Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Astaxanthin

Evidence Summary

Astaxanthin is an antioxidant derived from marine algae. Short trials suggest it may boost antioxidant capacity and improve memory but the reliability and strength of these benefits is not yet clear.

Neuroprotective Benefit: Numerous preclinical studies have shown antioxidative and anti-inflammatory effects, but cognitive benefits in humans have been modest and inconsistent.

Aging and related health concerns: Several small, short clinical trials suggest astaxanthin may boost anti-oxidative capacity (although one did not) and lower LDL cholesterol. Astaxanthin increases longevity in worms and flies and, in laboratory studies, has potential to benefit many age-related diseases, including atherosclerosis, hypertension, cancer and diabetes.

Safety: Astaxanthin is considered GRAS and that multiple short trials report few if any adverse events. However, existing safety data is for short-term use only and supplemental astaxanthin use has not been tested above 20 mg daily for more than 12 weeks.

Availability: OTC as well as in diet (salmon, lobster)	**Dose**: clinical trials typically used 20 mg/day	**Chemical formula:** $C_{40}H_{52}O_4$ **MW**: 596.841
Half-life: plasma elimination half-life of 52 hr	**BBB**: penetrant	
Clinical trials: largest double-blind controlled trial included 96 older adults	**Observational studies**: none	

What is it? Astaxanthin is a xanthophyll carotenoid found in marine algae and the animals that eat marine algae, such as salmon and lobster. The primary source of commercially available astaxanthin is the algae *Haematococcus pluvialis.* It is a GRAS compound marketed mostly as an antioxidant, a claim supported by several small clinical trials and a large body of preclinical evidence. Astaxanthin is sold in many different formulations by many different sources, although there is little evidence to suggest one formulation is better than another.

Neuroprotective Benefit: Numerous preclinical studies have shown antioxidative and anti-inflammatory effects, but cognitive benefits in humans have been modest and inconsistent.

Types of evidence:

- No meta-analyses
- 3 clinical trials
- No observational studies
- Numerous preclinical studies

Human research to suggest prevention of dementia and cognitive aging: One small exploratory clinical trial tested 2 mg astaxanthin daily in 104 patients with mild cognitive impairment (MCI) for 2 months in combination with other treatments including *Bacopa*, phosphatidylserine and vitamin E. While the majority of patients in the study reported benefits and improved on the ADAS-Cog scale, the trial had no comparison arm. It is also not possible to ascribe any benefits solely to astaxanthin (Bonoldi et al, 2014).

Human research to suggest benefits to patients with dementia or cognitive aging: One small, uncontrolled trial tested 12 mg astaxanthin daily in 10 older adults with subjective memory complaints

for 12 weeks (Satoh et al, 2009). Modest improvements were measured in reaction time, working memory and delayed recall. Given the small number of subjects these results should be taken with a grain of salt until validated by a larger, placebo-controlled study.

In a phase II double-blind randomized controlled trial of 96 older people with forgetfulness, supplementation with an astaxantion-rich *Haematococcus pluvialis* (algae) extract (6 or 12 mg of astaxanthin/day) for 12 weeks improved memory compared to baseline, but not compared to the placebo control group (Katagiri et al., 2012). The authors attributed the lack of statistically significant differences between groups to the small sample size and the average age being too young such that cognitive impairment was limited.

In a double-blind randomized controlled trial of 21 people with mild cognitive impairment, supplementation with astaxanthin (6 mg/day, derived from *Haematococcus pluvialis*) and sesamin (10 mg/day, derived from *Sesamum indicum*) for 12 weeks did not produce statistically significant improvement in the raw values of cognitive tests compared to the placebo group (Ito N et al., 2018). And no differences were observed between the placebo and treatment groups on the ADAS-cog test. However, the individuals in the astaxanthin-sesamin group showed a significantly greater amount of change between the baseline and 12 weeks in measures of psychomotor speed and processing speed, compared with individuals in the placebo group. They used the Japanese version of the Central Nervous System Vital Signs (CNSVS) test at baseline, after 6 weeks, and after 12 weeks of supplementation. CNSVS evaluates 11 neuropsychological domains (composite memory, verbal memory, visual memory, processing speed, psychomotor speed, executive function, reaction time, complex attention, simple attention, cognitive flexibility, and motor speed) using 7 measures: verbal and visual memory tests, the finger tapping test, the symbol digit coding (SDC) test, the Stroop test, the shifting attention test, and the continuous performance test. Although their data suggests that daily supplementation of astaxanthin-sesamin improved cognitive functions related to the ability to comprehend and perform complex tasks quickly and accurately, the study was small and some of the findings may have been due to chance because of the number of cognitive measures tested.

In a double-blind randomized controlled trial of 54 middle-aged adults (aged 45-64), astaxanthin supplementation (8 mg/day) for 8 weeks did not result in significant improvement in cognitive functions when compared to the placebo group (Hayashi M et al., 2018). They performed a subgroup analysis and in people under 55 years old, astaxanthin treatment significantly improved "words recalled after 5 minutes" in the word memory test when compared with the placebo group. This effect was not seen in

subjects over 55 years old. It is unclear why astaxanthin could be more beneficial in people under 55 years old.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: Two rodent studies report improved memory and cognition after astaxanthin treatment: 1.3 mg/kg/day for 30 days improved memory in wild-type mice (Zhang et al, 2007) while 6 months of a high-fat diet combined with 600 mg/kg (as well as supplemental vitamins C and E) prevented cognitive deficits in rats (Komaki et al, 2015).

Astaxanthin's two primary mechanisms of action appear to be anti-inflammatory and antioxidative. Several studies in rodent models report lower peripheral and neuroinflammation after astaxanthin treatment (Zhang et al, 2014; Zhou et al, 2015; Balietti et al, 2015), possibly by down-regulating TNF-⍰ (Zhou et al, 2015).

Other studies point to astaxanthin's antioxidative properties. Treatment reduced oxidative damage and rescued neurons in a rat epilepsy model (Lu et al, 2015) and increased systemic antioxidant capacity in hamsters fed a high-cholesterol diet (Chen et al, 2015). Cellular experiments suggest astaxanthin protects mitochondria from oxidative damage (Wolf et al, 2010), possibly by suppressing production of reactive oxygen species (Chang et al, 2010) or modulating Nrf-2 signaling (Saw et al, 2013).

Astaxanthin was also shown to protect cultured neurons from glutamate toxicity (part of the Alzheimer's disease process) (Wen et al, 2015) as well as prevent neuronal loss and brain damage in a rodent model of ischemia (Hussein et al, 2005).

Chemobrain: In a rat model of chemobrain (induced by doxorubicin), astaxanthin treatment (25 mg/kg) restored the architecture of the hippocampus while halting oxidative and inflammatory insults (El-Agamy SE et al., 2017). Astaxanthin also mitigated the increase in acetylcholinesterase (enzyme that breaks down the neurotransmitter acetylcholine) activity and downregulated apoptotic machineries.

TBI: In a mouse model of traumatic brain injury, astaxanthin treatment (25 or 75 mg/kg, oral gavage) for 28 days improved sensorimotor performance on the Neurological Severity Score (NSS) and the rotarod test while also enhancing cognitive function recovery (measured by the object recognition test and the Y-maze test)(Ji X et al., 2017). Moreover, astaxanthin treatment reduced the lesion size and neuronal loss in the cortex compared with the vehicle-treated TBI group. Astaxanthin also restored levels of the neurotrophic factor BDNF, the growth-associated protein-43 (GAP-43), and synaptic proteins synapsin,

and synaptophysin in the cerebral cortex, which together suggest improved neuronal survival and plasticity. Although the astaxanthin treatment almost completely restored object recognition and Y-maze measures, the lesion volume was only reduced by ~30%, and cell density was restored just slightly (mean values were closer to TBI+vehicle group than to the sham control group).

Ischemia: In a mouse model of repeated cerebral ischemia/reperfusion, astaxanthin treatment (10 mg/kg/day, intragastric) starting 1 hour after surgery and for 28 consecutive days ameliorated learning and memory deficits (Xue Y et al., 2017). Astaxanthin treatment also rescued the number of surviving pyramidal neurons in the hippocampus. Lipid peroxidation (concentration of malondialdehyde) was decreased, and antioxidative capacity (levels of reduced glutathione and superoxide dismutase) in the hippocampus were increased. Electron microscopy revealed that damage to the ultrastructure of neurons was also reduced with treatment. In addition, the expression levels of pro-apoptotic proteins (Cytochrome C, cleaved Caspase-3, and Bax) were lower and the expression of the anti-apoptotic Bcl-2 was higher compared to control mice. Based on these results, astaxanthin appeared to prevent learning and memory impairment by attenuation of oxidative stress.

Type 2 diabetes-associated cognitive decline: In a rat model of type 2 diabetes (induced by streptozotocin), astaxanthin (50 or 100 mg/kg) reduced blood glucose levels and significantly improved cognitive function (Li X et al., 2016). Treatment with astaxanthin activated the PI3K/Akt pathway and also suppressed oxidative stress. Pro-apoptotic and pro-inflammatory activities (e.g., iNOS, caspase-3 and caspase-9) were markedly reduced in the cortex and hippocampus with treatment.
APOE4 interactions: There is no evidence to suggest astaxanthin affects *APOE4* carriers differently than non-carriers.

Aging and related health concerns: Several small, short clinical trials suggest astaxanthin may boost anti-oxidative capacity (although one did not) and lower LDL cholesterol. Astaxanthin increases longevity in worms and flies and, in laboratory studies, has potential to benefit many age-related diseases, including atherosclerosis, hypertension, cancer and diabetes.

Types of evidence:

- No meta-analyses
- 6 small clinical trials/studies on oxidative stress and lowering LDL
- No observational studies
- Multiple preclinical studies, including 3 on lifespan in flies and worms

No clinical guidelines for astaxanthin use have been issued by any expert organization.

Several small, short clinical trials tested astaxanthin's ability to boost systemic anti-oxidative capacity in obese adults. Treatment with 20 mg daily astaxanthin given to 23 obese adults for 3 weeks boosted key blood markers of anti-oxidative capacity, including superoxide dismutase (Choi et al, 2011a). A study (for which the full text was not accessible) of elite soccer players reported that astaxanthin treatment (of unknown dose) for 90 days boosted anti-oxidative capacity (Djordjevic et al, 2012), although a similar study in elite cyclists treated with 20 mg daily for 4 weeks did not show similar benefits (Res et al, 2013). It could be that the obese subjects had an initial deficit in anti-oxidative capacity and were therefore easier subjects than elite athletes in which to show benefits.

Two trials report positive effects on cholesterol. In one trial 27 obese adults treated with 20 mg daily astaxanthin for 12 weeks reported lower LDL levels (Choi et al, 2011b). A different trial treated 61 mildly hyperlipidemic adults with up to 18 mg daily for 12 weeks and reported significantly lower triglycerides and increased HDL (Yoshida et al, 2010). These trials were well-conducted and hint that astaxanthin may be useful in managing hyperlipidemia but need to be validated by larger and longer trials.

Three preclinical studies demonstrated that astaxanthin treatment from birth increased lifespan in flies (Huangfu et al, 2013) and worms (Yazaki et al, 2011; Kashima et al, 2012).

Although clinical evidence is lacking, multiple preclinical studies suggest that astaxanthin may benefit many age-related diseases, including cancer, hypertension, cardiovascular disease, diabetes (reviewed by Fassett et al, 2012 and Zhang et al, 2015). One small clinical study reported inhibition of LDL oxidation in human subjects after consuming astaxanthin, suggesting it may be beneficial in preventing atherosclerosis (Iwamoto et al, 2000).

Fatigue: POTENTIAL BENEFIT. In a double-blind randomized controlled trial of 24 healthy volunteers, a combination treatment of astaxanthin (6 mg/day) and sesamin (10 mg/day) for 4 weeks was associated with significantly improved recovery from mental fatigue compared with placebo, though no treatment effect was observed during the mental tasks (a significant difference between groups was only observed after the mental task) (Imai A et al., 2018). Increased oxidative stress (measured by plasma phosphatidylcholine hydroperoxide levels) during mental and physical tasks was attenuated by astaxanthin-sesamin supplementation. No differences between astaxanthin-sesamin and placebo groups were detected in secondary outcomes, which included subjective measures such as work efficiency.

Sleep: INCONCLUSIVE. In a double-blind randomized controlled trial, 120 healthy subjects were divided into 4 groups: placebo, zinc-rich food, zinc-, and astaxanthin-rich food, and placebo supplemented with zinc-enriched yeast and astaxanthin oil (Saito H et al., 2017). Compared with the placebo group, the zinc-rich food group (oyster 40 g/day) efficiently decreased the time necessary to fall asleep and improved sleep efficiency, whereas the group that ingested zinc-enriched yeast and astaxanthin oil (scallop 40 g + zinc 15 mg + astaxanthin 3 mg) had significantly improved sleep onset latency. The authors initially speculated that ingesting astaxanthin and zinc-rich food together would allow astaxanthin to promote zinc absorption, but they were unable to confirm a difference in the rate of absorption with astaxanthin.

Safety: These ratings reflect the fact that astaxanthin is considered GRAS and that multiple short trials report few if any adverse events. However, existing safety data is for short-term use only and supplemental astaxanthin use has not been tested above 20 mg daily for more than 12 weeks.

Types of evidence:

- 4 short, small clinical trials
- FDA GRAS designation

Although evidence for long-term safety is lacking, safety of oral astaxanthin for up to 12 weeks is supported by small clinical trials that reported no serious safety issues (Choi et al, 2011a; Choi et al, 2011b; Res et al, 2013). One trial used 40 mg daily for 4 weeks when testing astaxanthin for treatment of male infertility and also reported no serious safety issues (Comhaire et al, 2005). Additionally, WebMD lists no serious side effects for short-term use. There is no information about potential drug interactions, most likely because the detailed studies have not been done. Both WebMD and Natural Standard list astaxanthin as "possibly safe" for short-term use. The astaxanthin found in salmon, lobsters and other marine life is most likely safe, based on widespread consumption.

Because of a lack of evidence, astaxanthin supplementation should be avoided by women who are pregnant or breastfeeding.

In a 2018 double-blind randomized controlled trial of 21 patients with mild cognitive impairment, no differences were observed in the frequency of adverse events between the astaxanthin-sesamin versus placebo groups. No adverse events were observed related to the ingestion of astaxanthin-sesamin supplement. Although some changes were seen in blood chemistry and hematology, all of these changes

were small and within normal values. The responsible doctor confirmed that the changes in values did not represent a safety concern. (Ito N et al., 2018).

In a different 2018 double-blind randomized controlled trial of 54 middle-aged adults (aged 45-64), astaxanthin supplementation (8 mg/day) for 8 weeks was not associated with any problems related to safety (Hayashi M et al., 2018). One subject reported a rash and another subject developed mild acne (9 occasions), but both adverse events were judged to be "unrelated" to the supplement. Other adverse events were also judged to be "unrelated" to the supplement. None of the changes in blood and urine measures were considered clinically significant.

In yet another 2018 double-blind randomized controlled trial of 24 healthy volunteers, a combination treatment of astaxanthin (6 mg/day) and sesamin (10 mg/day) for 4 weeks did not result in any adverse effects (Imai A et al., 2018).

Sources and dosing: Astaxanthin is found in many different types of seafood, including salmon and lobster, and is also widely available in many different formulations as a nutritional supplement. It is estimated that 6 oz of salmon contains ~ 3.6 mg astaxanthin. Clinical trials on astaxanthin supplementation often use around 20 mg per day but they have ranged from 2 mg to 40 mg per day.

There is no evidence that one formulation or source of astaxanthin is more beneficial or bioavailable than another, although a currently recruiting clinical trial is aiming to answer this question (see next section).

Research underway: One trial has compared the bioavailability of 6 different astaxanthin formulations (NCT02397811), though the results have not been published. A different clinical trial is currently recruiting patients to test the bioavailability of 3 different formulations of astaxanthin in healthy volunteers (NCT03443882). This study is scheduled to be completed in May 2018.

Other clinical trials are testing astaxanthin for different clinical indications. A trial is testing astaxanthin treatment (6 mg per day) for 12 weeks in patients with moderate to high untreated triglyceridemia (NCT02343497). A phase 1 double-blind randomized controlled trial is currently testing astaxanthin supplementation in patients with insulin resistance (NCT03310359). This study was scheduled to be completed in April 2018. A double-blind randomized controlled trial is testing an oral supplement containing astaxanthin (2 mg), lycopene (1.9 mg), and D-alpha-tocopherol (10 IU) for treating skin aging (NCT03460860). Outcomes include skin wrinkling measured by a Crow's Feet Wrinkle scale, skin

hydration measured by a corneometer, and pigmentation measured by a mexameter. This study is scheduled to be completed in August 2018.

The current evidence, particularly for safety of supplement use, could be greatly strengthened by a long-duration trial, since most trials have lasted for 3 months or less. Future trials in patients with dementia would benefit from using only astaxanthin (i.e. not in combination with other nutritional supplements) and by using double-blind, placebo-controlled designs.

Search terms:

Pubmed: astaxanthin + following terms with and without filters for "clinical trial", "meta-analysis", and "review"

- Alzheimer's disease
- Neurodegeneration
- Dementia
- Cognition
- Cognitive decline
- Aging
- Longevity
- Lifespan
- Telomere
- Telomerase
- Diabetes
- Lipids
- Cholesterol
- Hypertension
- Blood Pressure
- Toxicology
- Safety

Clinicaltrials.gov and clinicaltrialsregister.eu

- astaxanthin

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