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Research Article

Astaxanthin Supplementation Reduces Depression and Fatigue in Healthy Subjects

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Abstract

Objective: Natural Astaxanthin from *Haematococcus pluvialis* microalgae (NAX) has been researched in hundreds of clinical trials, pre-clinical animal studies and *in-vitro* surveys for various bioactive properties that indicate potential preventive and therapeutic health benefits. Among the most widely-researched properties of astaxanthin in the literature are broad-spectrum anti-inflammatory activity and powerful antioxidant capacity. In addition, both human and animal research have revealed a wide range of potential benefits for neurological and eye health, cardiovascular function, exercise endurance, enhancement of the immune response and skin health. This study's goal was to explore the effects of a daily dose of 12 mg per day of NAX on psychological mood state in healthy subjects.

Methods: This study employed placebo control and parallel design under double blind conditions. A total of 28 healthy subjects, half male and half female, with a median age of 42, supplemented with 12 mg per day of NAX or placebo. Before Day 0 and again at the end of the 8-week supplementation period, subjects completed a validated Profile of Mood States (POMS) survey to assess global mood state (GM) and related subscales: Vigor (V), Tension (T), Depression (D), Anger (A), Fatigue (F) and Confusion (C).

Results: Significant improvements were found in the NAX treatment group for positive mood state parameters: GM (+11%, $p < 0.05$) and V (+5%, NS); and negative mood state parameters: D (-57%, $p < 0.05$), F (-36%, $p < 0.05$), T (-20%, NS), A (-12%, NS), and C (-28%, NS).

Conclusions: While previous studies have shown NAX supplementation to improve parameters associated with brain health (neuro-inflammation and cognition), these data are the first to suggest that natural astaxanthin supplementation reduces negative mood state parameters (depression and fatigue) and improves global mood state and thus supports mental wellness.

Keywords: *Antioxidant; Astaxanthin; Carotenoid; Cardiovascular; Mood State; Mental Wellness*

Abbreviations

NAX: Natural Astaxanthin; POMS: Profile of Mood States; GM: Global Mood State; D: Depression; T: Tension; A: Anger; F: Fatigue; V: Vigor; C: Confusion; BW: Body Weight

Introduction

Natural astaxanthin (NAX) is a red carotenoid that provides characteristic color to pink flamingo feathers, red shrimp shells, and pink salmon flesh. The high level of NAX in these tissues is reflective of the animal's dietary intake of NAX from microalgae, copepods, krill, and other lower food chain organisms [1,2]. Astaxanthin is found in the human food chain in red-hued sea animals including crab, shrimp and lobster (in low quantities) and in the highest quantity in wild salmon [3-5]. NAX exists as one stereoisomeric form (3S,3'S) [2]. Other stereoisomeric forms of astaxanthin exist in yeast and bacteria as well as in astaxanthin produced synthetically from petrochemicals (SAX). The other forms found in these alternative sources are (3R,3'R), and (3R,3'S) (meso). Astaxanthin synthesized from petrochemicals is widely used in farmed fish such as salmon and trout. Synthetically produced astaxanthin contains all three stereoisomeric forms while wild salmon contains exclusively 3S,3'S [6]. NAX is found in nature in the highest concentration in *Haematococcus pluvialis* microalgae which is the source of the vast majority of astaxanthin consumed in supplement and functional food forms. NAX is widely accepted by regulatory bodies around the world as a human nutritional supplement and in functional foods. Other forms including SAX and forms from yeast and bacteria are generally not accepted by regulators or are accepted with restrictions due to lack of safety data and clinical research in humans. NAX contains small amounts of related carotenoids naturally occurring in the microalgae and is primarily esterified with fatty acid molecules attached at the end of the astaxanthin molecule. 3S,3'S stereoisomers comprise approximately 96% of the carotenoid fraction. The additional carotenoids found in NAX include zeaxanthin, lutein, canthaxanthin and beta-carotene. These chemical differences between forms of astaxanthin and the co-existence of other natural carotenoids may result in increased bioavailability and synergistic benefits for NAX as compared to SAX [7,8].

NAX has been studied for its antioxidant, anti-inflammatory, eye health benefits, cardioprotective properties, immune system modulatory activity and neuroprotective activities in humans [9-13]. Studies in rats and mice have indicated that NAX may reduce hypertension and increase blood flow [14,15]. The mechanisms proffered in this research were a modulatory effect on cellular stress pathways such as nitric oxide, nuclear factor E2 related factor 2 (Nrf2) and nuclear factor kB (NFkB) [16].

Astaxanthin has demonstrated wide-ranging benefits for athletes including improving endurance and performance, decreasing lactic acid levels after exercise and increasing fat oxidation/metabolism [17-27]. Dietary AX accumulates in muscle tissue in mammals. In muscles heavily worked during prolonged exercise, it prevents peroxidation of DNA and lipids and reduces muscle damage [17-19]. Furthermore, during exercise, AX may ameliorate fat oxidation. Mice supplemented with AX at 6 - 30 mg/kg BW over 4 - 5 weeks demonstrated increased fat utilization and longer treadmill running time/swimming time before exhaustion [19,20]. The mechanism for these effects was postulated as improvement in mitochondrial capacity of fatty acyl-CoA uptake through improvement of the function of carnitine palmitoyltransferase 1 (CPT1), which occurs due to astaxanthin's protective effect of the mitochondrial membrane from oxidative damage. Earlier research on NAX's effects in animal models demonstrated attenuation of exercise-induced damage to cardiac and skeletal muscle, along with improvement in fat oxidation, redox balance and time to exhaustion during exercise [17-22]. Several rodent studies supplemented NAX at 6 - 30 mg/kg which would translate to high dosages in humans [18-21]. Another rodent study employed a significantly lower dosage of 1 mg/kg and still found increased time to physical exhaustion and improvement in redox balance [23]. (Human trials have found positive results for a variety of health benefits at much lower dosages per kg BW than the rodent studies in the literature. The normal range in human clinical research has been 2 mg to 20 mg per day regardless of BW.) Many of astaxanthin's effects may be attributable to a hypothesized mitochondrial-centric mechanism, which could improve energy and redox cellular metabolism (e.g. via Nrf2-ARE pathway activation). Indeed, mitochondrial redox metabolism has been implicated in various neurological disorders including Alzheimer's, Parkinson's, and age-related dementia, so it is logical that NAX has been suggested to play a putative prophylactic role in cardiovascular as well as neurologic conditions [28-39].

Antioxidant status showed consistent improvement in human research on obese subjects leading a sedentary lifestyle [25,26] as well as in untrained men [27]. Athletes supplementing with NAX for 4 weeks experienced reduced lactic acid levels after running 1200 meters [22]. In a study on competitive cyclists, significant improvements in power output (15%) and improvement in cycling time trial (5% reduction over 20 km for an average 2 minute mean decrease) was found at a relatively low dosage of 4 mg per day over 4 weeks [24].

Material and Methods

Participants

Twenty-eight healthy, active, non-depressed adult subjects (14 men and 14 women) were supplemented with NAX for 8-weeks (age 42 ± 8, range 26 - 63 years; height 169 ± 10 cm; BW 69 ± 6 kg). An external ethics board reviewed informed consent forms which all subjects completed prior to commencement of the study.

Astaxanthin source

Using a double-blind method, the subjects were randomly separated into two pools. The treatment group received a NAX supplement (AstaZine® Natural Astaxanthin, BGG/AlgaeHealth Sciences) while the control group received identically-matching placebo (PL).

The NAX supplement contained an extract of *Haematococcus pluvialis* containing 12 mg of astaxanthin which was combined with medium chain triglyceride oil and a small amount of d-alpha tocopherol (10 IU) to maintain stability of the capsule formulation. Supplementation of NAX or PL continued by all subjects each day for the duration of the 8-week study period.

No adverse events related to ingestion of NAX or PL were reported.

Mood state assessment

Before and after the supplementation period, subjects completed a validated psychological mood state survey (POMS, Profile of Mood States) to assess Global Mood State and 6 related subscales; Vigor (V), Tension (T), Depression (D), Anger (A), Fatigue (F), and Confusion (C). The POMS survey is a self-administered 64-question assessment that takes approximately 20 minutes to complete and was collected before and after the 8-week supplementation period.

Data management and analysis

A database was employed in a central location to maintain participant data. Subject numbers were used to identify the data, with thorough examination for completeness and accuracy. JMP 8.0 (SAS Institute, Cary, NC) using standard parametric paired t tests was employed to analyze the tabulated data, with a 2-tailed alpha level set at 0.05 used to assess significance.

Results

Baseline characteristics for participants are presented in table 1. Significant improvements were found in NAX for positive mood state parameters (Figures 1 and 2): Global Mood (+11%, $p < 0.05$) and Vigor (+5%, NS); and negative mood state parameters: Depression (-57%, $p < 0.05$), Fatigue (-36%, $p < 0.05$), Confusion (-28%, NS), Tension (-20%, NS), and Anger (-12%, NS) indicating a beneficial psychological effect of NAX on overall mood and specifically in reducing depression and fatigue.

	NAX	PL
Height (cm)	169 (11)	168 (9)
Weight (kg)	70.0 (7.1)	69.3 (7.0)
Body Fat (%)	20.3 (6.3)	24.9 (8.4)

Table 1*: Baseline subject characteristics. Data represent average (Mean) values (±SD).*
Abbreviations: NAX: Natural Astaxanthin Group; PL: Placebo Group.

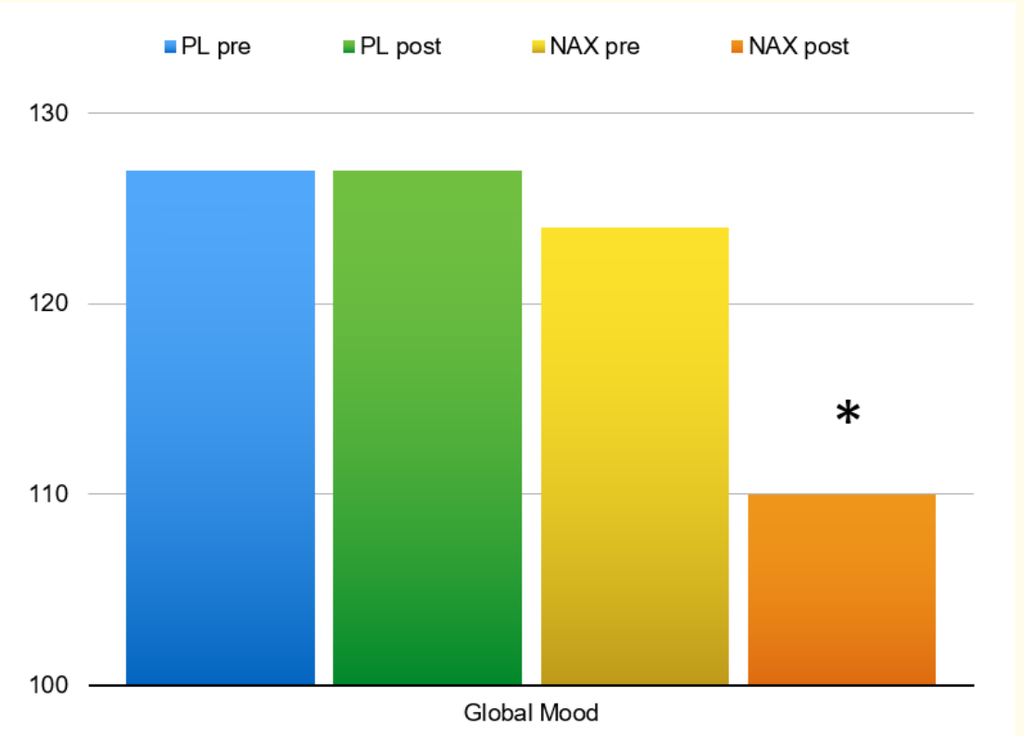

Figure 1: *Psychological Global Mood State at Baseline (pre-supplementation) and week 8 (post-supplementation). Improvements were found in NAX for Global Mood (-11%, NAX = 127+20 v. PL = 127+20; p < 0.05)* *Global Mood State = a lower score indicates a more positive psychological mood state. Abbreviations: NAX: Natural Astaxanthin Group; PL: Placebo Group.*

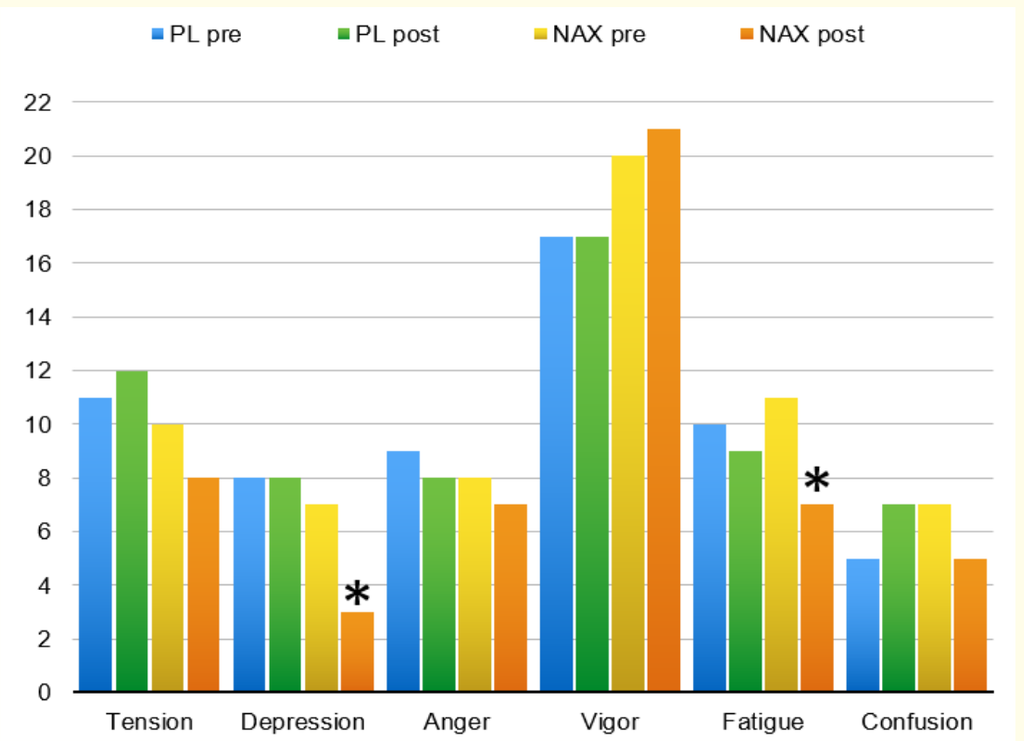

Figure 2: *Psychological Mood State Sub-Scales at Baseline (pre-supplementation) and week 8 (post-supplementation). Improvements were found in NAX for some mood state subscales: Tension (-20%, NS), *Depression (-57%, p < 0.05), Anger (-12%, NS), Vigor (+5%, NS), *Fatigue (-36%, p < 0.05), and Confusion (-28%, NS). Abbreviations: NAX: Natural Astaxanthin Group; PL: Placebo Group.*

Discussion

Jiang., *et al.* [28] recently demonstrated potential psychological effects of NAX, subsequent to serotonergic and anti-inflammatory effects, in an animal model of stress-induced depression. Other animal models suggest that NAX may be advantageous in neuroprotection due to its ability to locate inside the phospholipid membrane and at the membrane surface, as well as its facility in crossing the blood-brain barrier [28-31] leading to a wide range of potential psychological benefits including enhanced cognitive function [32,36,38], reduced depression [32], lower anxiety [34,35] and neuroprotection [38,39].

The heart is recognized to play a vital role not only as a circulatory pump, but as part of a psychophysiological network as a generator and transmitter of system-wide information throughout multiple body systems, including the nervous system [40-45]. Electrical input from the heart can dynamically influence homeostatic, cognitive, perceptual, and emotional processing in the brain, thus having the potential to affect myriad aspects of mood and behavior [40-43]. Thayer and Lane [40] reviewed the direct and indirect connections between the heart and the brain, including the physiological, behavioral, emotional, and cognitive processes involved in bi-directional control of cortical/cardiac function. Organ crosstalk between the brain/heart has been noted in stress-related cardiomyopathy syndromes and traumatic brain injury [41] including the use of heart rate variability (HRV) for its importance in gauging both the state of the heart (physical stress) as well as the state of the brain (psychological stress). Yoga, as an intervention to restore balance heart-brain crosstalk through plasticity and stability of the autonomic nervous system, has been used to reduce anxiety levels, atrial fibrillation episodes, blood pressure and neurocardiogenic syncope [42]. Studies have also shown that positive emotional states may improve function of both the cardiovascular and immune systems [44,45].

Human clinical research on astaxanthin's effects on brain health have shown some promising potential health benefits. In a trial on elderly subjects with age-related forgetfulness, improvement in age-related decline in cognitive and psychomotor function was found in the treatment group when supplementing with 12 mg per day of NAX over 12 weeks [46]. A subsequent study measured a marker for dementia, phospholipid hydroperoxides, which accumulate in the erythrocytes of dementia patients. The researchers tested 6mg of NAX and 12 mg of NAX against placebo over 12 weeks. At both dosages, NAX significantly reduced the levels of this dementia marker [47]. Lastly, a study testing for cognitive function of healthy elderly subjects who complained of age-related forgetfulness was done over 12 weeks. The subject pool was 96 people randomly assigned to take 6 mg of NAX, 12 mg of NAX or placebo. A variety of tests were done on these subjects including blood work, urine screens and assessments on two different cognitive tests called the Groton Maze Learning Test and CogHealth. Results in both the 6 mg and 12 mg treatment groups were significant, with slightly better results in the 12 mg group. The researchers concluded that NAX improves cognitive function in healthy aged subjects [48].

The current study found intriguing psychological mood state benefits of NAX supplementation. The results were in a different area of mental health as compared to the three clinical trials cited immediately above, which examined potential benefits for the brains of an aging population. The results in this present study may apply to a general population regardless of age. They indicate that people may feel better mentally by supplementing with NAX. Results leading to this hypothesis include a significantly higher overall mood (Global Mood State +11%, $p < 0.05$) and a significant reduction in Depression (-57%, $p < 0.05$) and Fatigue (-36, $p < 0.05$). This was the first study to demonstrate these results in a population of healthy human volunteers.

Conclusions

While previous studies have shown NAX supplementation to improve parameters associated with brain health (neuro-inflammation and cognition), these data are the first to suggest that natural astaxanthin supplementation reduces negative mood state parameters (depression and fatigue) and improves global mood state and thus supports mental wellness.

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Disclosure

This work was funded by Algae Health Sciences, a division of BGG. Talbott was principal investigator and reports no conflicts of interest in this work. Hantla reports no conflict of interest. Capelli is an employee of Algae Health Sciences, and Li, Ding and Artaria are employees of BGG, BGG North America and BGG Europe, which are companies involved in the production and distribution of NAX.

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