SUPPORTIVE INFORMATION for Bruce N. Ames Perspective

SI-1-Vitamin and Mineral Deficiencies

Numerous studies link poor nutrition to a variety of diseases of aging, as shown in the following sampling of recent references (1-12).

SI-2-Triage Theory

Vitamin K (phylloquinone) is necessary for the function of 16 enzymes. A triage rationing process is supported by an analysis of the behavior of these enzymes under a mimic of vitamin K shortage (13). Recent studies provide additional support: a Mendelian Randomization (MR) epidemiology study showed that both all-cause and cardiovascular disease (CVD) mortality are caused by vitamin K1 inadequacy, and confirmed that the low level of the inactive form of Mgp protein, which normally prevents arterial calcification, is diagnostic for vitamin K1 deficiency (14). Increased dietary intake of vitamin K1 and menaquinone (K2=MK2) and other derivatives (such as MK7 in natto) was associated with lower all-cause cancer and CVD mortality (15). A study of 166 adolescents supports the CVD findings by showing that subclinical cardiac structure and function variables are most favorable at higher phylloquinone (vitamin K1) levels (16).

Selenium is necessary for the function of 25 enzymes. A triage-related rationing was also shown to be operating in the case of selenium (17). A 4-year Randomized Clinical Trial (RCT) (18) of selenium supplementation (200 μg/d) +CoQ10 (200mg/d) significantly reduced CVD mortality risk by more than 40%, and also significantly reduced hypertension, IHD, impaired cardiac function, and diabetes in 443 elderly people in rural Sweden (where soil is low in selenium) during a follow-up time of 12 years; improvement in CVD biomarkers, such as echocardiography and natriuretic peptide levels, was also observed.

SI-3-Survival V/M that are also Longevity V/M

Vitamin D: A meta-analysis of vitamin D versus mortality in 5 Northern European countries (n=~29,000), using subjects of median age 62 years, showed that a blood level of 25(OH)D of less than 12 ng/ml was associated with maximum mortality, while levels between 30 to 40 ng/ml were associated with the lowest mortality (19). Rodent evidence also showed that mutations in the vitamin D receptor in mice resulted in premature aging (20). A meta-analysis of 32 studies (n = ~500,000) on vitamin D and all-cause mortality showed that the mortality hazard ratio between subjects with the lowest quantile (<9 ng/ml) and those with the highest (>50 ng/ml) serum levels of 25(OH)D was 1.9 (p=0.001). Levels of 25(OH)D less than or equal to 30 ng/ml were associated with significantly higher ($p < .01$) all-cause mortality than levels greater than 30 ng/ml (21). A 12-year German study of elderly individuals (n=9,579) in a statistically simulated intervention with vitamin D showed a large decrease in all-cause mortality and cancer (22).

A 29 year-long study of 95,000 Danes showed that a decreased plasma level of 25(OH)D was associated with early mortality and an increased risk of ischemic heart disease and myocardial infarction (23). An MR analysis of this study showed that a low 25(OH)D level was causally associated with all-cause mortality and cancer mortality

(although not with cardiovascular mortality) (24). The latter lack of effect of vitamin D on CVD was replicated in a Canadian MR study of 34,000 people of European descent (25). However, a recent study found that supplementation with high doses of vitamin D for a year significantly reduced blood pressure (26). A RCT on vitamin D3 supplementation on 70 young overweight African-Americans with vitamin D deficiency showed amelioration in arterial stiffness (27).

Deficiency of vitamin D is associated with increased risk of cancer incidence and risk of mortality, as reviewed recently (28). An estimate has been made that doubling the mean concentration of 25(OH)D in the population would reduce the mortality rate by about 20% and increase life expectancy by two years (29). Meta-analyses of the numerous vitamin D mortality studies showed a consistent correlation between increasing vitamin D levels and a decrease in cancer, CVD, and all-cause mortality (30). Another Mendelian Randomization study performed on 31,719 European women indicated that vitamin D deficiency is causally related to ovarian cancer (31).

The rate of decay of brain function in humans is faster in individuals with lower vitamin D levels (32). Executive function improvement, as measured by visual memory, was more effective with supplementation of 4,000 IU/day of vitamin D as compared to 400 IU/day (33). An inverse relationship was observed between maternal and umbilical cord blood concentrations of 25(OH)D and serotonin concentrations, leading to the proposal that vitamin D deficiency contributes to longer-term neurocognitive impairment in infants and children (34). Both of these studies are in agreement with the finding that vitamin D activates the gene for synthesizing brain serotonin which controls executive function (35). The importance of serotonin in brain executive function was also shown in a study that linked low serotonin levels to mild cognitive impairment in the brain (36).

Diabetes may also be affected by the level of vitamin D: a meta-analysis using 24 RCTs with 4,000 IU per day of vitamin D3 in 1,528 type-2 diabetics showed that vitamin D significantly reduced fasting plasma glucose, HOMA-IR, and hemoglobin A1C (37).

Magnesium: A prospective study of ~7,000 Mediterranean adults with high CVD risk and eating diets containing varying magnesium content showed that Mg intake is inversely associated with all-cause mortality; these results are consistent with previous studies, as reviewed (38). Adequate magnesium was shown to protect against colorectal adenoma in a study investigating the effect of the magnesium /calcium ratio (39); this study included an analysis of a polymorphism in a magnesium transporter which also implicated magnesium deficiency in raising colorectal cancer risk. A review of the effects of magnesium deficiency showed increased DNA damage, telomere shortening, increased ceramide level, and an association with aging, heart disease, and colorectal cancer risk (40). There is also a significant inverse association between magnesium intake (as well as potassium intake) and risk of stroke (41, 42). Magnesium is required by almost all of the ~50 DNA repair enzymes: low dietary magnesium intake was shown to be associated with poorer DNA repair capacity and increased risk of lung cancer (43). Various reviews on how to best assay for magnesium deficiency and to determine the optimum magnesium intake are available (44).

SI-4-Conditional Vitamins

Taurine: A large rodent literature on taurine is consistent with the many human studies. The essentiality of taurine was demonstrated in cats (which have unusually low

ability to synthesize taurine) (45) and mice for the embryonic/fetal development of the brain and CNS, eyes, skeletal system, muscles, and many other tissues/organs (46, 47). Taurine is present in high concentrations in rat heart. In several rat and mouse models of heart disease taurine decreases hypertension, impairment of intimal thickening, arteriosclerosis, vascular reactivity, oxidative stress, and inflammation (reviewed in (48)). It regulates the mitochondrial respiratory chain in rat heart: its deficiency impairs cardiac mitochondrial respiratory function and causes cardiac myopathy (49). In rodent models for stroke and abdominal aortic aneurism formation taurine was shown to have protective effects (50, 51).

The importance of taurine in brain function was shown in rats, where it is present at high concentrations (52). It displayed a dose-dependent protection in a rat model of brain injury (53) and protected against traumatic brain injury by increasing mitochondrial function and cerebral blood flow in rats (54).

Taurine's function as an osmolyte was shown by studying the effect of its depletion in a wide variety of species and on several organs. It participates in controlling cell volume in a variety of cells (55, 56); it modulates calcium flux, thus affecting the contractile response in heart and muscle, insulin levels, blood pressure, and membrane polarization (55); it is the most osmotically active molecule in the brain (57). Its supplementation helps reduce the risk of diseases involving defective protein-folding by acting as a stabilizing chaperone for the proper folding of proteins as they come off the endoplasmic reticulum (58-61).

Numerous studies in experimental animals have shown the importance of the ability to transport taurine, with damaging effects in several tissues if the transport system is defective: mouse brain, liver, eyes, skeletal muscles, immune cells, olfactory system, auditory system, and heart (62-68). Skeletal muscle aging is accelerated in taurine transporter knock-out mice (69).

SI-5-Putative Longevity Vitamins

a. Ergothioneine (ESH): One major function of ESH may be to reduce the level of the toxic oxidized ferryl form of heme proteins *in vivo,* such as myoglobin, not designed to function as heme peroxidases (70, 71). One of the problems in Alzheimer's disease appears to be that the amyloid-β peptide in the brain binds heme very tightly, which leads to a temporary shortage of heme; this causes complex IV in mitochondria to release hydrogen peroxide, which then converts the amyloid-β heme into a toxic ferryl heme peroxidase that damages the cell (72). ESH has been shown to be an effective inhibitor of myeloperoxidases and is more effective than glutathione and ascorbic acid (73). In vitro, ESH inhibits the amyloid-β heme peroxidase more effectively than any other antioxidant examined. Perhaps relevant to the primary role of ESH in reducing the level of ferryl heme is the presence of the ESH transporter gene within a cluster of genes involved in mitochondrial heme biosynthesis (74).

ESH effectively protects against copper-dependent oxidative damage to DNA and protein by forming a redox-inactive complex with Cu(I); redox-inactive copper may play a detrimental role in Alzheimer's disease (75).

b. Pyrroloquinoline quinone: Experiments in PQQ-deficient rats and mice lend additional support to the concept that PQQ is a longevity vitamin (76-81). PQQ influences the expression of many rat genes, including genes involved in metabolic stress, cell signaling, immune function, cellular transport, cellular growth, cell cycling,

extracellular matrix formation, mitochondrial functions, lipid-related and phospholipid-related functions (82). PQQ also modulates mitochondrial quantity and function (in mice) (83), and mitochondrial lipid and energy metabolism (in rats) (79). With respect to mitochondrial function, a study found that when PQQ was incorporated into mouse hepatocytes, it stimulated mitochondrial biogenesis *via* induced PGC-1α activation (84). Mice deprived of PQQ became osteolathyritic**,** which was reversed by the addition of PQQ to the diet. *In vivo*, PQQ improved glucose tolerance in type-2 diabetic mice (85). In surgically injured young rats, PQQ had an analgesic effect on neuropathic pain (86). PQQ enhanced cognitive function in rats and prevented cognitive deficit under oxidative stress (87, 88).

c. Queuine: Results from mice suggest that the intestinal-flora is capable of supplying queuine in sufficient quantities to metazoans. Animals fed a chemically defined diet that is devoid of queuine showed no change in the relative amounts of queuine-modified and unmodified tRNA (Farkas 1980). By contrast, mice maintained on a chemically-defined diet under germ-free conditions became fully depleted of queuine in all four tRNAs after one year (89). Feeding these animals purified *E. coli* tRNA showed that higher mammals can independently metabolise and recover queuine from tRNA (89).

The queuine modifications in aspartyl and tyrosyl tRNAs are then further modified with a mannose and a galactose, respectively (90), *via* a glycosyl linkage, whereas histidinyl and asparaginyl tRNA remain non-glycosylated (90). Notably, both cytosolic and mitochondrial tRNA are substrates for queuine-tRNA insertion (91, 92). Recently, a protein termed DUF2419 has been identified as a queuosine salvage enzyme in yeast which is conserved across diverse species (93). At the molecular level, queuine's position in the tRNA anticodon loop has been shown to influence the amino acid charging of the tRNA molecule (94) codon recognition on the ribosome (95) and the rate and accuracy of translation (96).

d. Carotenoids: Carotenoids are introduced into humans by way of their diet, where they perform the same antioxidant function of quenching singlet oxygen, which is generated either photochemically (in the human eye, for example, (97), or in dark reactions by the immune system in neutrophils (98-100), and in eosinophils (101).

Six carotenoids are present in the American diet accounting for 95% of the carotenoids found in human blood: lutein + zeaxanthin, α and β-carotene, lycopene, and β-cryptoxanthin (102). They are also found in the human brain (103, 104).

In support of the concept of carotenoids being longevity vitamins are several findings that they are involved in increasing long-term health. In a study of serum carotenoids in 13,000 Americans in the NHANES survey, an increase in all-cause mortality was associated with a low level of total carotenoids (α- and β-carotene, lutein and zeaxanthin, β-cryptoxanthin, and lycopene), or low lycopene alone (105). The more polar carotenoids (xanthophylls) and non-polar ones (such as lycopene) may display synergy (106-109). In addition, xanthophylls can rigidify membranes, thus protecting them by increasing the barrier to oxidation (108).

i). Lutein and Zeaxanthin are part of the antioxidant photosynthetic system of all higher plants. They are present in most common vegetables and fruits, in particularly high levels in kale, spinach, broccoli, and corn (110). Diet-derived lutein and zeaxanthin are found in the macula of the human eye and in lower concentrations in many other human tissues, particularly in the brain (111, 112). The macula also contains meso-

zeaxanthin, which is made in the eye from lutein (113) and will not be discussed here; see also (114). The key role of lutein and zeaxanthin in vision has been well reviewed recently (110, 114, 115).

Lutein and zeaxanthin help protect the retinal macula, which contains the photoreceptors that are critical for central vision (110, 111). They are taken up in high concentrations by the retina (116) and are bound by lutein- and zeaxanthin-binding proteins, thus forming the macular pigment (117-119).

Oral supplementation with lutein or zeaxanthin in humans or monkeys leads to a significantly increased macular pigment density (112, 120-123) and results in better eye function and protection. Lutein and zeaxanthin are believed to perform three main functions in eyes (which are the same they perform in plants) (111): 1) they filter out harmful wavelengths of strong blue light from the sky; 2) they have anti-singlet oxygen activity, and 3) they are inserted into membranes, preventing oxidation of omega-3 fatty acids, the most easily oxidized fatty acids (114, 124).

Long-term benefits derived from lutein and zeaxanthin include reducing the risk of age-related macular degeneration (AMD; the main cause of blindness in the elderly). Supplementation with lutein or zeaxanthin or both led to improved visual performance in patients with early AMD, including high contrast and low-contrast visual acuity, shape discrimination, glare recovery, and contrast sensitivity functions (125-127). A clinical trial in 112 patients with early AMD using various supplementation doses of lutein or lutein/zeaxanthin for 2 years resulted in increased macular pigment optical density and enhanced retinal sensitivity (128). The AREDS2 study (129) supports such conclusion, as shown by a secondary analysis of participants in the lowest quintile of dietary intake of lutein/zeaxanthin, which indicated a protective effect against progression to advanced AMD with a risk reduction of 26%, although this study is very complicated.

Some protection from cataract formation is obtained with an intake of a basal level of lutein and zeaxanthin (130) and protection is evident in other parts of the eye including the retinal pigment epithelium (131) and as also assessed by various parameters (116, 132, 133).

Lutein, the main carotenoid in the brain, appears to play a role in delaying brain aging (110, 134-137). For example, lutein levels in plasma and brain are associated with a higher volume of brain grey matter and with improved crystallized intelligence in the elderly (138). A double-blinded, randomized controlled trial showed that a lutein plus zeaxanthin supplement increased both neural processing speed and efficiency (139). Decreased processing speed is a major hallmark of cognitive decline. Lutein and zeaxanthin have also been shown to improve memory recall while using less brain power in older individuals (neural efficiency).

The following carotenoids are also important for human cardiovascular health: the polar marine xanthophyll, astaxanthin; the plant xanthophylls, lutein, zeaxanthin and β-cryptoxanthin; and the non-polar carotenoids lycopene and β-carotene (140). Lutein (but not β-carotene) supplementation resulted in a marked lowering of a risk factor for heart disease, carotid intima-media thickening (141-145).

Lutein, zeaxanthin, astaxanthin, and lycopene improve general health and healthy aging trough their prevention and treatment of non-alcoholic fatty liver disease (146) and diabetic microvascular complications (147). Lutein and zeaxanthin levels are associated

with longer telomeres in humans (148) and lutein extends the lifespan of Drosophila and protects against oxidative stress (149).

High intake and high serum levels of dietary lutein lower the risk of various types of cancer (150).

In agreement with the above studies on the importance of lutein for health the suggestion was made that "A healthy diet should be considered to do more than prevent deficiencies, it must promote optimal health during the life course" (110).

ii). Lycopene, the precursor of several other carotenoids found in plants, also appears to be a longevity vitamin. It is a potent non-polar anti-oxidant, containing 11 conjugated trans double bonds and is one of the most efficient singlet oxygen quenchers known (151, 152). The highest levels of lycopene are found in the tomato (85% of U.S. intake) (153, 154). Dietary lycopene reaches many tissues in the human body, particularly testes, adrenals, liver, prostate, brain, breast, and colon, in all of which it may exert its protective actions (155, 156).

The beneficial effects of lycopene metabolism on diseases of aging, in particular through its antioxidant mechanisms, have been reviewed (157). Epidemiological studies show inverse correlations between high levels of dietary or serum lycopene and reduction of the risk of various cancers (158-160), such as prostate cancer where an inverse correlation between lycopene intake (or lycopene serum levels) and prostate cancer risk, and aggressiveness levels was found (although null associations were found in some other studies) (161-166). Lycopene also helped to reduce oxidative stress, metabolic syndrome, high blood pressure (167), and heart disease (168), and carotid media-thickness (145); it lowered the risk of myocardial infarction (169) and of metabolic syndrome (170); it significantly protected against oxidative stress in DNA (171).

Possible mechanisms for lycopene action in a wide variety of diseases of aging have been suggested (167, 168, 172-176).

iii). α- and β-Carotene, and β-cryptoxanthin are precursors of vitamin A (104). Diets high in α- and β-carotene are associated with lower risk of type-2 diabetes (177). Significant protection against breast cancer risk in Chinese women has been shown to be associated with consumption of α- and β-carotene, lycopene, lutein/zeaxanthin (but not of β-cryptoxanthin). This finding is consistent with previous studies (178). β-cryptoxanthin has been shown to inhibit lung cancer (179). A significant increase (5-8%) in leukocyte telomeres was seen in humans in the highest quartile consuming α- and β-carotene and β-cryptoxanthin, as compared with the lowest quartile (180). Consumption of β-carotene, and β-cryptoxanthin has also been associated with protection against hearing loss in a large (12,789 women) prospective study of hearing loss (181). A positive effect of β-carotene on cognitive function was observed, but only after prolonged treatment (12 years) (182).

iv). Astaxanthin (ASX) also is a putative longevity vitamin. It is a marine orange-red carotenoid in the xanthophyll class present in salmon, trout, red snapper, tilapia, crab, shrimp and lobster, octopus, and squid, and many other kinds of seafood and freshwater fish (183-189). It is synthesized primarily by various kinds of marine microalgae and functions to counter oxidative stress (190-193). ASX is a 4, 4' diketo zeaxanthin (109) which contains 13 conjugated double bonds. It is somewhat similar in structure to zeaxanthin (109), which contains only 11 conjugated double bonds.

ASX is absorbed into the human bloodstream and eye (194-199) with consequent improvements in visual acuity and amplitude of accommodation, and thus to healthy aging (200, 201). ASX appears to enter cells through non-specific transport systems that transport xanthophylls such as zeaxanthin and lutein, since it is similar in structure to those compounds; they might spare each other.

ASX has been shown to be a particularly strong antioxidant in studies on lipid peroxidation (109, 202). It prevented lipid peroxidation in membranes and was considerably more potent than either lutein or zeaxanthin (109, 203, 204). It quenches singlet oxygen (106, 151). It has been suggested that the alternating polar-nonpolar-polar structure of ASX, and other oxygen-containing more polar xanthophylls, allows it to span cellular and organelle membranes and thus perform better antioxidant functions against lipid peroxidation (205). The family of xanthophyll carotenoids rigidify membranes and limit O_2 penetration (108). ASX has been shown to be an effective antioxidant against damage from reactive nitrogen species (in addition to lutein and zeaxanthin**),** such as peroxynitrite derived from nitrogen oxide, (206, 207). It is common only in diets containing abundant marine foods, such as in the Japanese diet.

A comprehensive review of ASX action (204) concluded that it has potential health-promoting effects in the prevention and treatment of numerous diseases related to aging. A recent review of the literature (208), including 3 positive Japanese RCTs, concludes that ASX reduces cognitive and memory dysfunction with age. A review of ASX studies in humans (10 trials) and animals (12 studies) with an emphasis on cardiovascular health and disease, concluded that ASX reduced thrombosis; myocardial infarct size; oxidative damage to DNA, protein, and lipids; and blood pressure (209). See also (210). ASX significantly decreased inflammation and DNA oxidation and it enhanced the immune response in humans (211). In a study on ulcers in humans infected with *H. pylori*, ASX significantly decreased gastric inflammation (212). In human clinical trials supplementation of ASX was shown to lead to significant reductions in oxidative stress, hyperlipidemia, and levels of inflammatory markers (213).

References

1. Sijtsma FP*, et al.* (2015) Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment. *Am J Clin Nutr* 102(6):1527-1533.
2. Smith GD & Wimalawansa SJ (2015) Reconciling the Irreconcilable: Micronutrients in Clinical Nutrition and Public Health. *Vitamins and Minerals* 4(1):1-4.
3. Song M & Giovannucci EL (2015) RE: Doll and Peto's Quantitative Estimates of Cancer Risks: Holding Generally True for 35 Years. *J Natl Cancer Inst* 107(10).
4. Bhushan A*, et al.* (2017) Adherence to Mediterranean diet and subjective cognitive function in men. *Eur J Epidemiol*.
5. Fenech M (2017) Vitamins Associated with Brain Aging, Mild Cognitive Impairment, and Alzheimer Disease: Biomarkers, Epidemiological and Experimental Evidence, Plausible Mechanisms, and Knowledge Gaps. *Adv Nutr* 8(6):958-970.

6. Micha R, *et al.* (2017) Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. *JAMA* 317(9):912-924.
7. Mueller NT & Appel LJ (2017) Attributing Death to Diet: Precision Counts. *JAMA* 317(9):908-909.
8. Sales CH, Fontanelli MM, Vieira DA, Marchioni DM, & Fisberg RM (2017) Inadequate dietary intake of minerals: prevalence and association with socio-demographic and lifestyle factors. *Br J Nutr* 117(2):267-277.
9. Schwingshackl L, *et al.* (2017) Dietary Supplements and Risk of Cause-Specific Death, Cardiovascular Disease, and Cancer: A Systematic Review and Meta-Analysis of Primary Prevention Trials. *Adv Nutr* 8(1):27-39.
10. Shlisky J, *et al.* (2017) Nutritional Considerations for Healthy Aging and Reduction in Age-Related Chronic Disease. *Adv Nutr* 8(1):17-26.
11. Yetley EA, *et al.* (2017) Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. *Am J Clin Nutr* 105(1):249S-285S.
12. Zaslavsky O, *et al.* (2017) Biomarker-calibrated nutrient intake and healthy diet index associations with mortality risks among older and frail women from the Women's Health Initiative. *Am J Clin Nutr* 105(6):1399-1407.
13. McCann JC & Ames BN (2009) Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging? *Am J Clin Nutr* 90(4):889-907.
14. Liu YP, *et al.* (2015) Inactive matrix Gla protein is causally related to adverse health outcomes: a Mendelian randomization study in a Flemish population. *Hypertension* 65(2):463-470.
15. Juanola-Falgarona M, *et al.* (2014) Dietary intake of vitamin K is inversely associated with mortality risk. *J Nutr* 144(5):743-750.
16. Douthit MK, *et al.* (2017) Phylloquinone Intake Is Associated with Cardiac Structure and Function in Adolescents. *J Nutr*.
17. McCann JC & Ames BN (2011) Adaptive dysfunction of selenoproteins from the perspective of the triage theory: why modest selenium deficiency may increase risk of diseases of aging. *FASEB J* 25(6):1793-1814.
18. Alehagen U, Aaseth J, Alexander J, & Johansson P (2018) Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four years: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly. *PLoS One* 13(4):e0193120.
19. Gaksch M, *et al.* (2017) Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. *PLoS One* 12(2):e0170791.
20. Keisala T, *et al.* (2009) Premature aging in vitamin D receptor mutant mice. *J Steroid Biochem Mol Biol* 115(3-5):91-97.
21. Garland CF, *et al.* (2014) Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D. *Am J Public Health* 104(8):e43-50.
22. Brenner H, Jansen L, Saum KU, Holleczek B, & Schottker B (2017) Vitamin D Supplementation Trials Aimed at Reducing Mortality Have Much Higher Power

When Focusing on People with Low Serum 25-Hydroxyvitamin D Concentrations. *J Nutr* 147(7):1325-1333.
23. Brondum-Jacobsen P, Benn M, Jensen GB, & Nordestgaard BG (2012) 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arteriosclerosis, thrombosis, and vascular biology* 32(11):2794-2802.
24. Afzal S, Brondum-Jacobsen P, Bojesen SE, & Nordestgaard BG (2014) Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. *Bmj* 349:g6330.
25. Manousaki D, Mokry LE, Ross S, Goltzman D, & Richards JB (2016) Mendelian Randomization Studies Do Not Support a Role for Vitamin D in Coronary Artery Disease. *Circ Cardiovasc Genet* 9(4):349-356.
26. Sluyter JD*, et al.* (2017) Effect of Monthly, High-Dose, Long-Term Vitamin D Supplementation on Central Blood Pressure Parameters: A Randomized Controlled Trial Substudy. *J Am Heart Assoc* 6(10).
27. Raed A*, et al.* (2017) Dose responses of vitamin D3 supplementation on arterial stiffness in overweight African Americans with vitamin D deficiency: A placebo controlled randomized trial. *PLoS One* 12(12):e0188424.
28. Moukayed M & Grant WB (2017) The roles of UVB and vitamin D in reducing risk of cancer incidence and mortality: A review of the epidemiology, clinical trials, and mechanisms. *Rev Endocr Metab Disord* 18(2):167-182.
29. Grant WB (2011) An estimate of the global reduction in mortality rates through doubling vitamin D levels. *Eur J Clin Nutr* 65(9):1016-1026.
30. Grober U, Reichrath J, & Holick MF (2015) Live longer with vitamin D? *Nutrients* 7(3):1871-1880.
31. Ong JS*, et al.* (2016) Association of vitamin D levels and risk of ovarian cancer: a Mendelian randomization study. *International journal of epidemiology* 45(5):1619-1630.
32. Miller JW*, et al.* (2015) Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults. *JAMA Neurol* 72(11):1295-1303.
33. Pettersen JA (2017) Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults. *Exp Gerontol* 90:90-97.
34. Murthi P*, et al.* (2017) Maternal 25-hydroxyvitamin D is inversely correlated with foetal serotonin. *Clin Endocrinol (Oxf)* 86(3):401-409.
35. Patrick RP & Ames BN (2014) Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB J* 28(6):2398-2413.
36. Smith GS*, et al.* (2017) Molecular imaging of serotonin degeneration in mild cognitive impairment. *Neurobiol Dis* 105:33-41.
37. Mirhosseini N, Vatanparast H, Mazidi M, & Kimball SM (2017) The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. *J Clin Endocrinol Metab* 102(9):3097-3110.
38. Guasch-Ferre M*, et al.* (2014) Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular disease risk. *J Nutr* 144(1):55-60.
39. Dai Q*, et al.* (2007) The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. *Am J Clin Nutr* 86(3):743-751.

40. Altura BM, Shah NC, Gatha JS, Perez-Abela JL, & Altura BT (2016) Magnesium Deficiency Results in Oxidation and Fragmentation of DNA, Down Regulation of Telomerase Activity, and Ceramide Release in Cardiovascular Tissues and Cells: Potential Relationship to Atherogenesis, Cardiovascular Diseases and Aging. *International Journal of Diabetology & Vascular Disease Research* 4(1e):1-5.
41. Adebamowo SN, Spiegelman D, Flint AJ, Willett WC, & Rexrode KM (2015) Intakes of magnesium, potassium, and calcium and the risk of stroke among men. *Int J Stroke*.
42. Adebamowo SN, Spiegelman D, Willett WC, & Rexrode KM (2015) Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. *Am J Clin Nutr* 101(6):1269-1277.
43. Mahabir S*, et al.* (2008) Dietary magnesium and DNA repair capacity as risk factors for lung cancer. *Carcinogenesis* 29(5):949-956.
44. Costello RB*, et al.* (2016) Perspective: The Case for an Evidence-Based Reference Interval for Serum Magnesium: The Time Has Come. *Adv Nutr* 7(6):977-993.
45. Hilton J (1988) The biosynthesis, function and deficiency signs of taurine in cats. *Can Vet J* 29(7):598-601.
46. Sturman JA (1991) Dietary taurine and feline reproduction and development. *J Nutr* 121(11 Suppl):S166-170.
47. Sturman JA (1993) Taurine in development. *Physiol Rev* 73(1):119-147.
48. Abebe W & Mozaffan MS (2011) Role of taurine in the vasculature: an overview of experimental and human studies. *Am J Cardiovasc Dis* 1(3):293-311.
49. Schaffer SW, Shimada-Takaura K, Jong CJ, Ito T, & Takahashi K (2016) Impaired energy metabolism of the taurinedeficient heart. *Amino Acids* 48(2):549-558.
50. Sun K*, et al.* (2012) Effect of taurine on IRAK4 and NF-kappa B in Kupffer cells from rat liver grafts after ischemia-reperfusion injury. *Am J Surg* 204(3):389-395.
51. Kim HW*, et al.* (2017) Role of myeloperoxidase in abdominal aortic aneurysm formation: mitigation by taurine. *Am J Physiol Heart Circ Physiol* 313(6):H1168-H1179.
52. Sun Q*, et al.* (2016) Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. *Hypertension* 67(3):541-549.
53. Sun M, Zhao Y, Gu Y, & Zhang Y (2015) Protective effects of taurine against closed head injury in rats. *J Neurotrauma* 32(1):66-74.
54. Wang Q*, et al.* (2016) Protective effects of taurine in traumatic brain injury via mitochondria and cerebral blood flow. *Amino Acids* 48(9):2169-2177.
55. Huxtable RJ (1992) Physiological actions of taurine. *Physiol Rev* 72(1):101-163.
56. Schaffer SW, Jong CJ, Ramila KC, & Azuma J (2010) Physiological roles of taurine in heart and muscle. *J Biomed Sci* 17 Suppl 1:S2.
57. Bouckenooghe T, Remacle C, & Reusens B (2006) Is taurine a functional nutrient? *Curr Opin Clin Nutr Metab Care* 9(6):728-733.
58. Welch WJ & Brown CR (1996) Influence of molecular and chemical chaperones on protein folding. *Cell Stress Chaperones* 1(2):109-115.

59. Yancey PH (2001) Water Stress, Osmolytes and Proteins. *American Zoologist* 41(4):699-709.
60. Street TO, Bolen DW, & Rose GD (2006) A molecular mechanism for osmolyte-induced protein stability. *Proc Natl Acad Sci U S A* 103(38):13997-14002.
61. Hu CY, Pettitt BM, & Roesgen J (2009) Osmolyte solutions and protein folding. *F1000 Biol Rep* 1:41.
62. Heller-Stilb B*, et al.* (2002) Disruption of the taurine transporter gene (taut) leads to retinal degeneration in mice. *FASEB J* 16(2):231-233.
63. Warskulat U*, et al.* (2004) Taurine transporter knockout depletes muscle taurine levels and results in severe skeletal muscle impairment but leaves cardiac function uncompromised. *FASEB J* 18(3):577-579.
64. Warskulat U*, et al.* (2006) Chronic liver disease is triggered by taurine transporter knockout in the mouse. *FASEB J* 20(3):574-576.
65. Warskulat U*, et al.* (2007) Phenotype of the taurine transporter knockout mouse. *Methods Enzymol* 428:439-458.
66. Ito T*, et al.* (2008) Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. *J Mol Cell Cardiol* 44(5):927-937.
67. Delic D*, et al.* (2010) Loss of ability to self-heal malaria upon taurine transporter deletion. *Infect Immun* 78(4):1642-1649.
68. Ito T*, et al.* (2010) Cardiac and skeletal muscle abnormality in taurine transporter-knockout mice. *J Biomed Sci* 17 Suppl 1:S20.
69. Ito T, Yamamoto N, Nakajima S, & Schaffer SW (2017) Beta-Catenin and SMAD3 Are Associated with Skeletal Muscle Aging in the Taurine Transpoeter Knockout Mouse. *Adv Exp Med Biol* 975:497-502.
70. Arduini A, Eddy L, & Hochstein P (1990) Detection of ferryl myoglobin in the isolated ischemic rat heart. *Free Radic Biol Med* 9(6):511-513.
71. Arduini A, Eddy L, & Hochstein P (1990) The reduction of ferryl myoglobin by ergothioneine: a novel function for ergothioneine. *Arch Biochem Biophys* 281(1):41-43.
72. Atamna H & Boyle K (2006) Amyloid-beta peptide binds with heme to form a peroxidase: relationship to the cytopathologies of Alzheimer's disease. *Proc Natl Acad Sci U S A* 103(9):3381-3386.
73. Asahi T*, et al.* (2016) A mushroom-derived amino acid, ergothioneine, is a potential inhibitor of inflammation-related DNA halogenation. *Biosci Biotechnol Biochem* 80(2):313-317.
74. Nilsson R*, et al.* (2009) Discovery of genes essential for heme biosynthesis through large-scale gene expression analysis. *Cell Metab* 10(2):119-130.
75. Zhu BZ*, et al.* (2011) Ergothioneine prevents copper-induced oxidative damage to DNA and protein by forming a redox-inactive ergothioneine-copper complex. *Chem Res Toxicol* 24(1):30-34.
76. Kilgore WW, Crosby DG, Craigmill AL, & Poppen NK (1981) Toxic plants as possible human teratogens. *Calif. Agric.* 35:6.
77. Steinberg F*, et al.* (2003) Pyrroloquinoline quinone improves growth and reproductive performance in mice fed chemically defined diets. *Exp Biol Med (Maywood)* 228(2):160-166.

78. Rucker R, Chowanadisai W, & Nakano M (2009) Potential physiological importance of pyrroloquinoline quinone. *Altern Med Rev* 14(3):268-277.
79. Bauerly K*, et al.* (2011) Altering pyrroloquinoline quinone nutritional status modulates mitochondrial, lipid, and energy metabolism in rats. *PLoS One* 6(7):e21779.
80. Akagawa M, Nakano M, & Ikemoto K (2015) Recent progress in studies on the health benefits of pyrroloquinoline quinone. *Biosci Biotechnol Biochem* 80(1):13-22.
81. Jonscher KR*, et al.* (2017) Early PQQ supplementation has persistent long-term protective effects on developmental programming of hepatic lipotoxicity and inflammation in obese mice. *FASEB J* 31(4):1434-1448.
82. Tchaparian E*, et al.* (2010) Identification of transcriptional networks responding to pyrroloquinoline quinone dietary supplementation and their influence on thioredoxin expression, and the JAK/STAT and MAPK pathways. *Biochem J* 429(3):515-526.
83. Stites T*, et al.* (2006) Pyrroloquinoline quinone modulates mitochondrial quantity and function in mice. *J Nutr* 136(2):390-396.
84. Chowanadisai W*, et al.* (2010) Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression. *J Biol Chem* 285(1):142-152.
85. Takada M*, et al.* (2012) Pyrroloquinoline quinone, a novel protein tyrosine phosphatase 1B inhibitor, activates insulin signaling in C2C12 myotubes and improves impaired glucose tolerance in diabetic KK-A(y) mice. *Biochem Biophys Res Commun* 428(2):315-320.
86. Gong D*, et al.* (2012) Effect of pyrroloquinoline quinone on neuropathic pain following chronic constriction injury of the sciatic nerve in rats. *Eur J Pharmacol* 697(1-3):53-58.
87. Ohwada K*, et al.* (2008) Pyrroloquinoline Quinone (PQQ) Prevents Cognitive Deficit Caused by Oxidative Stress in Rats. *J Clin Biochem Nutr* 42:29-34.
88. Kim J*, et al.* (2010) Pyrroloquinoline quinone inhibits the fibrillation of amyloid proteins. *Prion* 4(1):26-31.
89. Reyniers JP, Pleasants JR, Wostmann BS, Katze JR, & Farkas WR (1981) Administration of exogenous queuine is essential for the biosynthesis of the queuosine-containing transfer RNAs in the mouse. *J Biol Chem* 256(22):11591-11594.
90. Nishimura S (1983) Structure, biosynthesis, and function of queuosine in transfer RNA. *Prog Nucleic Acid Res Mol Biol* 28:49-73.
91. Boland C, Hayes P, Santa-Maria I, Nishimura S, & Kelly VP (2009) Queuosine formation in eukaryotic tRNA occurs via a mitochondria-localized heteromeric transglycosylase. *J Biol Chem* 284(27):18218-18227.
92. Suzuki T, Nagao A, & Suzuki T (2011) Human mitochondrial diseases caused by lack of taurine modification in mitochondrial tRNAs. *Wiley Interdiscip Rev RNA* 2(3):376-386.
93. Zallot R*, et al.* (2014) Plant, animal, and fungal micronutrient queuosine is salvaged by members of the DUF2419 protein family. *ACS Chem Biol* 9(8):1812-1825.

94. Singhal RP & Vakharia VN (1983) The role of queuine in the aminoacylation of mammalian aspartate transfer RNAs. *Nucleic Acids Res* 11(12):4257-4272.
95. Meier F, Suter B, Grosjean H, Keith G, & Kubli E (1985) Queuosine modification of the wobble base in tRNAHis influences 'in vivo' decoding properties. *EMBO J* 4(3):823-827.
96. Manickam N, Joshi K, Bhatt MJ, & Farabaugh PJ (2016) Effects of tRNA modification on translational accuracy depend on intrinsic codon-anticodon strength. *Nucleic Acids Res* 44(4):1871-1881.
97. Li B, Ahmed F, & Bernstein PS (2010) Studies on the singlet oxygen scavenging mechanism of human macular pigment. *Arch Biochem Biophys* 504(1):56-60.
98. Steinbeck MJ, Khan AU, & Karnovsky MJ (1992) Intracellular singlet oxygen generation by phagocytosing neutrophils in response to particles coated with a chemical trap. *J Biol Chem* 267(19):13425-13433.
99. Klotz LO, Kroncke KD, & Sies H (2003) Singlet oxygen-induced signaling effects in mammalian cells. *Photochem Photobiol Sci* 2(2):88-94.
100. Nishinaka Y, Arai T, Adachi S, Takaori-Kondo A, & Yamashita K (2011) Singlet oxygen is essential for neutrophil extracellular trap formation. *Biochem Biophys Res Commun* 413(1):75-79.
101. Kanofsky JR (1989) Singlet oxygen production by biological systems. *Chem Biol Interact* 70(1-2):1-28.
102. Maiani G*, et al.* (2009) Carotenoids: actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. *Mol Nutr Food Res* 53 Suppl 2:S194-218.
103. Craft NE, Haitema TB, Garnett KM, Fitch KA, & Dorey CK (2004) Carotenoid, tocopherol, and retinol concentrations in elderly human brain. *J Nutr Health Aging* 8(3):156-162.
104. Johnson EJ*, et al.* (2013) Relationship between Serum and Brain Carotenoids, alpha-Tocopherol, and Retinol Concentrations and Cognitive Performance in the Oldest Old from the Georgia Centenarian Study. *J Aging Res* 2013:951786.
105. Shardell MD*, et al.* (2011) Low-serum carotenoid concentrations and carotenoid interactions predict mortality in US adults: the Third National Health and Nutrition Examination Survey. *Nutr Res* 31(3):178-189.
106. Cantrell A, McGarvey DJ, Truscott TG, Rancan F, & Bohm F (2003) Singlet oxygen quenching by dietary carotenoids in a model membrane environment. *Arch Biochem Biophys* 412(1):47-54.
107. Daubrawa F, Sies H, & Stahl W (2005) Astaxanthin diminishes gap junctional intercellular communication in primary human fibroblasts. *J Nutr* 135(11):2507-2511.
108. Gruszecki WI & Strzalka K (2005) Carotenoids as modulators of lipid membrane physical properties. *Biochim Biophys Acta* 1740(2):108-115.
109. McNulty H, Jacob RF, & Mason RP (2008) Biologic activity of carotenoids related to distinct membrane physicochemical interactions. *Am J Cardiol* 101(10A):20D-29D.
110. Johnson EJ (2014) Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. *Nutr Rev* 72(9):605-612.

111. Krinsky NI, Landrum JT, & Bone RA (2003) Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. *Annu Rev Nutr* 23:171-201.
112. Schalch W*, et al.* (2007) Xanthophyll accumulation in the human retina during supplementation with lutein or zeaxanthin - the LUXEA (LUtein Xanthophyll Eye Accumulation) study. *Arch Biochem Biophys* 458(2):128-135.
113. Johnson EJ (2005) Obesity, lutein metabolism, and age-related macular degeneration: a web of connections. *Nutr Rev* 63(1):9-15.
114. Bernstein PS*, et al.* (2016) Lutein, zeaxanthin, and meso-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog Retin Eye Res* 50:34-66.
115. Scripsema NK, Hu DN, & Rosen RB (2015) Lutein, Zeaxanthin, and meso-Zeaxanthin in the Clinical Management of Eye Disease. *J Ophthalmol* 2015:865179.
116. Renzi LM & Hammond BR, Jr. (2010) The relation between the macular carotenoids, lutein and zeaxanthin, and temporal vision. *Ophthalmic Physiol Opt* 30(4):351-357.
117. Bhosale P & Bernstein PS (2005) Synergistic effects of zeaxanthin and its binding protein in the prevention of lipid membrane oxidation. *Biochim Biophys Acta* 1740(2):116-121.
118. During A, Doraiswamy S, & Harrison EH (2008) Xanthophylls are preferentially taken up compared with beta-carotene by retinal cells via a SRBI-dependent mechanism. *J Lipid Res* 49(8):1715-1724.
119. Vachali P, Li B, Nelson K, & Bernstein PS (2012) Surface plasmon resonance (SPR) studies on the interactions of carotenoids and their binding proteins. *Arch Biochem Biophys* 519(1):32-37.
120. Curran-Celentano J*, et al.* (2001) Relation between dietary intake, serum concentrations, and retinal concentrations of lutein and zeaxanthin in adults in a Midwest population. *Am J Clin Nutr* 74(6):796-802.
121. Junghans A, Sies H, & Stahl W (2001) Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. *Arch Biochem Biophys* 391(2):160-164.
122. Bone RA, Landrum JT, Guerra LH, & Ruiz CA (2003) Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. *J Nutr* 133(4):992-998.
123. Bone RA & Landrum JT (2010) Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. *Arch Biochem Biophys* 504(1):50-55.
124. Sujak A*, et al.* (1999) Lutein and zeaxanthin as protectors of lipid membranes against oxidative damage: the structural aspects. *Arch Biochem Biophys* 371(2):301-307.
125. Richer S*, et al.* (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 75(4):216-230.
126. Richer SP*, et al.* (2011) Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular

degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry* 82(11):667-680 e666.
127. Weigert G*, et al.* (2011) Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 52(11):8174-8178.
128. Huang YM*, et al.* (2015) 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* 99(3):371-375.
129. Age-Related Eye Disease Study 2 Research G (2013) Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA* 309(19):2005-2015.
130. Bernstein PS*, et al.* (2001) Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. *Experimental Eye Research* 72:215-223.
131. Sommerburg OG*, et al.* (1999) Lutein and zeaxanthin are associated with photoreceptors in the human retina. *Curr Eye Res* 19(6):491-495.
132. Stringham JM & Hammond BR, Jr. (2005) Dietary lutein and zeaxanthin: possible effects on visual function. *Nutr Rev* 63(2):59-64.
133. Renzi LM & Hammond BR (2010) The effect of macular pigment on heterochromatic luminance contrast. *Exp Eye Res* 91(6):896-900.
134. Johnson EJ (2012) A possible role for lutein and zeaxanthin in cognitive function in the elderly. *Am J Clin Nutr* 96(5):1161S-1165S.
135. Johnson EJ (2014) Response to Letter from Peter P Hoppe: Emerging Science on Lutein in the Brain and Why is Nutrition so Confusing? *Sight and Life* 28(2):71-73.
136. Vishwanathan R*, et al.* (2014) Macular pigment optical density is related to cognitive function in older people. *Age Ageing* 43(2):271-275.
137. Walk AM*, et al.* (2017) The Role of Retinal Carotenoids and Age on Neuroelectric Indices of Attentional Control among Early to Middle-Aged Adults. *Front Aging Neurosci* 9:183.
138. Zamroziewicz MK*, et al.* (2016) Parahippocampal Cortex Mediates the Relationship between Lutein and Crystallized Intelligence in Healthy, Older Adults. *Front Aging Neurosci* 8:297.
139. Bovier ER, Renzi LM, & Hammond BR (2014) A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency. *PLoS One* 9(9):e108178.
140. Gammone MA, Riccioni G, & D'Orazio N (2015) Carotenoids: potential allies of cardiovascular health? *Food Nutr Res* 59:26762.
141. Klipstein-Grobusch K*, et al.* (2000) Serum carotenoids and atherosclerosis. The Rotterdam Study. *Atherosclerosis* 148(1):49-56.
142. Dwyer JH*, et al.* (2001) Oxygenated carotenoid lutein and progression of early atherosclerosis: the Los Angeles atherosclerosis study. *Circulation* 103(24):2922-2927.
143. Zou Z*, et al.* (2011) High serum level of lutein may be protective against early atherosclerosis: the Beijing atherosclerosis study. *Atherosclerosis* 219(2):789-793.

144. Xu XR, *et al.* (2013) Effects of lutein supplement on serum inflammatory cytokines, ApoE and lipid profiles in early atherosclerosis population. *J Atheroscler Thromb* 20(2):170-177.
145. Zou ZY, *et al.* (2014) Effects of lutein and lycopene on carotid intima-media thickness in Chinese subjects with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 111(3):474-480.
146. Murillo AG, DiMarco DM, & Fernandez ML (2016) The Potential of Non-Provitamin A Carotenoids for the Prevention and Treatment of Non-Alcoholic Fatty Liver Disease. *Biology (Basel)* 5(4).
147. Murillo AG & Fernandez ML (2016) Potential of Dietary Non-Provitamin A Carotenoids in the Prevention and Treatment of Diabetic Microvascular Complications. *Adv Nutr* 7(1):14-24.
148. Sen A, *et al.* (2014) Association between higher plasma lutein, zeaxanthin, and vitamin C concentrations and longer telomere length: results of the Austrian Stroke Prevention Study. *J Am Geriatr Soc* 62(2):222-229.
149. Zhang Z, Han S, Wang H, & Wang T (2014) Lutein extends the lifespan of Drosophila melanogaster. *Arch Gerontol Geriatr* 58(1):153-159.
150. Ribaya-Mercado JD & Blumberg JB (2004) Lutein and zeaxanthin and their potential roles in disease prevention. *J Am Coll Nutr* 23(6 Suppl):567S-587S.
151. Di Mascio P, Kaiser S, & Sies H (1989) Lycopene as the Most Efficient Biological Carotenoid Singlet Oxygen Quencher. *Arch Biochem Biophys* 274(2):532-538.
152. Stahl W & Sies H (1996) Lycopene: a biologically important carotenoid for humans? *Arch Biochem Biophys* 336(1):1-9.
153. Holden JM, *et al.* (1999) Carotenoid Content of U.S. Foods: An Update of the Database. *J Food Composition and Analysis* 12(3):169-196.
154. Porrini M & Riso P (2005) What are typical lycopene intakes? *J Nutr* 135(8):2042S-2045S.
155. Agarwal S & Rao AV (2000) Tomato lycopene and its role in human health and chronic diseases. *CMAJ* 163(6):739-744.
156. Bramley PM (2000) Is lycopene beneficial to human health? *Phytochemistry* 54(3):233-236.
157. Kong KW, *et al.* (2010) Revealing the power of the natural red pigment lycopene. *Molecules* 15(2):959-987.
158. Story EN, Kopec RE, Schwartz SJ, & Harris GK (2010) An update on the health effects of tomato lycopene. *Annu Rev Food Sci Technol* 1:189-210.
159. Zu K, *et al.* (2014) Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. *J Natl Cancer Inst* 106(2):djt430.
160. Graff RE, *et al.* (2016) Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. *Am J Clin Nutr* 103(3):851-860.
161. Gann PH, *et al.* (1999) Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* 59(6):1225-1230.
162. Giovannucci E (2002) A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. *Exp Biol Med (Maywood)* 227(10):852-859.

163. Etminan M, Takkouche B, & Caamano-Isorna F (2004) The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev* 13(3):340-345.
164. Wertz K, Siler U, & Goralczyk R (2004) Lycopene: modes of action to promote prostate health. *Arch Biochem Biophys* 430(1):127-134.
165. Haseen F, Cantwell MM, O'Sullivan JM, & Murray LJ (2009) Is there a benefit from lycopene supplementation in men with prostate cancer? A systematic review. *Prostate Cancer Prostatic Dis* 12(4):325-332.
166. Ilic D & Misso M (2012) Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. *Maturitas* 72(4):269-276.
167. Li X & Xu J (2013) Lycopene supplement and blood pressure: an updated meta-analysis of intervention trials. *Nutrients* 5(9):3696-3712.
168. Jacques PF, Lyass A, Massaro JM, Vasan RS, & D'Agostino RB, Sr. (2013) Relationship of lycopene intake and consumption of tomato products to incident CVD. *Br J Nutr* 110(3):545-551.
169. Kohlmeier L*, et al.* (1997) Lycopene and myocardial infarction risk in the EURAMIC Study. *Am J Epidemiol* 146(8):618-626.
170. Sluijs I, Beulens JW, Grobbee DE, & van der Schouw YT (2009) Dietary carotenoid intake is associated with lower prevalence of metabolic syndrome in middle-aged and elderly men. *J Nutr* 139(5):987-992.
171. Devaraj S*, et al.* (2008) A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. *J Am Coll Nutr* 27(2):267-273.
172. Zhang LX, Cooney RV, & Bertram JS (1992) Carotenoids up-regulate connexin43 gene expression independent of their provitamin A or antioxidant properties. *Cancer Res* 52(20):5707-5712.
173. Aust O*, et al.* (2003) Lycopene oxidation product enhances gap junctional communication. *Food Chem Toxicol* 41(10):1399-1407.
174. Liu X, Allen JD, Arnold JT, & Blackman MR (2008) Lycopene inhibits IGF-I signal transduction and growth in normal prostate epithelial cells by decreasing DHT-modulated IGF-I production in co-cultured reactive stromal cells. *Carcinogenesis* 29(4):816-823.
175. Elgass S, Cooper A, & Chopra M (2011) Lycopene inhibits angiogenesis in human umbilical vein endothelial cells and rat aortic rings. *Br J Nutr* 108(3):431-439.
176. Sharoni Y*, et al.* (2012) The role of lycopene and its derivatives in the regulation of transcription systems: implications for cancer prevention. *Am J Clin Nutr* 96(5):1173S-1178S.
177. Sluijs I*, et al.* (2015) Dietary intake of carotenoids and risk of type 2 diabetes. *Nutr Metab Cardiovasc Dis* 25(4):376-381.
178. Yan B*, et al.* (2016) Specific serum carotenoids are inversely associated with breast cancer risk among Chinese women: a case-control study. *Br J Nutr* 115(1):129-137.
179. Iskandar AR*, et al.* (2016) beta-Cryptoxanthin Reduced Lung Tumor Multiplicity and Inhibited Lung Cancer Cell Motility by Downregulating Nicotinic

Acetylcholine Receptor alpha7 Signaling. *Cancer Prev Res (Phila)* 9(11):875-886.
180. Min KB & Min JY (2017) Association between leukocyte telomere length and serum carotenoid in US adults. *Eur J Nutr* 56(3):1045-1052.
181. Curhan SG*, et al.* (2015) Carotenoids, vitamin A, vitamin C, vitamin E, and folate and risk of self-reported hearing loss in women. *Am J Clin Nutr* 102(5):1167-1175.
182. Grodstein F, Kang JH, Glynn RJ, Cook NR, & Gaziano JM (2007) A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. *Arch Intern Med* 167(20):2184-2190.
183. Tanaka Y, Matsuguchi H, Katayama T, Simpson KL, & Chichester CO (1976) The biosynthesis of astaxanthin- XVI. The carotenoids in Crustacea. *Comp Biochem Physiol B* 54(3):391-393.
184. Katsuyama M, Komori T, & Matsuno T (1987) Metabolism of three stereoisomers of astaxanthin in the fish, rainbow trout and tilapia. *Comp Biochem Physiol B* 86(1):1-5.
185. Youngson AF, Mitchell AI, Noack PT, & Laird LM (1997) Carotenoid pigment profiles distinguish anadromous and nonanadromous brown trout (Salmo trutta). *Can J Fish Aquat Sci* 54:1064-1066.
186. Takaichi S, Matsui K, Nakamura M, Muramatsu M, & Hanada S (2003) Fatty acids of astaxanthin esters in krill determined by mild mass spectrometry. *Comp Biochem Physiol B Biochem Mol Biol* 136(2):317-322.
187. Hipfner JM, Hobson KA, Dale J, & McGraw KJ (2010) Stable isotopes link diet to avian yolk carotenoid allocation: a comparative study of five auk species (Charadriiformes: Alcidae). *Physiol Biochem Zool* 83(3):481-489.
188. Maoka T (2011) Carotenoids in marine animals. *Mar Drugs* 9(2):278-293.
189. Sila A*, et al.* (2015) Ability of natural astaxanthin from shrimp by-products to attenuate liver oxidative stress in diabetic rats. *Pharmacol Rep* 67(2):310-316.
190. Andersson M, Van Nieuwerburgh L, & Snoeijs P (2003) Pigment transfer from phytoplankton to zooplankton with emphasis on astaxanthin production in the Baltic Sea food web. *Marine Ecology Progress Series* 254:213-224.
191. Li Y, Sommerfeld M, Chen F, & Hu Q (2008) Consumption of oxygen by astaxanthin biosynthesis: a protective mechanism against oxidative stress in Haematococcus pluvialis (Chlorophyceae). *J Plant Physiol* 165(17):1783-1797.
192. Breitenbach J, Visser H, Verdoes JC, van Ooyen AJ, & Sandmann G (2010) Engineering of geranylgeranyl pyrophosphate synthase levels and physiological conditions for enhanced carotenoid and astaxanthin synthesis in Xanthophyllomyces dendrorhous. *Biotechnol Lett* 33(4):755-761.
193. Lemoine Y & Schoefs B (2010) Secondary ketocarotenoid astaxanthin biosynthesis in algae: a multifunctional response to stress. *Photosynth Res* 106(1-2):155-177.
194. Nagaki Y*, et al.* (2002) Effects of astaxanthin on accommodation, critical flicker fusion, and pattern visual evoked potential in visual display terminal workers. *J Trad Med* 19:170-173.
195. Sawaki K*, et al.* (2002) Effect on visual function and muscle fatigue recovery in athletes. *J Clin Ther and Med* 18:1085-1099.

196. Nakamura A*, et al.* (2004) Change in visual function from astaxanthin. *Jpn J Clin Ophthalmol* 58:1051-1054.
197. Nitta T*, et al.* (2005) Effects of astaxanthin on accommodation and asthenopia - dose finding study in healthy volunteers. *J Clin Ther and Med* 21:543-556.
198. Shiratori K*, et al.* (2005) Effects of astaxanthin on accommodation and asthenopia - efficacy identification study in healthy volunteers. *J Clin Ther and Med* 21:637-650.
199. Miyawaki H, Takahashi J, Tsukahara H, & Takehara I (2008) Effects of astaxanthin on human blood rheology. *J Clin Biochem Nutr* 43(2):69-74.
200. Osterlie M, Bjerkeng B, & Liaaen-Jensen S (2000) Plasma appearance and distribution of astaxanthin E/Z and R/S isomers in plasma lipoproteins of men after single dose administration of astaxanthin. *J Nutr Biochem* 11(10):482-490.
201. Rufer CE, Moeseneder J, Briviba K, Rechkemmer G, & Bub A (2008) Bioavailability of astaxanthin stereoisomers from wild (Oncorhynchus spp.) and aquacultured (Salmo salar) salmon in healthy men: a randomised, double-blind study. *Br J Nutr* 99(5):1048-1054.
202. Naguib YM (2000) Antioxidant activities of astaxanthin and related carotenoids. *J Agric Food Chem* 48(4):1150-1154.
203. Choi HD, Kim JH, Chang MJ, Kyu-Youn Y, & Shin WG (2011) Effects of astaxanthin on oxidative stress in overweight and obese adults. *Phytother Res* 25(12):1813-1818.
204. Yuan JP, Peng J, Yin K, & Wang JH (2011) Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. . *Mol Nutr Food Res* 55(1):150-165.
205. Pashkow FJ, Watumull DG, & Campbell CL (2008) Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. *Am J Cardiol* 101(10A):58D-68D.
206. Santocono M, Zurria M, Berrettini M, Fedeli D, & Falcioni G (2007) Lutein, zeaxanthin and astaxanthin protect against DNA damage in SK-N-SH human neuroblastoma cells induced by reactive nitrogen species. *J Photochem Photobiol B* 88(1):1-10.
207. Maoka T & Etoh H (2015) Biological Antioxidation Mechanisms: Quenching of Peroxynitrite. *Functional Food Ingredients and Nutraceuticals: Processing Technologies*, ed Shi J (Taylor & Francis Group, LLC, Boca Raton), 2nd Edition Ed, pp 589-608.
208. Grimmig B, Kim SH, Nash K, Bickford PC, & Douglas Shytle R (2017) Neuroprotective mechanisms of astaxanthin: a potential therapeutic role in preserving cognitive function in age and neurodegeneration. *Geroscience* 39(1):19-32.
209. Fassett RG & Coombes JS (2012) Astaxanthin in cardiovascular health and disease. *Molecules* 17(2):2030-2048.
210. Visioli F & Artaria C (2017) Astaxanthin in cardiovascular health and disease: mechanisms of action, therapeutic merits, and knowledge gaps. *Food Funct* 8(1):39-63.

211. Park JS, Chyun JH, Kim YK, Line LL, & Chew BP (2010) Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. *Nutr Metab (Lond)* 7:18.
212. Andersen LP*, et al.* (2007) Gastric inflammatory markers and interleukins in patients with functional dyspepsia treated with astaxanthin. *FEMS Immunol Med Microbiol* 50(2):244-248.
213. Riccioni G, D'Orazio N, Franceschelli S, & Speranza L (2011) Marine carotenoids and cardiovascular risk markers. *Mar Drugs* 9(7):1166-1175.