a polyene chain giving it powerful unique antioxidant (AO) and anti-inflammatory (AI) characteristics.[212,213,214] Besides being considered one of the best carotenoids for oxidative damage protection of cells, lipids and lipoproteins, its structure offers both lipophilic and hydrophilic properties and this allows AXN to, as L and Z, cross the blood-brain barrier to reach brain and eye structures.[34,212,215] Similar to other carotenoids, AXN's demonstrated health benefits such as protective actions in skin, brain/ocular, CV and nervous systems are related to their anti-inflammatory and antioxidant properties, which are also considered their primary mechanisms of actions. However, uniquely, AXNs adds protection against oxidative damage by scavenging/controlling reactive oxygen species (ROS) to prevent negative chain reactions in both the inner and outer layers of the cellular membranes thus helping preserve membrane structure as opposed to operating in one layer or the other as most antioxidant vitamins or other carotenoids may work.[4,29,216,217,218] AXNs unique localized antioxidant actions help restore balance between age, environmental or injury related exaggerated pro-oxidant and antioxidant activities, yielding a less pro-oxidant environment and therefore, help prevent/reduce the risk or progression of ROS associated ocular, skin or nervous system health and aging problems.[29,214,218,219,220,221,222,223]
The body's inflammation and oxidative stress responses to illness/infections, weight gain, photo-stress, pollution, aging or injury, feed off each other, and although there exists a cooperative relationship between the two reactions, a vicious cycle creating a non-homeostatic environment will often endure, leading to uncontrolled ailments and accelerated aging (see Figure 4).[224] The purpose of simultaneously supplying multiple micronutrients (e.g. various carotenoids, VMs, EFA, etc.) involved in AO (enzymatic or non-enzymatic AO) and AI actions, whether contributing as indispensable ingredient cofactors in dependent AO/AI systems or as part of a complete functional structure, is to leverage the individual nutrient/bio-active's unique properties and distribution throughout the body to systemically manage normal biological oxidation and inflammation activities into the homeostasis state throughout each life-phase.[224,225]
To be sure, astaxanthin has been shown to suppress NF-κB and activation, (which otherwise induces the expression of various pro-inflammatory genes), by inhibiting intracellular ROS accumulation, thus offering localized tissue/cellular protection via AXN antioxidant properties helping manage inflammation.[226,227] Through oxidative stress reduction and increasing intracellular calcium concentration, AXN has been reported to improve neutrophil phagocytic and microbicidal capacity, which normally decreases with aging and contributes to a weakened immune response common in the elderly population.[228,229] Further, as with the brain, immune cell's high membrane content of PUFA and high metabolic activity render them particularly susceptible to lipid peroxidation making oxidative stress control crucial in immune response and AXN may play a unique role through its AO/AI interplay described here.[230,231] Finally, depending on the condition, AXN presents either antiapoptotic (prevents cell death) or proapoptotic (promotes cell death) effects, purportedly acting through a mitochondrial-dependent pathway where activation would support healthy tissue survival and/or removal of invasive cells.[4,221,232]

Astaxanthin in Skin Health

For the same primary reasons as described above that other carotenoids (including the xanthophylls L an Z contained in this product) are credited for supporting skin health, AXN is promising in the area of dermatology as it adds its unique antioxidant and anti-inflammation actions including the ability to insert itself in the bilayers of cell membranes.[4,28] It is well known that aging reduces antioxidant production and unchecked oxidation in skin tissue contributes to its aging by causing inflammation and DNA damage, and the generation of matrix metalloproteinases (MMPs) that lead to an erosion of elastin and collagen in the dermal skin layer.[233,234] The Davinelli et al. comprehensive review on AXN effects on skin health and repair found it to be a safe supplement with doses ranging from two to 12 mg/day, while concluding: "*AXN inhibits collagenases, MMP activity, inflammatory mediators, and ROS induction, resulting in potent antiwrinkle and antioxidant effects. Moreover, ASX may prevent UV-induced immunosuppression.*"[214]

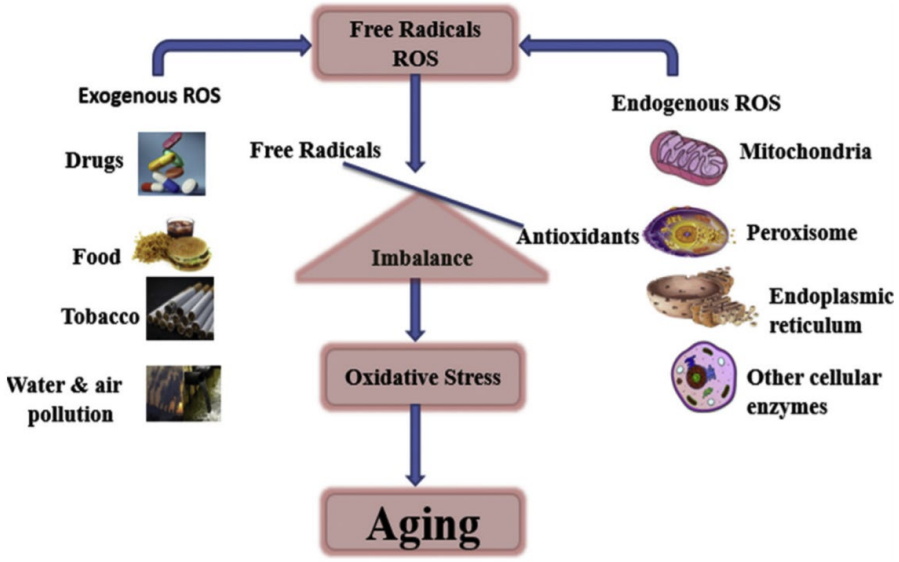
Astaxanthin in Exercise

The ability of AXN to upregulate the endogenous antioxidant defense system including through its interaction with Nrf2 and upregulation of antioxidant enzymes (e.g. superoxide dismutase, catalase and glutathione peroxidase and others) has led to supplementation by exercisers.[30,39] There is little available human evidence that AXN supplementation can improve exercise performance as shown in animal models, (including favorable substrate utilization, performance and recovery), other than AXNs antioxidant properties contributing to an accelerated post-activity recovery.[30,39,235] Indeed, 12 mg/day of AXN, supplemented with zinc and vitamin E in doses commonly found in complete multivitamin and mineral supplements, improved performance and mobility in elderly subjects compared to placebo supporting the daily use of MVM in combination with non-vitamin bioactive protectants as found in this formula.[236]

Astaxanthin Summary

In summary, AXN as other healthful carotenoids is generally under-consumed from diet alone (0-2 mg/day) compared to expert recommendations of 2-4 mg/day. Due to AXNs unique AO and AI properties/mechanisms of action and tissue distribution, it can deliver an additive contribution to other bio-actives involved in similar actions (e.g., vitamins, minerals, other carotenoids, etc.) in helping maintain cellular integrity, especially in aging and during regular bodily insults such as photo-aging, excess body fat and muscle damage, viral infections, injury and pollution. Supplementing in doses ranging from 2-12 mg/day appears safe and effective in supporting better health and recovery outcomes including daily cellular recovery. Figure 4 below depicts how free radicals and antioxidant imbalance causes oxidative stress and results in aging and endogenous and exogenous forces that contribute to this mechanism of aging)[224,237]

Figure 4 – Free Radicals and Aging[237]



Obligatory Inflammation and oxidative stress constantly interact throughout all areas of the body and depending on the degree of insults (e.g., excess body fat, sun or pollution exposure, physical injury, insufficient nutrient/bio-active intake, aging, etc.), these two actions can spiral into a detrimental cycle that leads to poor health and accelerated aging as shown in Figure 4. In other words, although the inflammatory response is necessary in the presence of insults/injury or infection, if left unchecked (upregulated ROS) it can cause runaway cellular damage leading to functional impairment in any affected tissue.[237] Inflammatory mediators (promote the inflammatory response - e.g. interleukin (IL)-1B, IL-6, IL-8 and TNF-α, etc.) are upregulated during tissue insults and subsequently increase the expression of ROS, which in turn increases the secretion of inflammatory cytokines, chemokines, and matrix-remodeling factors, which then starts the uncontrolled cycle of oxidative stress and chronic inflammation common in modern aging.[224,225,238] Source: Weidinger A, Kozlov AV. Biological Activities of Reactive Oxygen and Nitrogen Species: oxidative Stress versus Signal Transduction. Biomolecules. 2015 Apr 15;5(2):472-84. doi: 10.3390/biom5020472. PMID: 25884116; PMCID: PMC4496681.

Co-enzyme Q-10 and Alpha-lipoic Acid

Coenzyme Q-10 (CoQ_{10}) and alpha-lipoic acid (ALPA) are ubiquitous molecules essential to human metabolism and especially critical to energy production while also exerting unique powerful antioxidant activities that help protect health. Both CoQ_{10} and ALPA can be synthesized and acquired in foods in adequate amounts to support their respective basic functions in most healthy young humans but tissue levels of these indispensable molecules significantly decline with age as the ability for humans to synthesize and/or extract them from foods gradually weakens as part of natural aging, thus compromising their contribution to energy production and health, making supplementation common to assist in healthy aging.

Note: *While CoQ_{10} products (e.g., ubiquinol, ubiquinone, etc.) and alpha-lipoic supplements (R-enantiomer, S- enantiomer and racemic mixtures) are often used by physicians for clinical purposes, that application is not relevant to this paper and discussion. It is not within the scope of this document to discuss CoQ_{10} or ALPA supplementation as a therapy (other than using studies to highlight mechanisms of action within the human body). This section is solely dedicated to ALPA and CoQ_{10}'s indispensable contributions to energy production and health and forms the basis for supplemental amounts that may maximize their functions (individual & combined/synergistic) in their many areas of action at each life-stage. In other words, quantifying intakes for optimizing CoQ_{10} and ALAP's contributions to health and fitness outcomes including reducing health risks, not treatments.*

Co-enzyme Q-10 in Health, Recovery and Risk Reduction/Protection

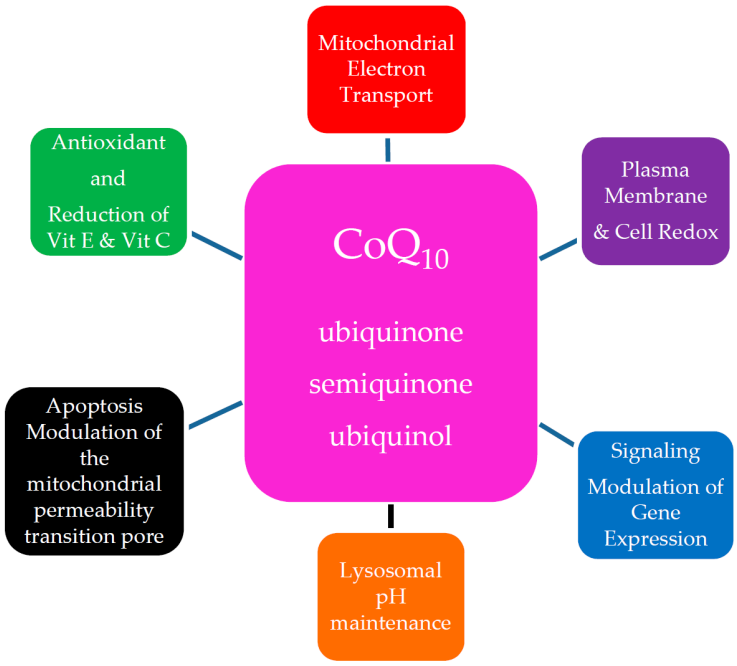
Basic Structure and Functions

Coenzyme Q-10 (CoQ_{10}) is a lipophilic structure with an isoprenoid side-chain (10 isoprene units in humans), part of the ubiquinone family, widely distributed in all cell membranes, and is intricately involved in energy production.[239] Along with typical dietary intake (primarily from animal protein) of 3-6 mg/day, [240] humans synthesize CoQ_{10} (from tyrosine or phenylalanine and mevalonic acid) utilizing a group of enzymes known as complex Q found in the mitochondrial matrix membrane.[5,239] The molecule's quinone ring is its functional group responsible for shuttling electrons from energy complexes I and II to complex III. [241,242] Therefore, CoQ_{10} is critical to oxidative phosphorylation and consequently in producing adenosine triphosphate (ATP) thus fundamental in cellular bioenergetics/energy production and the evolutionary rationale for the highest concentrations being found in tissues with high metabolic activity or energy requirements (e.g. heart, brain, liver, kidneys and muscle).[243] Additionally, CoQ_{10} (in its reduced form ubiquinol) functions as a powerful lipophilic antioxidant/anti-inflammatory while also serving to regenerate other antioxidants throughout the body.[26] In its antioxidant role, CoQ_{10} stabilizes intracellular membranes protecting membrane phospholipids from peroxidation and in its reduced sate, it participates in the recycling of other AO compounds such as ascorbate and tocopherols aiding in cellular redox homeostasis throughout the body.[25,26,242] Other noted CoQ_{10} properties include membrane stabilization, cell signaling and modulating gene expression.[243,244,245] $CoQ_{10's}$ primary functions are shown in Figure 5.

CoQ_{10} in Aging

Regardless of diet, CoQ_{10} tissue concentrations naturally diminish in aging and consequently so do their vital functions described above, giving rise to the use of Co-Q_{10} supplementation in an attempt to maintain or restore the related functional activities to levels found in healthy younger humans.[5,25,26,33,246,247,248] To be sure, chronic inflammation is a common aging problem and the age-related reduced activities of CoQ_{10} including losses of its AO protection, which leaves related pro-inflammatory cytokines unchecked (reduction in free radicals reduces the activation of NF-κB cells, subsequently decreasing tumor necrosis factor and interleukin 6), exposes membranes to peroxidation and increases C-reactive protein (CRP), thus areas where Co-Q_{10} supplementation has shown to be helpful via improved biomarkers.[242,249,250,251,252,253,254] Further, CoQ_{10} has demonstrated an anti-inflammatory action by epigenetic effects on genes connected to NFkappa-B1 (regulator of innate immunity).[255]

Figure 5 - Primary Mechanisms of Action of CoQ_{10}



Source: Barcelos IPd, Haas RH. CoQ10 and Aging. Biology. 2019; 8(2):28. https://doi.org/10.3390/biology8020028

CoQ_{10} supplementation is used clinically to help restore levels in deficiencies related to: aging/diet (including lack of nutritional components necessary for synthesis), disturbed CoQ_{10} synthesis based on genes, acquired disorders and/or statin use or other medical conditions.[5,25,26,247,256,257,258,259] Clinical use of CoQ_{10} supplementation requires testing for deficiency (measurement of muscle levels by high performance liquid chromatography) with subsequent wide correctional ranges of dosing (100-1200 mg/d) and is beyond the scope of this document and not relevant to the use of CoQ_{10} in this formula.[260,261] (Plasma levels of CoQ_{10} range between 0.40 and 1.91 µgmol/L [0.34–1.65µg/mL] in controls but are not necessarily representative of tissue levels).[261]
However, CoQ_{10} supplementation of 50-200 mg daily is often recommended and used successfully in many adult populations to improve/support cardiovascular functioning and health, especially in older subjects as levels naturally decline because the capacity for CoQ_{10} production decreases substantially with increasing age. Many clinical studies including systematic reviews support the safety and efficacy of this daily usage.[5,25,26,33,239,242,246,247,249,250,251,254,259,262,263,264]

CoQ_{10} in Exercise

While there is no clear evidence that short-term or acute supplementation of CoQ_{10} improves exercise performance (other than in clinically-dependent exercisers),[265] based on CoQ10's properties (e.g. AO, indispensable component in energy production, etc.), keeping CoQ_{10} tissue levels maximized may contribute to better daily recovery with compounding long-term effects, which could extend performance gains over the years, particularly in older athletes.[33] In other words, to clinically validate the point of improving long-term exercise outcomes by maintaining youthful CoQ_{10} levels throughout a lifetime would be unrealistic. However, based on factors, especially age, genetics and diet, that effect CoQ_{10} tissue levels, logic supports use of an inexpensive safe and effective correction dose (~100 mg/day) since there is no known downside and may in fact offer a significant potential prophylactic effect.[5,26,33,240,242,247,266] To be sure, the rationale for supplemental CoQ_{10} use in exercisers is related to its AO properties and role in the energy cycle, with the goal of maximizing $CoQ_{10's}$ properties described above to improve recovery and/or energy production.[33] By supplementing the diet combined with endogenous synthesis so CoQ_{10} tissue concentrations reach the body's

usage saturation levels, this would also help overcome potential individual shortages due to innate characteristics or diet (e.g. polymorphisms, food preferences, aging, stain use, etc.) that would otherwise compromise production or extraction and absorption from foods.[266,267,268] Interestingly, Ho, Chien-Chang et al. found that athletes had significantly lower levels of white blood cell (WBC) CoQ_{10} than control healthy subjects (0.34 ± 0.24 nmol/g vs. 0.65 ± 0.43 nmol/g) but no significant difference in plasma CoQ_{10} (0.54 ± 0.17 µM vs. 0.52 ± 0.11 µM).[269] Research has found that athletes had a marginal CoQ_{10} deficiency and that the level of WBC CoQ_{10} were associated with glycemic control and antioxidant capacity and therefore suggests that athletes find an adequate dose of CoQ_{10} supplementation to optimize their CoQ_{10} status, thus maximizing its contribution to long-term athletic performance and recovery from regular exercise.[269] Further, CoQ_{10}'s well known rapid exercise-induced depletion adds credence to the concept of supplementing to achieve daily adequate CoQ_{10} status in highly active adult humans.[33,270,271,272,273,274,275,276,277]

Alpha-Lipoic Acid in Health, Recovery and Risk Reduction/Protection

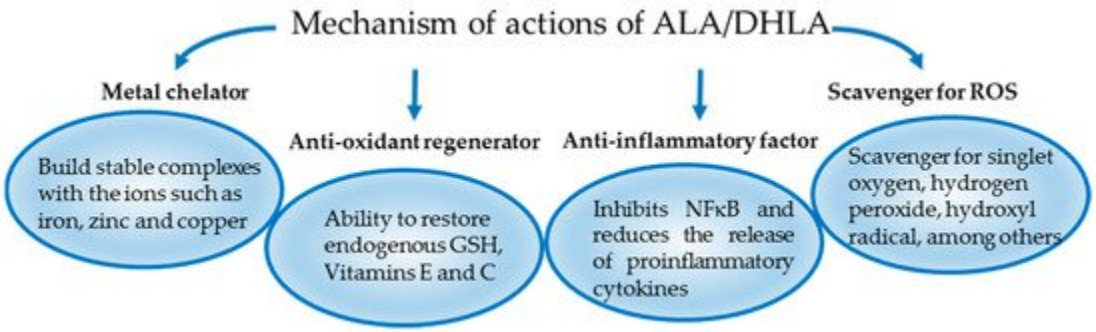
α–lipoic acid (ALPA), similar to CoQ10, functions as a powerful and universal antioxidant, essential in energy production, commonly found in mitochondria, necessary for numerous enzymatic reactions and naturally decreases with age, thus the rationale for supplementation.

Basic Structure and Functions

ALPA (1,2-dithiolane-3-pentanoic acid) is an organosulfur compound produced from plants and animals and can be synthesize to a certain extent by humans (enzymatically in the mitochondria from octanoic acid and cysteine[278,279])[280] but also supplied through diet from primarily red/organ meats and some fruits and vegetables.[281,282,283] Compared to other molecules with similar tissue distribution and AO actions (controlling oxidative stress and restoring other AO[281,284]), ALPA's unique molecular structure permits it to act as both a lipid and water soluble compound.[282,285] This quality allows ALPA to act as an enzymatic cofactor in the energy/Krebs cycle for pyruvate dehydrogenase and α-ketoglutarate-dehydrogenase complexes thus integral to cellular energy production,[286,287] operate as an universal AO/anti-inflammatory agent in common and unique areas including chelating metals[6,288,289,290,291] and also participate in glucose and lipid metabolism while managing gene transcription (see Figure 6).[286,292 293,294] In particular, as a powerful mitochondrial AO compound functioning through multiple mechanisms, ALPA promotes anti-inflammatory pathways and favorably influences nitric oxide-mediated vasodilation supporting cardiovascular health, especially endothelial function, which tends to otherwise deteriorate with age.[290,293,295,296] Liu et al. describes ALPA's known actions in modulating the immune response and suggests the potential mechanisms of action are related to ALPA signaling pathways in both the innate and adaptive immune response including apoptosis, regulation of the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK).[297] To be sure, in response to antigens, excessive immune cell production of ROS can exacerbate inflammation upsetting proper immune reaction balance causing immune dysfunction.[237,298] NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) has a major role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to improper immune development and responses.[299] Independent to ALPA's AO properties, it also inhibits NF-κB activation to help support proper/balanced immune reactions.[299,300] These unique AO, immune system, and energy cycle properties, give rise to the use of ALPA supplementation for both clinical purposes (including drug versions[292, 301]) such as, improving nerve, heart/vascular, immune and brain functioning and health, and in support of healthy aging.[6,281,283,285,287,288,289,290,295,296,297,298,302,303,304,305,306] To the latter, tissue levels naturally wane from age or genetic-(epigenetic regulation)-related decreasing de-novo synthesis (endogenous synthesis is the only source of ALPA as an enzymatic cofactor in energy production[307]) and/or diet molecular components availability (e.g. extraction from foods or diet amount/composition[308]) thus compromising ALPA's health/performance maintenance contributions described above. Like CoQ_{10}, the latter (non-clinical need) is the purpose of ALPA, and daily dosage being included in this formula. The clinical use or dosages (100-1200 mg/day taken without food[6,290,309]) are unrelated to the recommended use of the SuperiorAntioxidant, other than to explain and validate ALPAs mechanisms of action in supporting its health

maintenance/prophylactic effects via maintaining proper levels throughout each life phase, which to support natural declines, can be accomplished with 50-200 mg/day in healthy adults.[6,265,302,310,311]

Figure 6: Beyond Operating in the Energy Cycle, Alpha Lipoic Acid's Proposed Mechanisms of Actions.[300]



Source: Ambrosi N, Guerrieri D, Caro F, Sanchez F, Haeublein G, Casadei D, Incardona C, Chuluyan E. Alpha Lipoic Acid: A Therapeutic Strategy that Tend to Limit the Action of Free Radicals in Transplantation. International Journal of Molecular Sciences. 2018; 19(1):102. https://doi.org/10.3390/ijms19010102

ALPA in Aging, Exercise & Prevention

See CoQ10 section above for the rationale for ALPA supplementation in aging/exercise, substituting ALPA unique functions including contributions to energy transduction and AO/AI balance throughout the body described in previous section. The amount of ALPA in this formula is solely in support of reaching and maintaining tissue saturation throughout adulthood to maximize its contributions to lifelong energy production and health.

Regardless of diet, ALPA tissue concentrations naturally diminish in aging and consequently so do their vital functions described above, giving rise to the use of ALPA supplementation in an attempt to maintain or restore the molecules functional activities to levels found in healthy younger humans to support healthy aging from a protective/prophylactic standpoint.[303,306,308,310,312,313,314,315,316,317,318,319]

ALPA's unique mitochondria bio-energetic properties, effect on AMPK activity, unique AO/AI influences, and participation in glucose management have led to its use as a supplement in doses ranging from 200-1800 mg/day in exercise and weight loss with limited to moderate success and therefore as previously mentioned, not the purpose for including ALPA in this formula but does highlight described mechanisms of action.[320,321,322,323] To be sure, supplementation of ALPA in weight loss trials, while demonstrating modest enhanced weight/fat loss results compared to placebo, significantly improved overweight-related health conditions, presumably from the compound's properties described here[6,287,289,290,314,324,325] therefore, adding to the rationale of maintaining ALPA tissue concentrations for the prophylactic effect. Additionally, the use of the R-enantiomer for oral supplements of lipoic acid may be the more bioavailable form compared to the S-enantiomer or the racemic mixture.[320,326]

Co-enzyme Q-10 and Alpha-lipoic Acid Summary

Oxidative stress and related inflammation are a natural part of life, but the cycle becomes unbalanced due to aging, exercise, sickness, excess body weight, diet preferences, virus/infections, epigenetics, pollution and/or injury. This unbalanced condition going unchecked, along with age-related decline in energy production, leads to poor daily recovery including immune response, thus overall health, and accelerated aging.

Coenzyme Q-10 (CoQ_{10}) and alpha-lipoic acid (ALPA) are ubiquitous molecules essential to human metabolism (especially in mitochondria) and critical to energy production while also exerting unique powerful antioxidant and anti-inflammatory activities that help protect health including proper balancing of oxidative stress and subsequent reactions.

Both CoQ_{10} and ALPA can be synthesized and acquired in foods in adequate amounts to support their respective basic functions in most healthy young humans with the caveat that de-novo synthesis is the only source for their participation as an enzymatic cofactor in energy production. Tissue levels of these indispensable molecules significantly decline with age as the ability for humans to synthesize and/or extract necessary components from foods gradually weakens as part of natural aging, compromising their contribution to energy production and management of oxidative stress and subsequent inflammation leading to the use of supplementation in non-clinical dosages to restore or maintain tissue levels similar to youthful concentrations. These dosages are proposed to be 50-100 mg/day of CoQ10 and 100-200 mg/day of ALPA.

Summary

SuperiorAntioxidant is an NSF Certified for Sport (NSFCS) product containing corrective amounts, when combined with diet, of the natural bio-active compounds: lycopene, lutein, zeaxanthin, astaxanthin,[327](the Böhm et al. document, "From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations," forms the basis for the dosage of carotenoids found in the SuperiorAntioxidant[327]), CoQ_{10} and alpha lipoic acid, to achieve daily levels associated with better overall health and recovery outcomes at all adult life stages. The goals of achieving proper tissue concentrations of these combined ingredients are to 1) supply vital structural and functional bio-active components limited by diet, allergies or age; 2) offer differing individually unique non-vitamin/mineral antioxidant protection to manage free radical production from normal biological processes that become exacerbated (unbalanced) by stress, aging, exercise, and the environment; 3) help control obligatory inflammation – i.e. free radical and antioxidant/inflammation balance; and 4) cumulatively support daily energy and recovery.

Desired outcomes after 30 days of continuous daily use compared to a non-supplemented state and especially when combined with a complete daily multivitamin and mineral formula (MVM) containing at least the known under-consumed vitamins and minerals,[328] include enhanced energy, improved and reduced recovery time, and unique structural and functional support for the maintenance of eye, cardiovascular, skin, immune and brain health. Further, this product contains the individual ingredients (carotenoids, alpha-lipoic acid and CoQ-10) in amounts and forms shown to be consistent with what's needed to raise the food content of these bio-actives to match levels associated with the above goals including healthy aging and prolonging the ability to perform desired activities at the highest level. Mindful that these recommended amounts were not known or available during periods of significantly shorter lifespans but are now known and discovered to be important to support the human current lifespan's potential health.

Typical Use

- Adults seeking enhanced daily recovery and performance and subsequent healthier aging by adding vital nutrition that is part of structural and functional components that naturally decrease with age and/or diet. Daily addition of these critical bio-actives support energy production along with eye, cardiovascular, skin, immune and brain health by also helping manage normal free radical damage and common inflammation, the cycle that becomes overwhelmed from stress, environmental and physical insults that also lead to accelerated aging.
- Exercisers to assist in complete recovery between exercise bouts by helping manage increased free radical production and resulting tissue damage associated with intense and lengthy training sessions, thus helping facilitate a longer-term cumulative recovery effect to help prolong performance gains throughout the lifespan.
- Two vegetarian capsules daily before or after a main meal with fluid
- Recommended to be combined with a dotFIT™ multivitamin and mineral for maximum potential and associated benefits because essential nutrition and other bio-actives found in the human body work synergistically to create, develop and maintain the human structure and functions.

Precautions

The dotFIT SuperiorAntioxidant™ (SA) is considered safe for the general population at the recommended dosage in healthy users based on the fact that all ingredients are also found in foods and present in the human body with the formula amounts complementary to food intake and de-novo synthesis as to reach and remain in the safe and effective recommendation range described above. [5,6,327,329,330] Additionally, all ingredients have GRAS status.*

**Generally recognized as safe (GRAS)* is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.*

CoQ10: high dose long-term use has been shown to be safe in trials lasting up to five years.[331,332] Consult a physician if taking warfarin and/or other blood thinning medications as concomitant use might reduce the anticoagulation effects of warfarin.[333] Although some research suggests that taking CoQ_{10} along with other antioxidants may extend survival time by 40%,[334] individuals in drug treatment should consult their physician before taking the dotFIT antioxidant formula as high dosages of CoQ-10 decrease the effectiveness of radiation therapy in mice.[335] CoQ_{10} has been thought to alter glycemic control and insulin requirements in diabetic individuals; however, CoQ_{10} supplementation does not appear to alter glycemic control or insulin requirements.[336,337] In either case, diabetics should consult their physician before using the SuperiorAntioxidant.

α-lipoic acid: considered safe when used orally and properly. ALPA has been used safely in doses of up to two grams daily for three months to two years. Lower doses of 600 mg daily have been used safely for up to four years.[6,304,338,339,340,341,342,343] Studies of lipoic acid supplementation in people with conditions such as Type II diabetes and peripheral artery disease have reported potential minor side effects such as tingling in legs and feet and mild stomach queasiness. However, it was difficult to determine if this was caused by the supplement or the condition.[344]

Lutein, Zeaxanthin, Astaxanthin and Lycopene have no warnings at proper dosages unless an individual has a known related nutrition allergy or following advice from a qualified health professional.[332]

Contraindications

Unless recommended by a doctor to improve intake of lutein and zeaxanthin to help maximize their effects during fetal development,[130,131] the SA is contraindicated in pregnancy and lactation due to no clinical trials performed with this population (other than lutein and zeaxanthin) and for anyone suffering adverse reactions to any of the ingredients.

CoQ_{10}: Consult a physician if taking antihypertensive drugs or warfarin and/or other blood thinning medications as concomitant use might reduce the anticoagulation effects[333] and CoQ_{10} can decrease blood pressure and might have additive blood pressure lowering effects when used with antihypertensive drugs[345,346]

α-lipoic acid: in vitro, alpha-lipoic acid inhibits platelet aggregation.[347] Theoretically, alpha-lipoic acid can increase bleeding in patients taking anticoagulant/antiplatelet drugs such as warfarin. The use of any antioxidant such as ALPA during chemotherapy should be approved by attending physician[348] and likewise, with some thyroid medications because theoretically (although not seen in humans), concomitant use might decrease the effects of thyroid hormone drugs.[349]

Astaxanthin: in vitro research shows that astaxanthin induces cytochrome P450 2B6 (CYP2B6) and P450 3A4 (CYP3A4) activity in human hepatocytes.[350] Theoretically, astaxanthin may lower plasma levels and reduce the effectiveness of drugs metabolized by either of these complexes CYP2B6 such as some calcium channel blockers.

Lycopene: in vitro lycopene has shown antiplatelet effects, therefore, theoretically, adding lycopene supplements with anticoagulant or antiplatelet drugs might increase the risk of bruising and bleeding.[351]

Adverse Reactions

Serious side effects are unlikely with any ingredient in the SuperiorAntioxidant.[332] All ingredients have GRAS status. * *_Generally recognized as safe (GRAS)_ is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.*

CoQ_{10}: In short and long-term clinical studies, there have been no reports of significant adverse effects.[332] However, in less than 1% of patients taking high dose (>300 mg/day) CoQ_{10} led to minor gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort.[352]

α-lipoic acid: appears to be generally well tolerated when used orally, intravenously, or topically.[6,320,324,332,353.] Minor reported side effects are usually not seen unless dosage exceeds 600 mg/day. Reported reactions include headache, skin rash and stomach upset.[344,354,355]

Lutein, Zeaxanthin, and Lycopene: none reported, even in long-term use[34,134,327,330,356]

Astaxanthin: events from high doses, many times more than found in the SA, are typically minor and may include increased bowl movements and red fecal color.[357] Very high doses of astaxanthin (40 mg daily) may cause stomach/abdominal pain.[358]

Upper Limit/Toxicity

The National Academy of Sciences has not set an upper limit (UL) for any of the ingredients contained in the SA.

α-lipoic acid: No upper limit has been established for human use. A two-year study of laboratory rats reported a no-observed-adverse-effect level (NOAEL) of 60 mg per kilogram body weight.[359] Much higher doses (than contained in the SA) used for clinical purposes, have been used safe and effectively for extended periods of time[6,304,353]

Lutein/zeaxanthin: Human clinical trials have used doses up to 40 mg/day without any adverse or toxicological effects.[330,360] An upper limit has yet to be established.

Lycopene: There have been no reports of adverse or toxicological effects with doses as high as 150 mg/day.[330] An upper limit has yet to be established.

CoQ-10: Evidence from randomized human clinical trials indicates that the UL for CoQ-10 is 1200 mg. There have been no reports of toxicity in studies lasting up to 30 months.[5,352,361,362]

Astaxanthin: animal research shows that administering solution of Haematococcus pluvialis algal meal in a single dose ranging from 10.4 to 18 grams/kg does not cause mortality or abnormality in male or female mice.[363]

Summary

Purpose

The SuperiorAntioxidant is for all adults seeking to improve daily recovery from lifestyle activities, stress, and environmental and diet related daily insults, by supplying in corrective amounts, when combined with diet, the natural bio-active compounds: lycopene, lutein, zeaxanthin, astaxanthin, CoQ_{10} and alpha lipoic acid, to achieve or restore daily levels experts associate with better overall health and recovery outcomes at all adult life stages. Along with the effects of diet and amount of environmental (e.g., stress, pollution, etc.) and physical (exercise, body weight, viral exposure, etc.) insults, tissue levels of these vital nutrition complexes that help balance oxidative stress and inflammation while supporting energy production, significantly decline with age. SA is properly dosed to help restore or maintain tissue levels similar to youthful concentrations to help deliver enhanced energy, improved and reduced recovery time, and unique structural and functional support for the maintenance of eye, cardiovascular, skin, immune and brain health contributing to healthy aging and prolonging the ability to perform desired activities at the highest level, especially when combined with a ***complete*** daily multivitamin and mineral formula. *Notably, these recommended amounts were not known or available during periods of significantly shorter lifespans but are now known and discovered to be important to support the human current lifespan's potential health.*

Unique Features

- Inexpensive and convenient: a combination of antioxidant ingredients often purchased separately to achieve effective doses and forms found in this product. Most competitive products (by label claim or name) are significantly under-formulated and do not have this full range of non-vitamin/mineral antioxidants or energy compounds.
- Contains AstaReal® astaxanthin, the most studied brand of astaxanthin in the world for applications such as skin health, anti-aging, muscle endurance and recovery, and eye health*
- Formula considers the use of other dotFIT products to help maintain a safe and optimal range of total nutrient intake.
- Manufactured in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC
- 3rd party tested and NSF Certified for Sport

* *AstaReal® is the global pioneer of natural astaxanthin with over 150 studies, 60 of those human clinical trials on AstaReal's® astaxanthin alone. Astaxanthin is made by the algae Haematococcus pluvialis in response to stresses that produce free radicals. AstaReal® natural astaxanthin is only produced indoors in a clean, controlled environment where they filter the air through hospital grade HEPA filters and use only triple, reverse osmosis purified water.*

Supplement Facts Panel

Supplement Facts

Serving Size: 2 Vegetarian Capsules
Servings per Container: 60

	Amount Per Serving	% DV
Alpha Lipoic Acid	200 mg	*
Co-Enzyme Q10 (CoQ-10)	100 mg	*
Lycopene	10 mg	*
Lutein	6 mg	*
Astaxanthin (as AstaReal®)	4 mg	*
Zeaxanthin	3 mg	*
Meso Zeaxanthin	1 mg	*

* Daily Value (DV) not established

References

[1] Małgorzata Grabowska, et al. Let food be your medicine: nutraceutical properties of lycopene. Food Funct., 2019, 10, 3090. The Royal Society of Chemistry 2019

[2]Long AC, Kuchan M, Mackey AD. Lutein as an Ingredient in Pediatric Nutritionals. J AOAC Int. 2019;102(4):1034-1043. doi:10.5740/jaoacint.19-0014

[3] Murillo, Ana Gabriela et al. "Zeaxanthin: Metabolism, Properties, and Antioxidant Protection of Eyes, Heart, Liver, and Skin." Antioxidants (Basel, Switzerland) vol. 8,9 390. 11 Sep. 2019, doi:10.3390/antiox8090390

[4] Fakhri S, Abbaszadeh F, Dargahi L, Jorjani M. Astaxanthin: A mechanistic review on its biological activities and health benefits. Pharmacol Res. 2018;136:1-20. doi:10.1016/j.phrs.2018.08.012

[5] Raizner, Albert E. "Coenzyme Q_{10}." Methodist DeBakey cardiovascular journal vol. 15,3 (2019): 185-191. doi:10.14797/mdcj-15-3-185

[6] Salehi, Bahare et al. "Insights on the Use of α-Lipoic Acid for Therapeutic Purposes." Biomolecules vol. 9,8 356. 9 Aug. 2019, doi:10.3390/biom9080356

[7] Lee et al. Health Benefits of Carotenoids: A Role of Carotenoids in the Prevention of Non-Alcoholic Fatty Liver Disease. Prev. Nutr. Food Sci. 2019;24(2):103-113. https://doi.org/10.3746/pnf.2019.24.2.103.

[8] Elvira-Torales et al. Nutritional Importance of Carotenoids and Their Effect on Liver Health: A Review. Antioxidants 2019, 8, 229; doi:10.3390/antiox8070229

[9] Khachik, F. Distribution and metabolism of dietary carotenoids in humans as a criterion for development of nutritional supplements. Pure Appl. Chem. 2006, 78, 1551–1557.

[10] Eggersdorfer, M.;Wyss, A. Carotenoids in human nutrition and health. Arch. Biochem. Biophys. 2018, 652, 18–26

[11] P. D. Fraser and P. M. Bramley, The biosynthesis and nutritional uses of carotenoids, Prog. Lipid Res., 2004, 43, 228–265

[12] Yabuzaki, J. Carotenoids Database: Structures, chemical fingerprints and distribution among organisms. Database 2017, 2017, bax004

[13] Aune et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. Am J Clin Nutr 2018;108:1069–1091.

[14] Crowe-White, Kristi M et al. "Lycopene and cognitive function." Journal of nutritional science vol. 8 e20. 29 May. 2019, doi:10.1017/jns.2019.16

[15] Elia, M.; Stratton, R.J. Geographical inequalities in nutrient status and risk of malnutrition among English people aged 65 y and older. Nutrition 2005, 21, 1100–1106

[16] Rodriguez-Concepcion, M.; Avalos, J.; Bonet, M.L.; Boronat, A.; Gomez-Gomez, L.; Hornero-Mendez, D.; Ribot, J. A global perspective on carotenoids: Metabolism, biotechnology, and benefits for nutrition and health. Prog. Lipid Res. 2018, 70, 62–93

[17] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/. Chapter 2 (section 3). Shifts Needed to Align with Healthy Eating Patterns. A Closer Look at Current Intakes and Recommended Shifts.

[18] Van Het Hof, K.H.; West, C.E.; Weststrate, J.A.; Hautvast, J.G. Dietary factors that affect the bioavailability of carotenoids. J. Nutr. 2000, 130, 503–506

[19] Donhowe, E.G., Kong, F. Beta-carotene: Digestion, microencapsulation, and in vitro bioavailability. Food Bioprocess Technol. 2014, 7, 338–354

[20] Rein, M.J.; Renouf, M.; Cruz-Hernandez, C.; Actis-Goretta, L.; Thakkar, S.K.; Da Silva Pinto, M.; da Silva Pinto, M. Bioavailability of bioactive food compounds: A challenging journey to bio-efficacy. Br. J. Clin. Pharmacol. 2013, 75, 588–602

[21] Zukiewicz-Sobczak WA, Wro_blewska P, Adamczuk P, Kopczyn_ski P. Causes, symptoms and prevention of food allergy. Adv Dermatol Allergol Postępy Dermatol Alergol 2013;30:113–6

[22] Chow EJ, Sediva I. Influenza infection and anaphylaxis in a pediatric patient hospitalized for asthma exacerbation. R I Med J 2017;100(2013):35–6.

[23] Jansen, M.C.; Van Kappel, A.L.; Ocké, M.C.; Van't Veer, P.; Boshuizen, H.C.; Riboli, E.; Bueno-de-Mesquita, H.B. Plasma carotenoid levels in Dutch men and women, and the relation with vegetable and fruit consumption. Eur. J. Clin. Nutr. 2004, 58, 1386–1395

[24] Mozos et al. Lycopene and Vascular Health. REVIEW. Frontiers in Pharmacology. Published: 23 May 2018. doi: 10.3389/fphar.2018.00521

[25] Suárez-Rivero, Juan M et al. "Atherosclerosis and Coenzyme Q_{10}." International journal of molecular sciences vol. 20,20 5195. 20 Oct. 2019, doi:10.3390/ijms20205195

[26] Hargreaves IP, Mantle D. Coenzyme Q10 Supplementation in Fibrosis and Aging. Adv Exp Med Biol. 2019;1178:103-112. doi:10.1007/978-3-030-25650-0_6

[27] Salehi et al. Beneficial effects and potential risks of tomato consumption for human health: An overview. Nutrition 62 (2019) 201-208

[28]Balić, Anamaria, and Mislav Mokos. "Do We Utilize Our Knowledge of the Skin Protective Effects of Carotenoids Enough?" Antioxidants (Basel, Switzerland) vol. 8,8 259. 31 Jul. 2019, doi:10.3390/antiox8080259

[29]Aziz E, Batool R, Akhtar W, et al. Xanthophyll: Health benefits and therapeutic insights. Life Sci. 2020;240:117104. doi:10.1016/j.lfs.2019.117104

[30]Brown, Daniel R et al. "Astaxanthin in Exercise Metabolism, Performance and Recovery: A Review." Frontiers in nutrition vol. 4 76. 18 Jan. 2018, doi:10.3389/fnut.2017.00076

[31] Nouchi, Rui et al. "Effects of Lutein and Astaxanthin Intake on the Improvement of Cognitive Functions among Healthy Adults: A Systematic Review of Randomized Controlled Trials." Nutrients vol. 12,3 617. 27 Feb. 2020, doi:10.3390/nu12030617
[32] Nieman DC, Capps CL, Capps CR, Shue ZL, McBride JE. Effect of 4-Week Ingestion of Tomato-Based Carotenoids on Exercise-Induced Inflammation, Muscle Damage, and Oxidative Stress in Endurance Runners. Int J Sport Nutr Exerc Metab. 2018;28(3):266-273. doi:10.1123/ijsnem.2017-0272
[33] Sarmiento A, Diaz-Castro J, Pulido-Moran M, Kajarabille N, Guisado R, Ochoa JJ. Coenzyme Q10 Supplementation and Exercise in Healthy Humans: A Systematic Review. Curr Drug Metab. 2016;17(4):345-358. doi:10.2174/1389200216666151103115654
[34] Milani, Alireza et al. "Carotenoids: biochemistry, pharmacology and treatment." British journal of pharmacology vol. 174,11 (2017): 1290-1324. doi:10.1111/bph.13625
[35] Pallet KE, Young R. Carotenoids. In: Alscher RG, Hess JL, editors. Antioxidants in Higher Plants. CRC Press, Boca Raton, FL, USA. 2017. p 59-89
[36] Banfield EC, Liu Y, Davis JS, Chang S, Frazier-Wood AC. Poor Adherence to US Dietary Guidelines for Children and Adolescents in the National Health and Nutrition Examination Survey Population. J Acad Nutr Diet. 2016
[37] Moore LV, Thompson FE, Demissie Z. Percentage of Youth Meeting Federal Fruit and Vegetable Intake Recommendations, Youth Risk Behavior Surveillance System, United States and 33 States, 2013. J Acad Nutr Diet. 2017 Apr;117(4):545-553.e3. doi: 10.1016/j.jand.2016.10.012. Epub 2016 Dec 15
[38] Toti, Elisabetta et al. "Non-Provitamin A and Provitamin a Carotenoids as Immunomodulators: Recommended Dietary Allowance, Therapeutic Index, or Personalized Nutrition?" Oxidative medicine and cellular longevity vol. 2018 4637861. 9 May. 2018, doi:10.1155/2018/4637861
[39] Baralic I, Andjelkovic M, Djordjevic B77, Dikic N, Radivojevic N, Suzin-Zivkovic V, Radojevic-Skodric S, Pejic S. Effect of astaxanthin supplementation on salivary IgA, oxidative stress, and inflammation in young soccer players. Evid Based Complement Alternat Med 2015; 2015:783761783761.
[40] Lyu, Yi et al. "Carotenoid supplementation and retinoic acid in immunoglobulin A regulation of the gut microbiota dysbiosis." Experimental biology and medicine (Maywood, N.J.) vol. 243,7 (2018): 613-620. doi:10.1177/1535370218763760
[41] Hoffmann, J.; Linseisen, J.; Riedl, J.; Wolfram, G. Dietary fiber reduces the antioxidative effect of a carotenoid and alpha-tocopherol mixture on LDL oxidation ex vivo in humans. Eur. J. Nutr. 1999, 38, 278–285
[42] Desmarchelier, C.; Borel, P. Overview of carotenoid bioavailability determinants: From dietary factors to host genetic variations. Trends Food Sci. Technol. 2017, 69, 270–280
[43] Lemmens, L.; Colle, I.; Van Buggenhout, S.; Palmero, P.; Van Loey, A.; Hendrickx, M. Carotenoid bio-accessibility in fruit- and vegetable-based food products as a byproduct (micro) structural characteristic and the presence of lipids: A review. Trends Food Sci. Technol. 2014, 38, 125–135
[44] Priyadarshani, A.M.B. A review on factors influencing bio-accessibility and bio-efficacy of carotenoids. Crit. Rev. Food Sci. Nutr. 2017, 57, 1710–1717
[45]Bernhardt, S.; Schlich, E. Impact of different cooking methods on food quality: Retention of lipophilic vitamins in fresh and frozen vegetables. J. Food Eng. 2006, 77, 327–333
[46]Roodenburg, A.J.; Leenen, R.; Hof, K.H.; Weststrate, J.A.; Tijburg, L.B. Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. Am. J. Clin. Nutr. 2000, 71, 1187–1193
[47] Periago, M.J.; Bravo, S.; García-Alonso, F.J.; Rincón, F. Detection of key factors affecting lycopene in vitro accessibility. J. Agric. Food Chem. 2013, 61, 3859–3867
[48] Cohn W, Thurmann P, Tenter U, Aebischer C, Schierle J, Schalch W. Comparative multiple dose plasma kinetics of lycopene administered in tomato juice, tomato soup or lycopene tablets. Eur J Nutr 2004;43:304–12
[49] Akihiko Nagao, et. al. Effects of fats and oils on the bio-accessibility of carotenoids and Vitamin E in vegetables. Biosci. Biotechnol.Biochem.,77(5),1055-1060, 2013
[50] "Carotenoids: α-Carotene, β-Carotene, β-Cryptoxanthin, Lycopene, Lutein, and Zeaxanthin". Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis, OR. July 2016. Retrieved 29 May 2017.
[51] M. S. Donaldson, "A carotenoid health index based on plasma carotenoids and health outcomes," Nutrients, vol. 3, no. 12, pp. 1003–1022, 2011.
[52] Petyaev, Ivan M. "Lycopene Deficiency in Ageing and Cardiovascular Disease." Oxidative medicine and cellular longevity vol. 2016 (2016): 3218605. doi:10.1155/2016/3218605
[53] J. Shi, Y. Dai, Y. Kakuda, G. Mittal and S. J. Xue, Effect of heating and exposure to light on the stability of lycopene in tomato purée, Food Control, 2008, 19, 514–520.
[54] Dias, M.G.; Olmedilla-Alonso, B.; Hornero-Méndez, D.; Mercadante, A.Z.; Osorio, C.; Vargas-Murga, L.; Meléndez-Martínez, A.J. Comprehensive database of carotenoid contents in Ibero-American foods. A valuable tool in the context of functional foods and the establishment of recommended intakes of bioactives. J. Agric. Food Chem. 2018, 66, 5055–5107
[55] Murillo, A.G.; DiMarco, D.M.; Fernandez, M.L. The potential of non-provitamin A carotenoids for the prevention and treatment of non-alcoholic fatty liver disease. Biology 2016, 5, 42
[56] Burton-Freeman, B., and Sesso, H. D. (2014). Whole food versus supplement: comparing the clinical evidence of tomato intake and lycopene supplementation on cardiovascular risk factors. Adv. Nutr. 5, 457–485. doi: 10.3945/an.114.005231
[57] M. Porrini and P. Riso, "What are typical lycopene intakes?" Journal of Nutrition, vol. 135, no. 8, pp. 2042S–2045S, 2005

[58] Igielska-Kalwat, J., Gościańska, J., & Nowak, I. (2015). Carotenoids as natural antioxidants. Postępy Higieny i Medycyny Doświadczalnej, 69, 418–428. https://doi.org/10.5604/17322693.1148335
[59] D. Heber and Q. Y. Lu, Overview of mechanisms of action of lycopene, Exp. Biol. Med., 2002, 227, 920–923.
[60] Sahin K, Sahin N, Kucuk O. Lycopene and chemotherapy toxicity. Nutr Cancer. 2010 Oct;62(7):988-95.
[61] Fernández-Bedmar Z, Anter J, Alonso Moraga Á. Anti/genotoxic, longevity inductive, cytotoxic, and clastogenic-related bioactivities of tomato and lycopene. Environ Mol Mutagen. 2018;59(5):427-437. doi:10.1002/em.22185
[62] Jiang, Li-Ning et al. "Lycopene exerts anti-inflammatory effect to inhibit prostate cancer progression." Asian journal of andrology, vol. 21,1 80–85. 7 Sep. 2018, doi:10.4103/aja.aja_70_18
[63] Kawata, Akifumi et al. "Anti-inflammatory Activity of β-Carotene, Lycopene and Tri-n-butylborane, a Scavenger of Reactive Oxygen Species." In vivo (Athens, Greece) vol. 32,2 (2018): 255-264. doi:10.21873/invivo.11232
[64]Cicero AFG, Allkanjari O, Busetto GM, et al. Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer. Arch Ital Urol Androl. 2019;91(3):10.4081/aiua.2019.3.139. Published 2019 Oct 2. doi:10.4081/aiua.2019.3.139
[65] Gloria NF, Soares N, Brand C, Oliveira FL, Borojevic R, Teodoro AJ. Lycopene and β-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. Anticancer Res. 2014;34:1377–1386
[66] Cheng HM, Koutsidis G, Lodge JK, Ashor AW, Siervo M, Lara J. Lycopene and tomato and risk of cardiovascular diseases: A systematic review and meta-analysis of epidemiological evidence. Crit Rev Food Sci Nutr. 2019;59(1):141-158. doi:10.1080/10408398.2017.1362630
[67] Chen F, Sun ZW, Ye LF, Fu GS, Mou Y, Hu SJ. Lycopene protects against apoptosis in hypoxia/reoxygenation-induced h9c2 myocardioblast cells through increased autophagy. Mol Med Rep 2015;11:1358–65.
[68] Aust O, Ale-Agha N, Zhang L, Wollersen H, Sies H, Stahl W. Lycopene oxidation product enhances gap junctional communication. Food Chem Toxicol 2003;41:1399–407
[69] D. Y. Quansah, K. Ha, S. Jun, S. A. Kim, S. Shin, G. A. Wie and H. Joung, Associations of Dietary Antioxidants and Risk of Type 2 Diabetes: Data from the 2007-2012 Korea National Health and Nutrition Examination Survey, Molecules, 2017, 22, 1664
[70] G. M. Han, G. A. Soliman, J. L. Meza, K. M. Islam and S. Watanabe-Galloway, The influence of BMI on the association between serum lycopene and the metabolic syndrome, Br. J. Nutr., 2016, 115, 1292–1300
[71] Mozos, I., and Luca, C. T. (2017). Crosstalk between oxidative and nitrosative stress and arterial stiffness. Curr. Vasc. Pharmacol. 15, 446–456. doi: 10.2174/1570161115666170201115428
[72] Nakamura, A., Itaki, C., Saito, A., Yonezawa, T., Aizawa, K., Hirai, A., et al. (2017). Possible benefits of tomato juice consumption: a pilot study on irradiation human lymphocytes from healthy donors. Nutr. J. 16:27. doi: 10.1186/s12937-017-0248-3
[73] Abdel-Daim, M. M., Eltaysh, R., Hassan, A., and Mousa, S. A. (2018). Lycopene attenuates tulathromycin and diclofenac sodium-induced cardiotoxicity in mice. Int. J. Mol. Sci. 19:e344. doi: 10.3390/ijms19020344
[74] Opatrilova, R., Kubatka, P., Caprnda, M., Büsselberg, D., Krasnik, V., Veselz, P., et al. (2017). Nitric oxide in the pathophysiology of retinopathy: evidence from preclinical and clinical research. Acta Ophthalmol. 96, 222–231.
doi: 10.1111/aos.13384
[75] Yücel, G., Zhao, Z., El-Battrawy, I. et al. Lipopolysaccharides induced inflammatory responses and electrophysiological dysfunctions in human-induced pluripotent stem cell derived cardiomyocytes. Sci Rep 7, 2935 (2017). https://doi.org/10.1038/s41598-017-03147-4
[76] Bae JW, Bae JS (2011). Barrier protective effects of lycopene in human endothelial cells. Inflamm Res 60: 751–758
[77] Hung, C. F., Huang, T. F., Chen, B. H., Shieh, J. M., Wu, P. H., and Wu, W. B. (2008). Lycopene inhibits TNF-alpha-induced endothelial ICAM- 1 expression and monocyte-endothelial adhesion. Eur. J. Pharmacol. 586, 275–282. doi: 10.1016/j.ejphar.2008.03.001
[78] He, Q., Zhou, W., Xiong, C., Tan, G., and Chen, M. (2015). Lycopene attenuates inflammation and apoptosis in post-myocardial infarction remodeling by inhibiting the nuclear factor-kappaB signaling pathway. Mol. Med. Rep. 11, 374–378. doi: 10.3892/mmr.2014.2676
[79]Jeong Y, Lim JW, Kim H. Lycopene Inhibits Reactive Oxygen Species-Mediated NF-κB Signaling and Induces Apoptosis in Pancreatic Cancer Cells. Nutrients. 2019;11(4):762. Published 2019 Apr 1. doi:10.3390/nu11040762
[80] Costa-Rodrigues J, Pinho O, Monteiro PRR. Can lycopene be considered an effective protection against cardiovascular disease? Food Chem. 2018;245:1148-53.
[81]Montesano D, Blasi F, Cossignani L. Lycopene and Cardiovascular Disease: An Overview. Ann Short Reports. 2019; 2: 1033.
[82]Cheng HM, Koutsidis G, Lodge JK, Ashor A, Siervo M, Lara J. Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis. Atherosclerosis. 2017;257:100-108. doi:10.1016/j.atherosclerosis.2017.01.009
[83] Karppi J, Laukkanen JA, Sivenius J, Ronkainen K, Kurl S. Serum lycopene decreases the risk of stroke in men: a population-based follow-up study. Neurology. 2012 Oct 9;79(15):1540-7. doi: 10.1212/WNL.0b013e31826e26a6.
[84] Agarwal S, Rao AV. Tomato lycopene and low-density lipoprotein oxidation: a human dietary intervention study. Lipids 1998;33(981-4)
[85] Rissanen T, Boutilainen S, Nyyssonen K Salonen JT. Lycopene, atherosclerosis, and coronary heart disease. Exp Biol Med (Maywood) 2002 Nov;227(10):900-7.
[86] Hadley CW, Clinton SK, Schwartz SJ. The consumption on processed tomato products enhances plasma Lycopene concentrations in association with a reduced lipoprotein sensitivity to oxidative damage. J Nutr 2003 Mar;133(3):727-32.
[87] Rao AV. Lycopene, tomatoes, and the prevention of coronary heart disease. Exp Biol Med (Maywood) 2002 Nov;227(10):908-13.
[88] Sesso HD, Buring JE, Norkus EP, Gaziano JM. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in men. Am J Clin Nutr. 2005 May;81(5):990-7.

[89] Petyaev, Ivan M et al. "Effect of lycopene supplementation on cardiovascular parameters and markers of inflammation and oxidation in patients with coronary vascular disease." Food science & nutrition vol. 6,6 1770-1777. 13 Aug. 2018, doi:10.1002/fsn3.734
[90] NIH National Institute on Aging. Cognitive Health. https://www.nia.nih.gov/health/cognitive-health-and-older-adults#:~:text=Cognitive%20health%E2%80%94the%20ability%20to,interpret%20and%20respond%20to%20emotions
[91] Di Mascio P, Kaiser S & Sies H (1989) Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys 274, 532–538.
[92] Crichton GE, Bryan J & Murphy KJ (2013) Dietary antioxidants, cognitive function and dementia – a systematic review. Plant Foods Hum Nutr 68, 279–292.
[93] A.V. Rao, L.G. Rao, Carotenoids and human health, Pharmacol. Res. 55 (2007) 207–216.
[94] F. Khachik, L. Carvalho, P.S. Bernstein, G.J. Muir, D.Y. Zhao, N.B. Katz, Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health, Exp. Biol. Med. (Maywood) 227 (2002) 845–851.
[95] H.Y. Lin, B.R. Huang, W.L. Yeh, C.H. Lee, S.S. Huang, C.H. Lai, H. Lin, D.Y. Lu, Anti-neuroinflammatory effects of lycopene via activation of adenosine monophosphate-activated protein kinase-α1/heme oxygenase-1 pathways, Neurobiol. Aging 35 (2014) 191–202.
[96] F. Zhang, Y. Fu, X. Zhou, W. Pan, Y. Shi, M. Wang, X. Zhang, D. Qi, L. Li, K. Ma, R. Tang, K. Zheng, Y. Song, Depression-like behaviors and heme oxygenase-1 are regulated by lycopene in lipopolysaccharide-induced neuroinflammation, J. Neuroimmunol. 298 (2016) 1–8
[97] Glade MJ (2010) Oxidative stress and cognitive longevity. Nutrition 26, 595–603.
[98] Chen D, Huang C, Chen Z. A review for the pharmacological effect of lycopene in central nervous system disorders. Biomed Pharmacother. 2019;111:791-801. doi:10.1016/j.biopha.2018.12.151
[99] Y. Zhao, Z. Xin, N. Li, S. Chang, Y. Chen, L. Geng, H. Chang, H. Shi, Y.Z. Chang, Nano-liposomes of lycopene reduces ischemic brain damage in rodents by regulating iron metabolism, Free Radic. Biol. Med. 124 (2018) 1–11.
[100] Q. Yin, Y. Ma, Y. Hong, X. Hou, J. Chen, C. Shen, M. Sun, Y. Shang, S. Dong, Z. Zeng, J.J. Pei, X. Liu, Lycopene attenuates insulin signaling deficits, oxidative stress, neuroinflammation, and cognitive impairment in fructose-drinking insulin resistant rats, Neuropharmacology 86 (2014) 389–396.
[101] A. Lau, M. Tymianski, Glutamate receptors, neurotoxicity and neurodegeneration, D. Chen et al. Biomedicine & Pharmacotherapy 111 (2019) 791–801 800 Pflugers Arch–Eur. J. Physiol. 460 (2010) 525–542.
[102] R. Fan, P.C. Hu, Y. Wang, H.Y. Lin, K. Su, X.S. Feng, L. Wei, F. Yang, Betulinic acid protects mice from cadmium chloride-induced toxicity by inhibiting cadmium-induced apoptosis in kidney and liver, Toxicol. Lett. 299 (2018) 56–66.
[103] Clark PE, HallMC, Borden LS Jr, Miller AA, Hu JJ, LeeWR et al. (2006). Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. Urology 67: 1257–1261
[104] Diwadkar-Navsariwala V, Novotny JA, Gustin DM, Sosman JA, Rodvold KA, Crowell JA et al. (2003). A physiological pharmacokinetic model describing the disposition of lycopene in healthy men. J Lipid Res 44: 1927–1939
[105] Trumbo PR (2005). Are there adverse effects of lycopene exposure? J Nutr 135: 2060S–2061S
[106] Akbaraly NT, Faure H, Gourlet V, 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
[107] Polidori MC, Praticóc D, Mangialasche F, et al. (2009) High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. J Alzheimer's Dis 17, 921–927.
[108] Min J & Min K (2014) Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults. Dement Geriatr Cogn Disord 37, 246–256.
[109] Palozza P.a · Catalano A.a · Simone R.E.a · Mele M.C.b · Cittadini A. Effect of Lycopene and Tomato Products on Cholesterol Metabolism. Ann Nutr Metab 2012;61:126–134 (DOI:10.1159/000342077)
[110] Chen, Ping et al. "Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis." Medicine vol. 94,33 (2015): e1260. doi:10.1097/MD.0000000000001260
[111] Calogero AE , Aversa A, La Vignera S, Corona G, Ferlin A. The use of nutraceuticals in male sexual and reproductive disturbances: position statement from the Italian Society of Andrology and Sexual Medicine (SIAMS). J Endocrinol Invest 2017; 40: 1389-1397
[112] Yamamoto Y, Aizawa K, Mieno M, Karamatsu M, Hirano Y, Furui K, Miyash ita T, Yamazaki K, Inakuma T, Sato I, Suganuma H, Iwamoto T. The effects of tomato juice on male infertility. Asia Pac J Clin Nutr 2017; 26: 65-71
[113] Liang ZW, Guo KM, Dai XF, Liu LY , Xu SQ, Zhao LJ, Li FB, Wang HL. Protective effect of lycopene on human spermatozoa during cryopreservation and its mechanism. Zhonghua Nan Ke Xue 2015; 21: 521-526.
[114] Applegate, Catherine C et al. "Can Lycopene Impact the Androgen Axis in Prostate Cancer? A Systematic Review of Cell Culture and Animal Studies." Nutrients vol. 11,3 633. 15 Mar. 2019, doi:10.3390/nu11030633
[115] X. Gong, R. Marisiddaiah, S. Zaripheh, D. Wiener and L. P. Rubin, Mitochondrial Beta-Carotene Oxygenase Modulates Prostate Cancer Growth via NF-kappaB Inhibition: A Lycopene-Independent Function, Mol. Cancer Res., 2016, 14, 966–975.
[116] Tjahjodjati et al. "The Protective Effect of Lycopene on Prostate Growth Inhibitory Efficacy by Decreasing Insulin Growth Factor-1 in Indonesian Human Prostate Cancer Cells." Research and reports in urology vol. 12 137-143. 17 Apr. 2020, doi:10.2147/RRU.S232745
[117]F. Chen, M. Du, J. B. Blumberg, K. K. Ho Chui, M. Ruan, G. Rogers, Z. Shan, L. Zeng and F. F. Zhang, Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults: A Cohort Study, Ann. Intern. Med., 2019, 170, 604–613

[118] Filipcikova R, Oborna I, Brezinova J, Novotny J, Wojewodka G, De Sanctis JB, Radova L, Hajduch M, Radzioch D.Lycopene improves the distorted ratio between AA/DHA in the seminal plasma of infertile males and increases the likelihood of successful pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015; 159: 77-82.
[119] Cannarella R, Calogero AE, Condorelli RA, Giacone F, Mongioi' LM, La Vignera S. Non-hormonal treatment for male infertility: the potential role of Serenoa repens, selenium and lycopene. Eur Rev Med Pharmacol Sci. 2019;23(7):3112-3120. doi:10.26355/eurrev_201904_17595
[120] Durairajanayagam D, Agarwal A1, Ong C, Prashast P. Lycopene and male infertility. Asian J Androl. 2014 May-Jun;16(3):420-5. doi: 10.4103/1008-682X.126384
[121] Scarmo, S., Cartmel, B., Lin, H., Leffell, D. J., Welch, E., Bhosale, P., …Mayne, S. T. (2010). Significant correlations of dermal total carotenoids and dermal lycopene with their respective plasma levels in healthy adults. Archives of Biochemistry and Biophysics, 504, 34–39. https://doi.org/10.1016/j.abb.2010.07.004
[122] Grether-Beck S, Marini A, Jaenicke T, Stahl W, Krutmann J. Molecular evidence that oral supplementation with lycopene or lutein protects human skin against ultraviolet radiation: results from a double-blinded, placebo-controlled, crossover study. Br J Dermatol. 2017;176(5):1231-1240. doi:10.1111/bjd.15080
[123] Petyaev, Ivan M et al. "Lycopene presence in facial skin corneocytes and sebum and its association with circulating lycopene isomer profile: Effects of age and dietary supplementation." Food science & nutrition vol. 7,4 1157-1165. 13 Mar. 2019, doi:10.1002/fsn3.799
[124] Heinrich U, Tronnier H, Stahl W, Béjot M, Maurette JM. Antioxidant supplements improve parameters related to skin structure in humans. Skin Pharmacol Physiol. 2006;19(4):224-231. doi:10.1159/000093118
[125] Heinrich U, Gärtner C, Wiebusch M, et al. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. J Nutr. 2003;133(1):98-101. doi:10.1093/jn/133.1.98
[126] Blume-Peytavi, U., Rolland, A., Darvin, M. E., Constable, A., Pineau, I., Voit, C., … Lademann, J. (2009). Cutaneous lycopene and β-carotene levels measured by resonance Raman spectroscopy: High reliability and sensitivity to oral lactolycopene deprivation and supplementation. European Journal of Pharmaceutics and Biopharmaceutics, 73, 187–194. https://doi.org/10.1016/j.ejpb.2009.04.017
[127] Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev. 2014 Sep;72(9):605-12. doi: 10.1111/nure.12133. Epub 2014 Aug 8
[128] Xavier AAO, Pérez-Gálvez A. Carotenoids as a Source of Antioxidants in the Diet. Subcell Biochem. 2016; 79:359–375. [PubMed: 27485230]
[129] Giordano, Elena, and Loredana Quadro. "Lutein, zeaxanthin and mammalian development: Metabolism, functions and implications for health." Archives of biochemistry and biophysics vol. 647 (2018): 33-40. doi:10.1016/j.abb.2018.04.008
[130]Zielińska MA, Wesołowska A, Pawlus B, Hamułka J. Health Effects of Carotenoids during Pregnancy and Lactation. Nutrients. 2017; 9:838
[131] Lai, Jun S et al. "Maternal Lutein and Zeaxanthin Concentrations in Relation to Offspring Visual Acuity at 3 Years of Age: The GUSTO Study." Nutrients vol. 12,2 274. 21 Jan. 2020, doi:10.3390/nu12020274
[132] Scripsema NK, Hu DN, Rosen RB. Lutein, zeaxanthin, and meso-zeaxanthin in the clinical management of eye disease. J Ophthalmol. 2015;2015:865179.
[133] Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA. Intakes of lutein, zeaxanthin, and other carotenoids and age-related macular degeneration during 2 decades of prospective follow-up. JAMA Ophthalmol. 2015; 133:1415–24. [PubMed: 26447482]
[134] Mares, Julie. "Lutein and Zeaxanthin Isomers in Eye Health and Disease." Annual review of nutrition vol. 36 (2016): 571-602. doi:10.1146/annurev-nutr-071715-051110
[135] Eisenhauer B, Natoli S, Liew G, Flood VM. Lutein and Zeaxanthin-food Sources, Bioavailability and Dietary Variety in Age-related Macular Degeneration Protection. Nutrients. 2017;9(2):120. Published 2017 Feb 9. doi:10.3390/nu9020120
[136] U.S. Dep. Agric., Agric. Res. Serv. What We Eat in America, NHANES 011–2012. Washington, DC: USDA ARS; 2014. http://www.ars.usda.gov/Services/docs.htm?docid=13793
[137] Harrison EH, Curley RW. Carotenoids and retinoids: nomenclature, chemistry, and analysis. Subcell Biochem. 2016; 81:1–19. [PubMed: 27830499]
[138] Nwachukwu, I.D.; Udenigwe, C.C.; Aluko, R.E. Lutein and zeaxanthin: Production technology, bioavailability, mechanisms of action, visual function, and health claim status. Trends Food Sci. Technol. 2016, 49, 74–84
[139] Micozzi MS, Brown ED, Edwards BK, Bieri J, Taylor PR, Khachik F, Beecher GR, Smith J. Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. Am J Clin Nutr. 1992; 55:1120–1125. [PubMed: 1595584]
[140] Khachik F, Beecher GR, Smith JC. Lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer. J Cell Biochem. 1995; 59:236–246.
[141] Renzi LM, Hammond BR, Dengler M, Roberts R. The relation between serum lipids and lutein and zeaxanthin in the serum and retina: results from cross-sectional, case-control and case study designs. Lipids Health Dis. 2012; 11:33. [PubMed: 22375926]
[142] Renzi-Hammond, Lisa M et al. "Effects of a Lutein and Zeaxanthin Intervention on Cognitive Function: A Randomized, Double-Masked, Placebo-Controlled Trial of Younger Healthy Adults." Nutrients vol. 9,11 1246. 14 Nov. 2017, doi:10.3390/nu9111246
[143] Palombo, P.; Fabrizi, G.; Ruocco, V.; Ruocco, E.; Fluhr, J.; Roberts, R.; Morganti, P. Beneficial long-term effects of combined oral/topical antioxidant treatment with the carotenoids, lutein and zeaxanthin on human skin: A double-blind, placebo-controlled study. Skin Pharmacol. Physiol. 2007, 20, 199–210.
[144] Schwartz, S.; Frank, E.; Gierhart, D.; Simpson, P.; Frumento, R. Zeaxanthin-based dietary supplement and topical serum improve hydration and reduce wrinkle count in female subjects. J. Cosmet. Dermatol. 2016, 15, e13–e20

[145]Shete V, Quadro L. Mammalian metabolism of β-carotene: gaps in knowledge. Nutrients. 2013; 5:4849–4868. [PubMed: 24288025]
[146] Wang W, Connor SL, Johnson EJ, Klein ML, Hughes S, Connor WE. Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. Am J Clin Nutr. 2007 Mar;85(3):762-9.
[147]Craft NE, Haitema TB, Garnett KM, Fitch KA, Dorey CK. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J Nutr Health Aging. 2004; 8:156–62. [PubMed: 15129301]
[148]Vishwanathan R, Schalch W, Johnson EJ. Macular pigment carotenoids in the retina and occipital cortex are related in humans. Nutr Neurosci. 2016; 19:95–101. [PubMed: 25752849]
[149] Bernstein PS, Khackik F, Carvalho LS, Muir GJ, Zhao DY, Katz NB. Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. Exp Eye Res 2001 Mar;72(3):215-23.
[150]Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, Nolan JM. Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. Prog Retin Eye Res. 2016; 50:34–66. [PubMed: 26541886]
[151] Bone RA, Landrum JT, Dixon Z, Chen Y, Llerena CM. Lutein and zeaxanthin in the eyes, serum and diet of human subjects. Exp Eye Res. 2000; 71:239–245. [PubMed: 10973733]
[152] Johnson EJ, Hammond BR, Yeum KJ, Qin J, Dong Wang X, Castaneda C, Snodderly DM, Russell RM. Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density. Am J Clin Nutr 2000;71:1555-62.
[153] Yeum KJ, Shang FM, Schalch WM, Russell RM, Taylor A. Fat-soluble nutrient concentrations in different layers of human cataractous lens. Curr Eye Res. 1999; 19:502–5. [PubMed: 10550792]
[154] Billsten, H.H.; Bhosale, P.; Yemelyanov, A.; Bernstein, P.S.; Polivka, T. Photophysical Properties of Xanthophylls in Carotenoproteins from Human Retina. Photochem. Photobiol. 2003, 78, 138–145
[155]Barker FM 2nd, Snodderly DM, Johnson EJ, Schalch W, Koepcke W, et al. Nutritional manipulation of primate retinas, V: effects of lutein, zeaxanthin, and n-3 fatty acids on retinal sensitivity to blue-light-induced damage. Investig Ophthalmol Vis Sci. 2011; 52:3934–42. [PubMed: 21245404]
[156]Landrum, JT., Bone, RA. Mechanistic evidence for eye diseases and carotenoids. In: Krinsky, NI.Mayne, ST., Sies, H., editors. Carotenoids in Health and Disease. New York: Marcel Dekker; 2004. p. 445-72
[157] Palozza P, Krinsky NI. Antioxidant effects of carotenoids in vivo and in vitro: an overview. In Methods in Enzymology Vol 213. San Diego: Academic Press;1992. Pp 403-420.
[158]Widomska J, Subczynski WK. Why has nature chosen lutein and zeaxanthin to protect the retina? J Clin Exp Ophthalmol. 2014; 5:326. [PubMed: 24883226]
[159] Bian Q, Gao S, Zhou J, Qin J, Taylor A, et al. Lutein and zeaxanthin supplementation reduces photooxidative damage and modulates the expression of inflammation-related genes in retinal pigment epithelial cells. Free Radic Biol Med. 2012; 53:1298–307. [PubMed: 22732187]
[160] Ouimet, M.; Barrett, T.J.; Fisher, E.A. Review Basic Mechanisms and Their Roles in Vascular Health and Disease. Circ. Res. 2019, 124, 1505–1518
[161] Hammond, B.R.; Fletcher, L.M.; Roos, F.;Wittwer, J.; Schalch,W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. Investig. Ophthalmol. Vis. Sci. 2014, 55, 8583–8589
[162] Khoo, Hock Eng et al. "Nutrients for Prevention of Macular Degeneration and Eye-Related Diseases." *Antioxidants (Basel, Switzerland)* vol. 8,4 85. 2 Apr. 2019, doi:10.3390/antiox8040085
[163] Nolan, J.M.; Power, R.; Stringham, J.; Dennison, J.; Stack, J.; Kelly, D.; Moran, R.; Akuffo, K.O.; Corcoran, L.; Beatty, S. Enrichment of macular pigment enhances contrast sensitivity in subjects free of retinal disease: Central Retinal Enrichment Supplementation Trials–Report 1. Investig. Ophthalmol. Vis. Sci. 2016, 57, 3429–3439
[164] Ma, L.; Lin, X.M. Effects of lutein and zeaxanthin on aspects of eye health. J. Sci. Food Agric. 2010, 90, 2–12
[165] Roark MW, Stringham JM. Visual Performance in the "Real World": Contrast Sensitivity, Visual Acuity, and Effects of Macular Carotenoids. *Mol Nutr Food Res*. 2019;63(15):e1801053. doi:10.1002/mnfr.201801053
[166] Akuffo KO, Beatty S, Peto T, et al. The Impact of Supplemental Antioxidants on Visual Function in Nonadvanced Age-Related Macular Degeneration: A Head-to-Head Randomized Clinical Trial. *Invest Ophthalmol Vis Sci*. 2017;58(12):5347-5360. doi:10.1167/iovs.16-21192
[167] Liu R, Wang T, Zhang B, Qin L, Wu C, et al. Lutein and zeaxanthin supplementation and association with visual function in age-related macular degeneration. Investig Ophthalmol Vis Sci. 2015; 56:252–58.
[168] Landrum JT, Bone RA, Kilburn MD. The macular pigment: a possible role in protection from age-related macular degeneration. Adv in Pharmacol 1997;38:537-56.
[169] Rehak M, Fric E, Wiedemann P.Lutein and antioxidants in the prevention of age-related macular degeneration. Ophthalmologe. 2008 Jan;105(1):37-8, 40-5. Review. German.
[170] Pinazo-Durán MD1, Gómez-Ulla F, Arias L, Araiz J, Casaroli-Marano R, Gallego-Pinazo R, García-Medina JJ, López-Gálvez MI, Manzanas L, Salas A10, Zapata M11, Diaz-Llopis M, García-Layana A. Do nutritional supplements have a role in age macular degeneration prevention? J Ophthalmol. 2014;2014:901686. doi: 10.1155/2014/901686. Epub 2014 Jan 23.
[171] Ma L, Lin XM, Zou ZY, Xu XR, Li Y, Xu R. A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure. *Br J Nutr*. 2009;102(2):186-190. doi:10.1017/S0007114508163000
[172]Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. Investig Ophthalmol Vis Sci. 2013; 54:1781–88. [PubMed: 23385792]

[173] Nolan JM, Loughman J, Akkali MC, et al. The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Res. 2011;51(5):459-469. doi:10.1016/j.visres.2010.12.016
[174] Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition. 2013;29(7-8):958-964. doi:10.1016/j.nut.2012.10.017
[175] Loughman J, Nolan JM, Howard AN, Connolly E, Meagher K, Beatty S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. Investig Ophthalmol Vis Sci. 2012; 53:7871–80. [PubMed: 23132800]
[176] Bovier ER, Renzi LM, Hammond BR. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency. PLoS One. 2014;9(9):e108178. Published 2014 Sep 24. doi:10.1371/journal.pone.0108178
[177]Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. BioMed Res Int. 2015; 2015:564738. [PubMed: 25815324]
[178] Hammond BR Jr, Fletcher LM. Influence of the dietary carotenoids, lutein and zeaxanthin on visual performance: application to baseball. Am J Clin Nutr. 2012;96(5):1207S-13S. doi:10.3945/ajcn.112.034876
[179] Ceravolo SA, Hammond BR, Oliver W, Clementz B, Miller LS, Renzi-Hammond LM. Dietary Carotenoids Lutein and Zeaxanthin Change Brain Activation in Older Adult Participants: A Randomized, Double-Masked, Placebo-Controlled Trial. Mol Nutr Food Res. 2019;63(15):e1801051.
[180] Mewborn CM, Lindbergh CA, Robinson TL, et al. Lutein and Zeaxanthin Are Positively Associated with Visual-Spatial Functioning in Older Adults: An fMRI Study. Nutrients. 2018;10(4):458. Published 2018 Apr 7. doi:10.3390/nu10040458
[181] Bovier ER, Hammond BR. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. Arch Biochem Biophys. 2015;572:54-57. doi:10.1016/j.abb.2014.11.012
[182] Jia YP, Sun L, Yu HS, et al. The Pharmacological Effects of Lutein and Zeaxanthin on Visual Disorders and Cognition Diseases. Molecules. 2017;22(4):610. Published 2017 Apr 20. doi:10.3390/molecules22040610
[183] Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. JAMA Ophthalmol. 2014;132(2):142-149. doi:10.1001/jamaophthalmol.2013.7376
[184] Jiang H, Yin Y, Wu CR, et al. Dietary vitamin and carotenoid intake and risk of age-related cataract. Am J Clin Nutr. 2019;109(1):43-54. doi:10.1093/ajcn/nqy270
[185] Ma L1, Yan SF, Huang YM, Lu XR, Qian F, Pang HL, Xu XR, Zou ZY, Dong PC, Xiao X, Wang X, Sun TT, Dou HL, Lin XM. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. Ophthalmology. 2012 Nov;119(11):2290-7. doi: 10.1016/j.ophtha.2012.06.014. Epub 2012 Aug 1
[186] Huang YM , Dou HL , Huang FF , Xu XR , Zou ZY , Lu XR , Lin XM. Changes following supplementation with lutein and zeaxanthin in retinal function in eyes with early age-related macular degeneration: a randomised, double-blind, placebo-controlled trial. Br J Ophthalmol. 2014 Sep 16. pii: bjophthalmol-2014-305503. doi: 10.1136/bjophthalmol-2014-305503. [Epub ahead of print]
[187] Davis, R.L. Preliminary results in macular pigment optical density associated with and without zeaxanthin and lutein supplementation. Adv. Ophthalmol. Vis. Syst. 2015, 2, 0066
[188] Gorusupudi, Aruna et al. "The Age-Related Eye Disease 2 Study: Micronutrients in the Treatment of Macular Degeneration." Advances in nutrition (Bethesda, Md.) vol. 8,1 40-53. 17 Jan. 2017, doi:10.3945/an.116.013177
[189] Tariq Aslam, Cécile Delcourt, Frank Holz, Alfredo García-Layana, Anita Leys, Rufino M Silva, Eric Souied. European survey on the opinion and use of micronutrition in age-related macular degeneration: 10 years on from the Age-Related Eye Disease Study. Clinical Ophthalmology 10 October 2014
[190] The Economic Benefits of Using Lutein and Zeaxanthin Food Supplements in the European Union. Available at www.frost.com. 2017
[191]Feeney J, Finucane C, Savva GM, Cronin H, Beatty S, Nolan JM, Kenny RA. Low macular pigment optical density is associated with lower cognitive performance in a large population-based sample of older adults. Neurobiol Aging. 2013; 34(11), 2449-56
[192] Johnson EJ, 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, LW. 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. 2013;2013:951786.
[193] Vishwanathan R, Iannaccone A, Scott TM, Kritchevsky SB, Jennings BJ, Carboni G, Forma G, Satterfield S, Harris T, Johnson KC, Schalch W, Rosano C, Johnson EJ. Macular pigment optical density is related to cognitive function in older people. Age Ageing 2014; 43(2):271-5
[194] Saint SE, Renzi-Hammond LM, Khan NA, Hillman CH, Frick JE, Hammond BR. The Macular Carotenoids are Associated with Cognitive Function in Preadolescent Children. Nutrients. 2018;10(2).
[195] Stringham, James M et al. "Lutein across the Lifespan: From Childhood Cognitive Performance to the Aging Eye and brain." Current developments in nutrition vol. 3,7 nzz066. 4 Jun. 2019, doi:10.1093/cdn/nzz066
[196] Feeney J, O'Leary N, Moran R, et al. Plasma Lutein and Zeaxanthin Are Associated with Better Cognitive Function Across Multiple Domains in a Large Population-Based Sample of Older Adults: Findings from The Irish Longitudinal Study on Aging. J Gerontol a Biol Sci Med Sci. 2017;72(10):1431-1436. doi:10.1093/gerona/glw330
[197] Walk AM, Edwards CG, Baumgartner NW, et al. The Role of Retinal Carotenoids and Age on Neuroelectric Indices of Attentional Control among Early to Middle-Aged Adults. Front Aging Neurosci. 2017;9:183. Published 2017 Jun 9. doi:10.3389/fnagi.2017.00183
[198] Chung RWS, Leanderson P, Lundberg AK, Jonasson L. Lutein exerts anti-inflammatory effects in patients with coronary artery disease. Atherosclerosis. 2017;262:87-93. doi:10.1016/j.atherosclerosis.2017.05.008

[199] Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam Study. Arch Neurol. 2004;61:668–672
[200] Vishwanathan, R.; Kuchan, M.J.; Sen, S.; Johnson, E.J. Lutein and Preterm Infants with Decreased Concentrations of Brain Carotenoids. J. Pediatr. Gastroenterol. Nutr. 2014, 59, 659–665
[201] Friedman J.Why is the nervous system vulnerable to oxidative stress? In: Gadoth N Göbel HH, editors. Oxidative stress and free radical damage in neurology [Internet]. New York: Humana Press; 2011 [cited 4 May 2017]. p. 19–27. Oxidative Stress in Applied Basic Research and Clinical Practice. Available from: http://link.springer.com/chapter/10.1007/978-1-60327-514-9_2.
[202] Erdman JW Jr, Smith JW, Kuchan MJ, Mohn ES, Johnson EJ, Rubakhin SS, Wang L, Sweedler JV, Neuringer M. Lutein and brain function. Foods 2015;4(4):547–64
[203] Wisniewska A, Subczynski WK. Accumulation of macular xanthophylls in unsaturated membrane domains. Free Radic Biol Med 2006;40(10):1820–6.
[204] Khan NA, Walk AM, Edwards CG, et al. Macular Xanthophylls Are Related to Intellectual Ability among Adults with Overweight and Obesity. Nutrients. 2018;10(4):396. Published 2018 Mar 23. doi:10.3390/nu10040396
[205] Cannavale, Corinne N et al. "Serum Lutein is related to Relational Memory Performance." Nutrients vol. 11,4 768. 2 Apr. 2019, doi:10.3390/nu11040768
[206] Stringham NT, Holmes PV, Stringham JM. Effects of macular xanthophyll supplementation on brain-derived neurotrophic factor, pro-inflammatory cytokines, and cognitive performance. Physiol Behav. 2019;211:112650. doi:10.1016/j.physbeh.2019.112650
[207] Pruunsild P, Kazantseva A, Aid T, et al. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics. 2007;90:397–406. doi: 10.1016/j.ygeno.2007.05.004
[208] Lima Giacobbo, Bruno et al. "Brain-Derived Neurotrophic Factor in Brain Disorders: Focus on Neuroinflammation." Molecular neurobiology vol. 56,5 (2019): 3295-3312. doi:10.1007/s12035-018-1283-6
[209] Stringham NT, Holmes PV, Stringham JM. Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and sub-optimal symptoms of physical and emotional health in young adults. Nutr Neurosci. 2018;21(4):286-296. doi:10.1080/1028415X.2017.1286445
[210] Lindbergh CA, Renzi-Hammond LM, Hammond BR, et al. Lutein and Zeaxanthin Influence Brain Function in Older Adults: A Randomized Controlled Trial. J Int Neuropsychol Soc. 2018;24(1):77-90. doi:10.1017/S1355617717000534
[211] U.S. Department of Agriculture, Agricultural Research Service. What we eat in America, 2011-2012. 2015
[212] Nishida Y, Yamashita E, Miki W (2007) Quenching Activities of Common Hydrophilic and Lipophilic Antioxidants against Singlet Oxygen Using Chemiluminescence Detection System. Carotenoid Science 11:16-20.
[213] Ambati RR, Phang SM, Ravi S, Aswathanarayana RG (2014). Astaxanthin: sources, extraction, stability, biological activities and its commercial applications: a review. Mar Drugs 12: 128–152
[214] Davinelli, S.; Nielsen, M.E.; Scapagnini, G. Astaxanthin in skin health, repair, and disease: A comprehensive review. Nutrients 2018, 10, 522.
[215] Schweigert F, Britton G, Liaaen-Jensen S, Pfander H (1998). Metabolism of carotenoids in mammals. Carotenoids Biosynthesis Metabol 3: 249–284
[216] Naguib, Y.M. Antioxidant activities of astaxanthin and related carotenoids. J. Agric. Food Chem. 2000, 48, 1150–1154
[217] McNulty, H.P.; Byun, J.; Lockwood, S.F.; Jacob, R.F.; Mason, R.P. Differential e_ects of carotenoids on lipid peroxidation due to membrane interactions: X-ray di_raction analysis. Biochim. Biophys. Acta 2007, 1768, 167–174
[218] Shimokawa, T.; Yoshida, M.; Fukuta, T.; Tanaka, T.; Inagi, T.; Kogure, K. E_cacy of high-affinity liposomal astaxanthin on up-regulation of age-related markers induced by oxidative stress in human corneal epithelial cells. J. Clin. Biochem. Nutr. 2019, 64, 27–35.
[219] Yeh, P.T.; Huang, H.W.; Yang, C.M.; Yang, W.S.; Yang, C.H. Astaxanthin Inhibits Expression of Retinal Oxidative Stress and Inflammatory Mediators in Streptozotocin-Induced Diabetic Rats. PLoS ONE 2016, 11, e0146438
[220] Camera, E.; Mastrofrancesco, A.; Fabbri, C.; Daubrawa, F.; Picardo, M.; Sies, H.; Stahl, W. Astaxanthin, canthaxanthin and _-carotene di_erently a_ect UVA-induced oxidative damage and expression of oxidative stress-responsive enzymes. Exp. Dermatol. 2009, 18, 222–231
[221] Giannaccare, Giuseppe et al. "Clinical Applications of Astaxanthin in the Treatment of Ocular Diseases: Emerging Insights." Marine drugs vol. 18,5 239. 1 May. 2020, doi:10.3390/md18050239
[222] Natural Astaxanthin: A Comprehensive Review of Human Clinical Studies. Issue date: 04 September 2017. https://algalif.com/wp-content/uploads/2017/04/Algalif_Natural-Astaxanthin_Review-of-Human-Clinical-Studies-_0917_web.pdf
[223] Galasso, Christian et al. "On the Neuroprotective Role of Astaxanthin: New Perspectives?" Marine drugs vol. 16,8 247. 24 Jul. 2018, doi:10.3390/md16080247
[224] Warraich, Umm-E-Ammara et al. "Aging - Oxidative stress, antioxidants and computational modeling." Heliyon vol. 6,5 e04107. 31 May. 2020, doi:10.1016/j.heliyon.2020.e04107
[225] Simioni, C., Zauli, G., Martelli, A.M., Vitale, M., Sacchetti, G., Gonelli, A., Neri, L.M., 2018. Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. Oncotarget 9 (24), 17181.
[226] Lee, S.J.; Bai, S.K.; Lee, K.S.; Namkoong, S.; Na, H.J.; Ha, K.S.; Han, J.A.; Yim, S.V.; Chang, K.; Kwon, Y.G.; et al. Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing I(kappa)B kinase-dependent NF-kappaB activation. Mol. Cells 2003, 16, 97–105
[227] Kauppinen, A.; Paterno, J.J.; Blasiak, J.; Salminen, A.; Kaarniranta, K. Inflammation and its role in age-related macular degeneration. Cell Mol. Life Sci. 2016, 73, 1765–1786
[228] Wenisch, C., Patruta, S., Daxbock, F., Krause, R., Horl, W. (2000) Effect of age on human neutrophil function. J. Leukoc. Biol. 67, 40 –45

[229] Macedo, R.C.; Bolin, A.P.; Marin, D.P.; Otton, R. Astaxanthin addition improves human neutrophils function:
In vitro study. Eur. J. Nutr. 2010, 49, 447–457
[230] De la Fuente, M. E_ects of antioxidants on immune system ageing. Eur. J. Clin. Nutr. 2002, 56, S5–S8
[231] Park, J.S.; Chyun, J.H.; Kim, Y.K.; Line, L.L.; Chew, B.P. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. Nutr. Metab. (Lond.) 2010, 7, 18
[232] Song, X.D.; Zhang, J.J.; Wang, M.R.; Liu, W.B.; Gu, X.B.; Lv, C.J. Astaxanthin induces mitochondria-mediated apoptosis in rat hepatocellular carcinoma CBRH-7919 cells. Biol. Pharm. Bull. 2011, 34, 839–844.
[233] Kammeyer, A.; Luiten, R.M. Oxidation events and skin aging. Ageing Res. Rev. 2015, 21, 16–29
[234] Davinelli, S.; Bertoglio, J.C.; Polimeni, A.; Scapagnini, G. Cytoprotective Polyphenols Against Chronological Skin Aging and Cutaneous Photodamage. Curr. Pharm. Des. 2017, 8.
[235] Kato, Takao et al. "Effects of 3-Month Astaxanthin Supplementation on Cardiac Function in Heart Failure Patients with Left Ventricular Systolic Dysfunction-A Pilot Study." Nutrients vol. 12,6 1896. 26 Jun. 2020, doi:10.3390/nu12061896
[236] Liu, Sophia Z et al. "Building strength, endurance, and mobility using an astaxanthin formulation with functional training in elderly." Journal of cachexia, sarcopenia and muscle vol. 9,5 (2018): 826-833. doi:10.1002/jcsm.12318
[237] Weidinger, A., Kozlov, A.V., 2015. Biological activities of reactive oxygen and nitrogen species: oxidative stress versus signal transduction. Biomolecules 5 (2), 472–484.
[238] Peng, W.; Cai, G.; Xia, Y.; Chen, J.; Wu, P.; Wang, Z.; Li, G.; Wei, D. Mitochondrial Dysfunction in Atherosclerosis. DNA Cell Biol. 2019, 38, 597–606.
[239] Awad, A.M.; Bradley, M.C.; Fernandez-Del-Rio, L.; Nag, A.; Tsui, H.S.; Clarke, C.F. Coenzyme Q10 deficiencies: Pathways in yeast and humans. Essays Biochem. 2018, 62, 361–376.
[240] Pravst I, Žmitek K, Žmitek J: Coenzyme Q10 contents in foods and fortification strategies. Crit Rev Food Sci Nutr 2010, 50:269–280.
[241] Salama M , Yuan TF, Machado S, Murillo-Rodríguez E, Vega JA, Menéndez-González M, Nardi AE, Arias-Carrión O. Co-enzyme Q10 to treat neurological disorders: basic mechanisms, clinical outcomes, and future research direction. CNS Neurol Disord Drug Targets. 2013 Aug;12(5):641-64
[242] Gutierrez-Mariscal, F.M.; Yubero-Serrano, E.M.; Villalba, J.M.; Lopez-Miranda, J. Coenzyme Q10: From bench to clinic in aging diseases, a translational review. Crit. Rev. Food Sci. Nutr. 2018
[243] Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. Free Radic Res. 2006 May;40(5):445-53.
[244] Sevin DC, Sauer U. Ubiquinone accumulation improves osmotic-stress tolerance in Escherichia coli. Nat Chem Biol. 2014;10:266–272
[245] Groneberg, D.A.; Kindermann, B.; Althammer, M.; Klapper, M.; Vormann, J.; Littarru, G.P.; Doring, F. Coenzyme Q10 a_ects expression of genes involved in cell signaling, metabolism and transport in human caco-2 cells. Int. J. Biochem. Cell Biol. 2005, 37, 1208–1218
[246] Hernández-Camacho, J.D.; Bernier, M.; López-Lluch, G.; Navas, P. Coenzyme Q10 supplementation in aging and disease. Front. Physiol. 2018
[247] Barcelos, Isabella Peixoto de, and Richard H Haas. "CoQ10 and Aging." Biology vol. 8,2 28. 11 May. 2019, doi:10.3390/biology8020028
[248] Liu, Z., Ren, Z., Zhang, J., Chuang, C.-C., Kandaswamy, E., Zhou, T., Zuo, L., 2018. Role of ROS and nutritional antioxidants in human diseases. Front. Physiol. 9.
[249] Olivieri, F.; Lazzarini, R.; Babini, L.; Prattichizzo, F.; Rippo, M.R.; Tiano, L.; Di Nuzzo, S.; Graciotti, L.; Festa, R.; Bruge, F.; et al. Anti-inflammatory effect of ubiquinol-10 on young and senescent endothelial cells via mir-146a modulation. Free Radic. Biol. Med. 2013, 63, 410–420.
[250] Fan, L.; Feng, Y.; Chen, G.C.; Qin, L.Q.; Fu, C.L.; Chen, L.H. Effects of coenzyme Q10 supplementation on inflammatory markers: Asystematic review and meta-analysis of randomized controlled trials. Pharmacol. Res. 2017, 119, 128–136
[251] Zhai, J.; Bo, Y.; Lu, Y.; Liu, C.; Zhang, L. Effects of coenzyme Q10 on markers of inflammation: A systematic review and meta-analysis. PLoS ONE 2017, 12, e0170172
[252] Farhangi, M.A.; Alipour, B.; Jafarvand, E.; Khoshbaten, M. Oral coenzyme Q10 supplementation in patients with nonalcoholic fatty liver disease: Effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress. Arch. Med. Res. 2014, 45, 589–595
[253] Perez-Sanchez, C.; Aguirre, M.A.; Ruiz-Limon, P.; Abalos-Aguilera, M.C.; Jimenez-Gomez, Y.; Arias-de la Rosa, I.; Rodriguez-Ariza, A.; Fernandez-Del Rio, L.; Gonzalez-Reyes, J.A.; Segui, P.; et al. Ubiquinol effects on antiphospholipid syndrome prothrombotic profile: A randomized, placebo-controlled trial. Arterioscler. Thromb. Vasc. Biol. 2017, 37, 1923–1932
[254] Jorat, M.V.; Tabrizi, R.; Mirhosseini, N.; Lankarani, K.B.; Akbari, M.; Heydari, S.T.; Mottaghi, R.; Asemi, Z.
The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis. 2018, 17, 230
[255] Schmelzer, C.; Lindner, I.; Rimbach, G.; Niklowitz, P.; Menke, T.; Doring, F. Functions of coenzyme Q10 in inflammation and gene expression. BioFactors 2008, 32, 179–183
[256] Gempel, K.; Topaloglu, H.; Talim, B.; Schneiderat, P.; Schoser, B.G.; Hans, V.H.; Palmafy, B.; Kale, G.; Tokatli, A.; Quinzii, C.; et al. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. Brain 2007, 130, 2037–2044
[257] Bentinger, M.; Tekle, M.; Dallner, G. Coenzyme Q–biosynthesis and functions. Biochem. Biophys. Res. Commun. 2010, 396, 74–79. [
[258] Garrido-Maraver, J.; Cordero, M.D.; Oropesa-Avila, M.; Vega, A.F.; de la Mata, M.; Pavon, A.D.; Alcocer-Gomez, E.; Calero, C.P.; Paz, M.V.; Alanis, M.; et al. Clinical applications of coenzyme Q10. Front. Biosci. (Landmark Ed) 2014, 19, 619–633

[259] Martelli, Alma et al. "Coenzyme Q_{10}: Clinical Applications in Cardiovascular Diseases." Antioxidants (Basel, Switzerland) vol. 9,4 341. 22 Apr. 2020, doi:10.3390/antiox9040341
[260]Duncan, A.J.; Heales, S.J.; Mills, K.; Eaton, S.; Land, J.M.; Hargreaves, I.P. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. Clin. Chem. 2005, 51, 2380–2382
[261] Bhagavan, H.N.; Chopra, R.K. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. Free Radic. Res. 2006, 40, 445–453
[262] Jafari M, Mousavi SM, Asgharzadeh A, Yazdani N. Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews. Indian Heart J. 2018 Jul;70 Suppl 1:S111-S117
[263] Sabbatinelli J, Orlando P, Galeazzi R, Silvestri S, Cirilli I, Marcheggiani F, Dludla PV, Giuliani A, Bonfigli AR, Mazzanti L, Olivieri F, Antonicelli R, Tiano L. Ubiquinol Ameliorates Endothelial Dysfunction in Subjects with Mild-to-Moderate Dyslipidemia: A Randomized Clinical Trial. Nutrients. 2020; 12(4):1098.
[264] Kikkawa K., Takehara I., Miyakoshi T., Miyawaki H. Safety of High Dose Supplementation of Coenzyme Q_{10} in Healthy Human Adults. Jpn. J. Food Chem. 2007;14:76–81
[265] Mason, Shaun A et al. "Antioxidant supplements and endurance exercise: Current evidence and mechanistic insights." Redox biology vol. 35 (2020): 101471. doi:10.1016/j.redox.2020.101471
[266]Guescini, Michele et al. "The Combination of Physical Exercise with Muscle-Directed Antioxidants to Counteract Sarcopenia: A Biomedical Rationale for Pleiotropic Treatment with Creatine and Coenzyme Q10." Oxidative medicine and cellular longevity vol. 2017 (2017): 7083049. doi:10.1155/2017/7083049
[267] Montero, Raquel et al. "Plasma coenzyme Q_{10} status is impaired in selected genetic conditions." Scientific reports vol. 9,1 793. 28 Jan. 2019, doi:10.1038/s41598-018-37542-2
[268]Bloomer, Richard J et al. "Impact of oral ubiquinol on blood oxidative stress and exercise performance." Oxidative medicine and cellular longevity vol. 2012 (2012): 465020. doi:10.1155/2012/465020
[269] Ho, Chien-Chang et al. "Coenzyme Q10 status, glucose parameters, and antioxidative capacity in college athletes." Journal of the International Society of Sports Nutrition vol. 17,1 5. 10 Jan. 2020, doi:10.1186/s12970-020-0334-3
[270] Littarru GP, Lippa S, Oradei A, et al. . Coenzyme Q10: blood levels and metabolic demand. Int. J. Tissue React. 1990;12:145–148.
[271] Battino M, Amadio E, Oradei A, et al. . Metabolic and antioxidant markers in the plasma of sportsmen from a Mediterranean town performing non-agonistic activity. Mol. Aspects Med. 1997;18:241–245
[272] Kaikkonen J, Nyyssönen K, Tuomainen TP, et al. . Determinants of plasma coenzyme Q_{10} in humans. FEBS Lett. 1999;443:163–166.
[273] Karlsson J, Lin L, Sylvén C, et al. . Muscle ubiquinone in healthy physically active males. Mol Cell Biochem. 1996;156:169–172. doi: 10.1007/BF00426340
[274] Laaksonen R, Riihimäki A, Laitila J, et al. . Serum and muscle tissue ubiquinone levels in healthy subjects. J Lab Clin Med. 1995;125:517–521
[275] Bahls M, Groß S, Ittermann T, et al. . Statins are related to impaired exercise capacity in males but not females. PLoS One. 2017;12:0179534. doi: 10.1371/journal.pone.0179534
[276] Orlando, Patrick et al. "Effect of ubiquinol supplementation on biochemical and oxidative stress indexes after intense exercise in young athletes." Redox report : communications in free radical research vol. 23,1 (2018): 136-145. doi:10.1080/13510002.2018.1472924
[277] Emami, Ali et al. "Effect of Short-term Coenzyme Q10 Supplementation and Precooling on Serum Endogenous Antioxidant Enzymes of Elite Swimmers." Journal of strength and conditioning research vol. 32,5 (2018): 1431-1439. doi:10.1519/JSC.0000000000001971
[278]Szela̧g, M.; Mikulski, D.; Molski, M. Quantum-chemical investigation of the structure and the antioxidant properties of alpha-lipoic acid and its metabolites. J. Mol. Modeling 2012, 18, 2907–2916
[279] Akiba, S.; Matsugo, S.; Packer, L.; Konishi, T. Assay of protein-bound lipoic acid in tissues by a new enzymatic method. Anal. Biochem. 1998, 258, 299–304
[280] Cronan, John E. "Assembly of Lipoic Acid on Its Cognate Enzymes: An Extraordinary and Essential Biosynthetic Pathway." Microbiology and molecular biology reviews : MMBR vol. 80,2 429-50. 13 Apr. 2016, doi:10.1128/MMBR.00073-15
[281]A. Goraca, H. Huk-Kolega, A. Piechota, P. Kleniewska, E. Ciejka, and B. Skibska, "Lipoic acid—biological activity and therapeutic potential," Pharmacological Reports, vol. 63, no. 4, pp. 849–858, 2011.
[282] Brufani, M. Acido _-lipoico farmaco o integratore. Una panoramica sulla farmacocinetica, le formulazioni disponibili e le evidenze cliniche nelle complicanze del diabete. Prog. Nutr. 2014, 16, 62–74.
[283] Pashaj, A.; Xia,M.;Moreau, R. _-Lipoic acid as a triglyceride-lowering nutraceutical. Can. J. Physiol. Pharmacol. 2015, 93, 1029–1041
[284] Han, D.; Handelman, G.; Marcocci, L.; Sen, C.K.; Roy, S.; Kobuchi, H.; Tritschler, H.J.; Flohé, L.; Packer, L. Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization. Biofactors 1997, 6, 321–338
[285] Singh, U.; Jialal, I. Retracted: Alpha-lipoic acid supplementation and diabetes. Nutr. Rev. 2008, 66, 646–657.
[286]Packer L1, Cadenas E. Lipoic acid: energy metabolism and redox regulation of transcription and cell signaling. J Clin Biochem Nutr. 2011 Jan;48(1):26-32. doi: 10.3164/jcbn.11-005FR. Epub 2010 Dec 29.
[287] Rinninella E, Pizzoferrato M, Cintoni M, Servidei S, Mele MC. Nutritional support in mitochondrial diseases: the state of the art. Eur Rev Med Pharmacol Sci. 2018;22(13):4288-4298. doi:10.26355/eurrev_201807_15425
[288] Li RJ, Ji WQ, Pang JJ, Wang JL, Chen YG, Zhang YTohoku J Exp Med. Alpha-lipoic acid ameliorates oxidative stress by increasing aldehyde dehydrogenase-2 activity in patients with acute coronary syndrome.2013;229(1):45-51.

[289] Rochette L1, Ghibu S, Richard C, Zeller M, Cottin Y, Vergely C. Direct and indirect antioxidant properties of α-lipoic acid and therapeutic potential. Mol Nutr Food Res. 2013 Jan;57(1):114-25. doi: 10.1002/mnfr.201200608
[290] Tromba, Luciana et al. "Effect of Alpha-Lipoic Acid Supplementation on Endothelial Function and Cardiovascular Risk Factors in Overweight/Obese Youths: A Double-Blind, Placebo-Controlled Randomized Trial." Nutrients vol. 11,2 375. 12 Feb. 2019, doi:10.3390/nu11020375
[291] Ou, P.; Tritschler, H.J.; Wol_, S.P. Thioctic (lipoic) acid: A therapeutic metal-chelating antioxidant? Biochem. Pharmacol. 1995, 50, 123–126
[292] Konrad, D.; Somwar, R.; Sweeney, G.; Yaworsky, K.; Hayashi, M.; Ramlal, T.; Klip, A. The antihyperglycemic drug alpha-lipoic acid stimulates glucose uptake via both GLUT4 translocation and GLUT4 activation: Potential role of p38 mitogen-activated protein kinase in GLUT4 activation. Diabetes 2001, 50, 1464–1471
[293] Estrada, D.E.; Ewart, H.S.; Tsakiridis, T.; Volchuk, A.; Ramlal, T.; Tritschler, H.; Klip, A. Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: Participation of elements of the insulin signaling pathway. Diabetes 1996, 45, 1798–1804
[294] Chen,W.-L.; Kang, C.-H.;Wang, S.-G.; Lee, H.-M. _-Lipoic acid regulates lipid metabolism through induction of sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase. Diabetologia 2012, 55, 1824–1835.
[295] Castro, M.C.; Villagarcía, H.G.; Massa, M.L.; Francini, F. Alpha-lipoic acid and its protective role in fructose induced endocrine-metabolic disturbances. Food Funct. 2019, 10, 16–25.
[296] Park, S.; Karunakaran, U.; Jeoung, N.H.; Jeon, J.H.; Lee, I.K. Physiological effect and therapeutic application of alpha lipoic acid. Curr. Med. Chem. 2014, 21, 3636–3645.
[297] Liu W, Shi LJ, Li SG. The Immunomodulatory Effect of Alpha-Lipoic Acid in Autoimmune Diseases. Biomed Res Int. 2019;2019:8086257. Published 2019 Mar 20. doi:10.1155/2019/8086257
[298] A. Perl, "Oxidative stress in the pathology and treatment of systemic lupus erythematosus," Nature Reviews Rheumatology, vol. 9, no. 11, pp. 674–686, 2013.
[299] Ying,Z.,Kampfrath,T.,Sun,Q., Parthasarathy,S., and Rajagopalan, S. (2011).Evidence that α-lipoic acid inhibits NFκ-B activation independent of its antioxidant function. Inflamm.Res. 60, 219–225.
[300] Ambrosi et al. Alpha Lipoic Acid: A Therapeutic Strategy that Tend to Limit the Action of Free Radicals in Transplantation Int. J. Mol. Sci. 2018, 19(1), 102; https://doi.org/10.3390/ijms19010102
[301] Ziegler, D.; Nowak, H.; Kempler, P.; Vargha, P.; Low, P.A. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A meta-analysis. Diabet. Med. 2004, 21, 114–121.
[302] Carbonelli MG, Di Renzo L, Bigioni M, Di Daniele N, De Lorenzo A, Fusco MA. Alpha-lipoic acid supplementation: a tool for obesity therapy? Curr Pharm Des. 2010;16(7):840-6.
[303] Ghibu S, Richard C, Vergely C, Zeller M, Cottin Y, Rochette L. Antioxidant properties of an endogenous thiol: Alpha-lipoic acid, useful in the prevention of cardiovascular diseases. J Cardiovasc Pharmacol. 2009 Nov;54(5):391-8. Review.
[304] Costantino M1, Guaraldi C, Costantino D, De Grazia S, Unfer V. Peripheral neuropathy in obstetrics: efficacy and safety of α-lipoic acid supplementation. Eur Rev Med Pharmacol Sci. 2014 Sep;18(18):2766-71
[305] Gębka A1, Serkies-Minuth E1, Raczyńska D2.Effect of the administration of alpha-lipoic acid on contrast sensitivity in patients with type 1 and type 2 diabetes. Mediators Inflamm. 2014;2014:131538. doi: 10.1155/2014/131538. Epub 2014 Feb 10.
[306] Dos Santos, Sávio Monteiro et al. "Mitochondrial Dysfunction and Alpha-Lipoic Acid: Beneficial or Harmful in Alzheimer's Disease?" Oxidative medicine and cellular longevity vol. 2019 8409329. 30 Nov. 2019, doi:10.1155/2019/8409329
[307] Zehnpfennig B,Wiriyasermkul P, Carlson DA, Quick M. Interaction of α-lipoic acid with the human Na+/multivitamin transporter (hSMVT). J Biol Chem 2015;290(26):16372–82.
[308] Prasad PD, Wang H, Kekuda R, Fujita T, Fei YJ, Devoe LD, Leibach FH, Ganapathy V. Cloning and functional expression of a cDNA encoding a mammalian sodium-dependent vitamin transporter mediating the uptake of pantothenate, biotin, and lipoate. J Biol Chem. 1998;273:7501–6
[309] Gleiter, C.H.; Schug, B.S.; Hermann, R.; Elze, M.; Blume, H.H.; Gundert-Remy, U. Influence of food intake on the bioavailability of thioctic acid enantiomers. Eur. J. Clin. Pharmacol. 1996, 50, 513–514
[310]Ames BN. Optimal micronutrients delay mitochondrial decay and age-associated diseases. Mech Ageing Dev. 2010;131(7-8):473-479. doi:10.1016/j.mad.2010.04.005
[311] Parikh S, Saneto R, Falk MJ, Anselm I, Cohen BH, Haas R, Medicine Society TM. A modern approach to the treatment of mitochondrial disease. Curr Treat Options Neurol 2009; 11: 414-430.
[312] Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, Hagen TM. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci U S A 2004;101:3381–6.
[313] El Barky, A.R.; Hussein, S.A.; Mohamed, T.M. The potent antioxidant alpha lipoic acid. J. Plant Chem. Ecophysiol. 2017, 2, 1016
[314] Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochim Biophys Acta. 2009;1790(10):1149-1160. doi:10.1016/j.bbagen.2009.07.026
[315]Nobakht-Haghighi N, Rahimifard M, Baeeri M, et al. Regulation of aging and oxidative stress pathways in aged pancreatic islets using alpha-lipoic acid. Mol Cell Biochem. 2018;449(1-2):267-276. doi:10.1007/s11010-018-3363-3
[316] Zaid AN, Al Ramahi R. Depigmentation and Anti-aging Treatment by Natural Molecules. Curr Pharm Des. 2019;25(20):2292-2312. doi:10.2174/1381612825666190703153730

[317] Patel MK, Riley MA, Hobbs S, Cortez-Cooper M, Robinson VJ. Can α-lipoic acid mitigate progression of aging-related decline caused by oxidative stress? South Med J. 2014;107(12):780-787. doi:10.14423/SMJ.0000000000000198
[318] Molinari, Claudio et al. "Role of Combined Lipoic Acid and Vitamin D3 on Astrocytes as a Way to Prevent Brain Ageing by Induced Oxidative Stress and Iron Accumulation." Oxidative medicine and cellular longevity vol. 2019 2843121. 28 Feb. 2019, doi:10.1155/2019/2843121
[319] Miquel J. Can antioxidant diet supplementation protect against age-related mitochondrial damage? Ann N Y Acad Sci. 2002;959:508-516. doi:10.1111/j.1749-6632.2002.tb02120.x
[320] Gerd Bobe, Alexander J Michels, Wei-Jian Zhang, Jonathan Q Purnell, Clive Woffendin, Cliff Pereira, Joseph A Vita, Nicholas O Thomas, Maret G Traber, Balz Frei, Tory M Hagen, A Randomized Controlled Trial of Long-Term (R)-α-Lipoic Acid Supplementation Promotes Weight Loss in Overweight or Obese Adults without Altering Baseline Elevated Plasma Triglyceride Concentrations, The Journal of Nutrition, , nxaa203, https://doi.org/10.1093/jn/nxaa20
[321] Kucukgoncu, S et al. "Alpha-lipoic acid (ALA) as a supplementation for weight loss: results from a meta-analysis of randomized controlled trials." Obesity reviews : an official journal of the International Association for the Study of Obesity vol. 18,5 (2017): 594-601. doi:10.1111/obr.12528
[322] Pérez-López A, Martin-Rincon M, Santana A, et al. Antioxidants Facilitate High-intensity Exercise IL-15 Expression in Skeletal Muscle. Int J Sports Med. 2019;40(1):16-22. doi:10.1055/a-0781-252
[323] Ding S, Gan T, Song M, et al. C/EBPB-CITED4 in Exercised Heart. Adv Exp Med Biol. 2017;1000:247-259. doi:10.1007/978-981-10-4304-8_14
[324] Akbari, Maryam et al. "The effects of alpha-lipoic acid supplementation on inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials." Nutrition & metabolism vol. 15 39. 5 Jun. 2018, doi:10.1186/s12986-018-0274-y
[325] Kadlec AO, Barnes C, Durand MJ, Gutterman DD. Microvascular Adaptations to Exercise: Protective Effect of PGC-1 Alpha. Am J Hypertens. 2018;31(2):240-246. doi:10.1093/ajh/hpx162
[326] DL, Christensen JM, Pereira C, Hagen TM. Age and gender dependent bioavailability of R- and R,S-α-lipoic acid: a pilot study. Pharmacol Res 2012;66(3):199–206
[327] Böhm et al. From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations, Nutrition Reviews. August 2020. nuaa008, https://doi.org/10.1093/nutrit/nuaa008.
[328] O'Halloran AM, Laird EJ, Feeney J, et al. Circulating Micronutrient Biomarkers Are Associated With 3 Measures of Frailty: Evidence from the Irish Longitudinal Study on Ageing. J Am Med Dir Assoc. 2020;21(2):240-247.e5. doi:10.1016/j.jamda.2019.06.011
[329] John N. Hathcock, Ph.D. with a foreword by James C. Griffiths, Ph.D. Edited by Douglas MacKay, N.D. Andrea Wong, Ph.D. Haiuyen Nguyen. Vitamin and mineral safety, 3rd Edition. Published by Council for Responsible Nutrition (CRN), Washington, D.C. © Copyright 2014 Council for Responsible Nutrition
[330] Shao A, Hathcock JN. Risk assessment for the carotenoids lutein and lycopene. Regul Toxicol Pharmacol. 2006 Aug;45(3):289-98. Epub 2006 Jun 30. Review.
[331] McGarry A, McDermott M, Kieburtz K, de Blieck EA, Beal F, Marder K, et al; Huntington Study Group 2CARE Investigators and Coordinators. A randomized, double-blind, placebo-controlled trial of coenzyme Q10 in Huntington disease. Neurology. 2017;88(2):152-159. doi: 10.1212/WNL.0000000000003478
[332] TRC Natural Medicines Data Base. Authoritative resource on dietary supplements, natural medicines, and complementary alternative and integrative therapies. Coenzyme Q10
https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=938
[333] Heck AM, DeWitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health Syst Pharm 2000;57:1221-7.
[334] Hertz, N. and Lister, R. E. Improved survival in patients with end-stage cancer treated with coenzyme Q(10) and other antioxidants: a pilot study. J Int.Med Res 2009;37(6):1961-1971
[335] Lund EL, Quistorff B, Spang-Thomsen M, Kristjansen PE. Effect of radiation therapy on small-cell lung cancer is reduced by ubiquinone intake. Folia Microbiol (Praha). 1998;43(5):505-6.
[336] Henriksen JE, Andersen CB, Hother-Nielsen O, Vaag A, Mortensen SA, Beck-Nielsen H. Impact of ubiquinone (coenzyme Q10) treatment on glycaemic control, insulin requirement and well-being in patients with Type 1 diabetes mellitus. Diabet Med. 1999 Apr;16(4):312-8.
[337] Eriksson JG, Forsén TJ, Mortensen SA, Rohde M. The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. Biofactors. 1999;9(2-4):315-8.
[338] Reljanovic M, Reichel G, Rett K, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): A 2-year, multicenter, randomized, double-blind, placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy [abstract]. Free Radic Res 1999;31:171-7.
[339] Ziegler D, Hanefeld M, Ruhnau K, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A 7-month, multicenter, randomized, controlled trial (ALADIN III Study). Diabetes Care 1999;22:1296-301.
[340] Ametov AS, Barinov A, Dyck PJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid. Diabetes Care 2003;26:770-6.
[341] Fruzzetti F, Fidecicchi T, Palla G, Gambacciani M. Long-term treatment with a-lipoic acid and myo-inositol positively affects clinical and metabolic features of polycystic ovary syndrome. Gynecol Endocrinol. 2020;36(2):152-155.
[342] Lai S, Petramala L, Muscaritoli M, et al. a-lipoic acid in patients with autosomal dominant polycystic kidney disease. Nutrition. 2020;71:110594

[343] Li N, Yan W, Hu X, et al. Effects of oral a-lipoic acid administration on body weight in overweight or obese subjects: a crossover randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf) 2017;86(5):680-7.
[344] Vincent HK, Bourguignon CM, Vincent KR, Taylor AG. Effects of alpha-lipoic acid supplementation in peripheral arterial disease: a pilot study. J Alt Complement Med 2007;13:577-84.
[345]Rosenfeldt, F. L., Haas, S. J., Krum, H., Hadj, A., Ng, K., Leong, J. Y., and Watts, G. F. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum.Hypertens. 2007;21(4):297-306
[346]Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension (review). Cochrane Database Syst Rev 2009;(4):CD007435
[347] Karkabounas S, Papadopoulos N, Anastasiadou C, et al. Effects of a-lipoic Acid, carnosine, and thiamine supplementation in obese patients with type 2 diabetes mellitus: A randomized, double-blind study. J Med Food. 2018;21(12):1197-1203
[348]Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-8
[349] Segermann J, Hotze A, Ulrich H, Rao GS. Effect of alpha-lipoic acid on the peripheral conversion of thyroxine to triiodothyronine and on serum lipid-, protein- and glucose levels. Arzneimittelforschung 1991;41:1294-8
[350] Kistler, A., Liechti, H., Pichard, L., Wolz, E., Oesterhelt, G., Hayes, A., and Maurel, P. Metabolism and CYP-inducer properties of astaxanthin in man and primary human hepatocytes. Arch.Toxicol. 2002;75(11-12):665-675
[351] Sawardekar SB, Patel TC, Uchil D. Comparative evaluation of antiplatelet effect of lycopene with aspirin and the effect of their combination on platelet aggregation: an in vitro study. Indian J Pharmacol 2016;48:26-31
[352] Zhu ZG, Sun MX, Zhang WL, Wang WW, Jin YM, Xie CL. The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials. Neurol Sci 2017;38(2):215-224
[353] Ziegler D., Low P. A., Litchy W. J., Boulton A. J., Vinik A. I., Freeman R., Samigullin R., Tritschler H., Munzel U., Maus J., Schütte K., Dyck P. J. Efficacy and safety of antioxidant treatment with a-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care 2011;34(9):2054-2060
[354] Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care. 2006 Nov;29(11):2365-70.
[355] Murray GL, Colombo J. (r)Alpha lipoic acid is a safe, effective pharmacologic therapy of chronic orthostatic hypotension associated with low sympathetic tone. Int J Angiol. 2019;28(3):188-193
[356] Dawczynski J , Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. 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. 2013 Dec;251(12):2711-23. doi: 10.1007/s00417-013-2376-6. Epub 2013 May 22
[357] Choi HD, Youn YK, Shin WG. Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. Plant Foods Hum Nutr. 2011;66:363-369
[358]Kupcinskas L, Lafolie P, Lignell A, et al. Efficacy of the natural antioxidant astaxanthin in the treatment of functional dyspepsia in patients with or without Helicobacter pylori infection: A prospective, randomized, double blind, and placebo-controlled study. Phytomedicine. 2008;15:391-99
[359] Cremer DR, Rabeler R, Roberts A, Lynch B. Long-term safety of alpha-lipoic acid (ALA) consumption: A 2-year study. Regul Toxicol Pharmacol. 2006 Dec;46(3):193-201.
[360] Ravikrishnan R, Rusia S, Ilamurugan G, Salunkhe U, Deshpande J, Shankaranarayanan J, Shankaranarayana M, Soni MG. Safety assessment of lutein and zeaxanthin (Lutemax™ 2020): Subchronic toxicity and mutagenicity studies. Food Chem Toxicol. 2011; 49:2841–2848. [PubMed: 21872637]
[361] Hathcock JN, Shao A. Risk assessment for coenzyme Q10 (Ubiqu inone). Regul Toxicol Pharmacol. 2006 Aug;45(3):282-8. Epub 2006 Jun 30. Review.
[362] Langsjoen PH, Langsjoen PH, Folkers K: Long-term efficacy and safety of coenzyme Q10 therapy for idiopathic dilated cardiomyopathy. Am J Cardiol 1990, 65:521–523.
[363] Haematococcus pluvialis and astaxanthin safety for human consumption. Technical Report TR.3005.001 1999