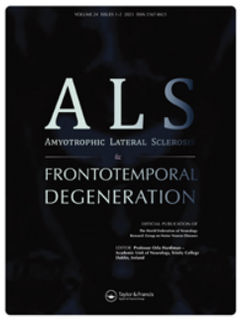

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SHORT REPORT

ALSUntangled # 69: astaxanthin

TIMOTHY FULLAM[1], CARMEL ARMON[2], PAUL BARKHAUS[3], BENJAMIN BARNES[4], MORGAN BEAUCHAMP[5], MICHAEL BENATAR[6], TULIO BERTORINI[7], ROBERT BOWSER[8], MARK BROMBERG[9], JAVIER MASCIAS CADAVID[10], GREGORY T. CARTER[11], MAZEN DIMACHKIE[12], DAVE ENNIST[13], EVA L. FELDMAN[14], TERRY HEIMAN-PATTERSON[15], SARTAJ JHOOTY[16], ISAAC LUND[17], CHRISTOPHER MCDERMOTT[18], GARY PATTEE[19], DYLAN RATNER[20], PAUL WICKS[21] & RICHARD BEDLACK[22]

[1]Department of Neurology, UTSA, San Antonio, TX, USA, [2]Department of Neurology, Loma Linda University, Loma Linda, CA, USA, [3]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA, [4]Department of Neurology, Medical College of Georgia, Augusta, GA, USA, [5]Neurosciences Clinical Trials Unit, UNC Chapel Hill, NC, USA, [6]Department of Neurology, University of Miami, Miami, FL, USA, [7]Neurology Department, University of Tennessee Health Science Center, Memphis, TN, USA, [8]Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA, [9]Department of Neurology, University of Utah, Salt Lake City, UT, USA, [10]ALS Department, Hospital Carlos III-La Paz, Madrid, Spain, [11]Department of Rehabilitation, Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA, [12]Department of Neurology, University of Kansas, Kansas City, KS, USA, [13]Origent Data Sciences, Inc, Vienna, VA, USA, [14]Department of Neurology, University of Michigan, Ann Arbor, MI, USA, [15]Department of Neurology, Temple Health, Philadelphia, PA, USA, [16]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [17]Green Hope High School, Cary, NC, USA, [18]Department of Neuroscience, University of Sheffield, Sheffield, UK, [19]Department of Neurology, University of Nebraska Medical Center, Omaha, NE, USA, [20]Tulane University, New Orleans, LA, USA, [21]Independent Consultant, Lichfield, UK, and [22]Department of Neurology, Duke University, Durham, NC, USA

Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review astaxanthin which has plausible mechanisms for slowing ALS progression including antioxidant, anti-inflammatory, and anti-apoptotic effects. While there are no ALS-specific pre-clinical studies, one verified "ALS reversal" occurred in a person using a combination of alternative therapies which included astaxanthin. There have been no trials of astaxanthin in people living with ALS. Natural astaxanthin appears to be safe and inexpensive. Based on the above information, we support further pre-clinical and/or clinical trials of astaxanthin in disease models and PALS, respectively, to further elucidate efficacy.

Keywords: *Amyotrophic lateral sclerosis, astaxanthin, oxidative stress, neurodegeneration, alternative therapy*

Overview

Astaxanthin is a red-orange natural pigment belonging to a group of carotenoids called xanthophylls (1–4). In nature, astaxanthin is synthesized by microalgae and phytoplankton and biomagnifies in higher marine animals through the food chain. *Haematococcus pluvialis (H. pluvialis)* produces the largest quantity of natural astaxanthin; however cheaper synthetic production is the predominant source of astaxanthin used for animal feeds. Synthetic astaxanthin comprises a different mixture of isomers as compared to the natural compound and may show only 50% of the biological activity, in addition to potentially containing trace amounts of residual solvents and chemical reagents (5–7).

Correspondence: Richard Bedlack, Neurology Department, Duke University, 932 Morreene Rd, Durham, NC 27708-0187, USA. E-mail: bedla001@mc.duke.edu

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While astaxanthin has a similar molecular structure to β-carotene and other carotenoids, its central non-polar moiety contains 13 bonds versus 11 in β-carotene, which enhances the antioxidant effects of the molecule. In addition, astaxanthin has both lipophilic and hydrophilic properties allowing it to function both inside and outside of the cell and enhancing its ability to cross the blood brain barrier (3). These features allow astaxanthin to function as a more potent antioxidant, with some in vitro studies suggesting it is up to 10 times stronger compared to other carotenoids and 100–500 times stronger versus vitamin E (α-tocopherol) (8–11). Astaxanthin demonstrates antioxidant, anti-inflammatory, and anti-apoptotic properties in various *in vitro* and *in vivo* models and is widely available without a prescription in the form of capsules, soft gels, tablets, powders, creams, energy drinks, oils, and extracts (6).

Given the molecular properties and availability described above, this alternative treatment is of interest to people living with amyotrophic lateral sclerosis (PALS) with benefits being touted on at least 2 websites (e.g. https://tongyubio.com/astaxanthin-against-amyotrophic-lateral-sclerosis-als/, https://www.alswinners.com/supplements.html). These websites are not science-based. This review will focus on the science behind astaxanthin's possible role in treating ALS.

Mechanisms

Antioxidant effects

Biochemical evidence of oxidative stress has been demonstrated in both familial and sporadic ALS with downstream effects of protein misfolding and insoluble intracellular inclusions which can further augment oxidative stress by sequestering nuclear-genome-encoded mitochondrial proteins which further disrupt oxidative balance (12–14). The hydroxyl and keto groups on each of astaxanthin's ionone rings can neutralize free radicals, which contributes to astaxanthin's stronger antioxidant properties versus other carotenoids. The polyene chain in astaxanthin is long and traps radicals in the cell membrane, in addition to the antioxidant properties of the terminal rings, which scavenge radicals in both the inner and outer cell membranes (6,15). The hydrophilic terminal ionone rings and internal hydrophobic polyene moieties of astaxanthin can orient it across cell membranes; the internal hydrophobic polyene resides within the membrane, where it traps free radicals, whereas the terminal ionone rings can scavenge radicals at the membrane surface, either from the cytoplasmic or extracellular side.

Besides its direct antioxidant properties, astaxanthin activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway with downstream signaling through nuclear factor erythroid related factor 2 (Nrf2, 16–20). Nrf2 can upregulate various antioxidant proteins including heme-oxygenase 1, NAD(P)H quinone oxiodoreductase-1 (NQO-1), glutathione-S-transferase-α1, glutamate-cysteine ligase modifier subunit, glutamate-cysteine ligase catalytic subunit, and superoxide dismutase (SOD).

We found no studies of astaxanthin in ALS-specific cell or animal models. We did find evidence of astaxanthin's antioxidant-mediated neuroprotection in rat spinal motor neurons (14), and in pre-clinical models of stroke, subarachnoid hemorrhage, spinal cord injury, Alzheimer's, and Parkinson's diseases (20–23). As far as human studies demonstrating its antioxidant mechanisms, a randomized trial of 6 or 12 mg/d of astaxanthin in thirty middle aged and senior adults demonstrated lower levels of phospholipid hydroperoxides (PLOOH) in erythrocytes and plasma after 12 weeks of treatment (24). PLOOH have been shown to be biomarkers of lipid peroxidation and major drivers of ferroptosis, which potentially plays a key role in motor neuron degeneration in ALS (24,25)

Anti-inflammatory effects

Neuroinflammation, characterized by lymphocyte and macrophage infiltration, microglial activation, and abnormal complement activation, has been associated with ALS progression and is a current target of several experimental therapeutics (26). Astaxanthin has been associated with upregulated expression and downregulated phosporylation of IκB-α, both of which can decrease NF-κB signaling, ultimately lowering production of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. In addition, astaxanthin inhibits pro-inflammatory cyclooxygenase-1 activity and nitric oxide generation (27–29). While there are no trials of astaxanthin specifically addressing immune effects in PALS, in healthy volunteers or patients with gastric inflammation it did shift the inflammatory milieu from CD8 predominant T-lymphocytes to CD4 T-lymphocytes, improving mucosal immunity, and immune-enhancing effects. Astaxanthin dose ranges in these studies ranged from 2 mg/day to 40 mg/day (3,30–32).

Mitochondrial and anti-apoptotic effects

Endoplasmic reticulum stress and cytoplasmic misfolded protein accumulations contribute to mitochondrial dysfunction and initiate apoptotic signaling cascades, which are relevant pathways in ALS pathology (33). Astaxanthin improves mitochondrial integrity and decreased apoptotic signaling, however, the mechanism appears to be primarily driven by the anti-oxidative properties

discussed above (3,6,9,20,34); direct effects on mitochondria remain unclear. Astaxanthin has also been shown to protect against excitotoxicity and triggering of downstream apoptotic pathways through regulation of ionotropic glutamate receptors and buffering excess intracellular calcium and decreasing mitochondrial uptake of calcium (35).

Because astaxanthin therapy reduces markers of oxidative stress and inflammation in multiple human studies (24,30–32), ALSUntangled assigns a TOE "Mechanism" grade of A (Table 1).

Pre-clinical models

Astaxanthin has not been formally studied in any accepted in vitro or animal models of ALS. Therefore, ALSUntangled assigns a TOE "Pre-clinical models" grade of U (Table 1).

Data in PALS

Cases

In the online community PatientsLikeMe, three members report using astaxanthin as a potential treatment for ALS or progressive muscular atrophy (PMA). There is, however, no documentation of response to therapy, positive or negative (36). Google search identified the website of a single individual, who reports that his ALS reversed on a regimen which included natural astaxanthin (4mg daily) and other vitamin/mineral supplements, hyperbaric oxygen therapy, ozone therapy, detox, special diets, and attitude changes (37). His ALS diagnosis and his recovery of lost motor function were previously independently verified by our group (38,39). However, associations like this do not prove causality; there may be multiple other explanations this person's improvements besides a benefit from astaxanthin. Based upon these cases, we assign a TOE 'Cases' grade of C (Table 1).

Table 1. Table of evidence for astaxanthin.

	Grade	Explanation
Mechanism	A	Shown in peer-reviewed publications to act on relevant mechanisms of antioxidant and anti-inflammatory pathways in middle aged and elderly adults.
Pre-Clinical	U	No studies in pre-clinical models of ALS.
Cases	C	One unpublished case report with validated diagnosis and improvements (though astaxanthin was part of many treatments used)
Trials	U	Astaxanthin therapy has not been studied in ALS trials
Risks	B	No exposed patients appear to have experienced serious adverse events related to natural astaxanthin; less than 1% of exposed patients experienced non-serious gastrointestinal adverse events (ex. abdominal pain, reddish stool discoloration) at doses up to 12 mg/day.

Trials

Astaxanthin therapy has not been evaluated in an ALS clinical trial. Therefore, ALSUntangled assigns a TOE 'Trials' grade of U (Table 1). Of potential interest, there are human clinical trials in middle aged and healthy adults assessing the effects of astaxanthin on various domains of cognitive function (40,41).

Dosing, risks, and costs

Astaxanthin exists as both natural and synthetic forms which differ in the proportion of specific stereoisomers and biologic activity. Synthetic astaxanthin is up to 50% less biologically active compared to the natural form (5–7). Safety concerns have arisen with synthetic astaxanthin due to trace amounts of residual reagents or solvents. Prior animal studies of synthetic astaxanthin found no evidence of tumorigenic effects, non-genotoxic, or genotoxic effects in mice. However, rat studies found evidence of hepatocellular vacuolation and an increase in hepatocellular adenomas at doses of 200 mg/kg body weight/day and above (42). No other studies have found any association of synthetic astaxanthin with liver or other organ injury and, therefore, these effects may be species specific and not relevant to human consumption. However, until natural astaxanthin has been established in human trials to show potential health benefits, synthetic astaxanthin should be considered unique and not be used for human consumption (42,43).

Natural astaxanthin is available as capsules, soft gels, tablets, powders, biomass, creams, energy drinks, oils and extracts and often contains other carotenoids. The compound is available as a United States Pharmacopeia (USP) verified supplement which ensures federally recognized standards for quality and purity (https://www.quality-supplements.org/verified-products/verified-products-listings). Some authors recommend taking astaxanthin with omega-3 rich dietary fats such as chia, flaxseed, fish, walnuts, and almonds to increase bioavailability/absorption (6). No serious adverse events related to astaxanthin have been identified at any dose for any duration of time in at least 87 human clinical trials involving over 2,000 participants (reviewed in 43). Adverse events of any kind were very rare (less than 1% of all exposed patients) and were gastrointestinal in nature (ex. stomach/abdominal pain, reddish stool discoloration). While average dose ranges were 8–12 mg, short-term doses up to 100mg have also been used. Specific dosing for ALS has not been

identified, however, human clinical trials targeting cognitive function and dementia used doses ranging from 6–12 mg/day (24,40,41) Based on the safety record on daily doses at least up to 12 mg/day, we assign a TOE "Risks" grade of B.

A month's supply of oral, natural astaxanthin tablets at 8 to 12mg/day will cost between $6 to $12 per month depending on brand selected (44).

Conclusion

In conclusion, there are theoretical mechanisms supporting a potential role of astaxanthin in the treatment of ALS, however, there are no ALS-specific pre-clinical data exploring this treatment. One verified "ALS reversal" occurred while taking astaxanthin in the setting of a cocktail of various other therapies—an association that does not prove causality. There have been no clinical trials of astaxanthin in PALS. Natural astaxanthin appears to be generally safe and is inexpensive. We believe there is a need for further pre-clinical and/or clinical trials of natural astaxanthin in disease models and PALS, respectively, to further elucidate efficacy.

Declaration of interest

Timothy Fullam reports no conflicts of interest. Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from AB Science, Alexion, ALSA, Amylyx, Biogen, Black Swan, Brainstorm Cell, Corcept, Cytokinetics, GenieUs, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, Shinkei, and Woolsey Pharma.

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ORCID

Michael Benatar http://orcid.org/0000-0003-4241-5135
Robert Bowser http://orcid.org/0000-0001-5404-7259
Christopher Mcdermott http://orcid.org/0000-0002-1269-9053
Paul Wicks http://orcid.org/0000-0002-2293-9284

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