Revista Brasileira de Farmacognosia
Brazilian Journal of Pharmacognosy
21(2): 283-289, Mar./Apr. 2011

Putative benefits of microalgal astaxanthin on exercise and human health

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Abstract: Astaxanthin (ASTA) is a pinkish-orange carotenoid produced by microalgae, but also commonly found in shrimp, lobster and salmon, which accumulate ASTA from the aquatic food chain. Numerous studies have addressed the benefits of ASTA for human health, including the inhibition of LDL oxidation, UV-photoprotection and prophylaxis of bacterial stomach ulcers. ASTA is recognized as a powerful scavenger of reactive oxygen species (ROS), especially those involved in lipid peroxidation. Both aerobic and anaerobic exercise are closely related to overproduction of ROS in muscle tissue. Post-exercise inflammatory processes can even exacerbate the oxidative stress imposed by exercise. Thus, ASTA is suggested here as a putative nutritional alternative/coadjutant for antioxidant therapy to afford additional protection to muscle tissues against oxidative damage induced by exercise, as well as for an (overall) integrative redox re-balance and general human health.

Article

Received 22 Dec 2010
Accepted 20 Jan 2011
Available online 22 Apr 2011

Keywords:
algae
antioxidant
astaxanthin
carotenoid
exercise
oxidative stress

ISSN 0102-695X
doi: 10.1590/S0102-695X2011005000068

Biosynthesis and biological properties of astaxanthin

Carotenoids belong to a large class of compounds called terpenoids, which also includes steroids, retinol, calciol, and several secondary plant/algal metabolites. These compounds are all derived from polymerization of isoprene units through the mevalonate biosynthetic pathway (Miao et al., 2010). Carotenoids are highly conjugated polyene systems with vivid colors, interesting chemical behavior and key physiological and nutrition functions (Higuera-Ciapara et al., 2006).

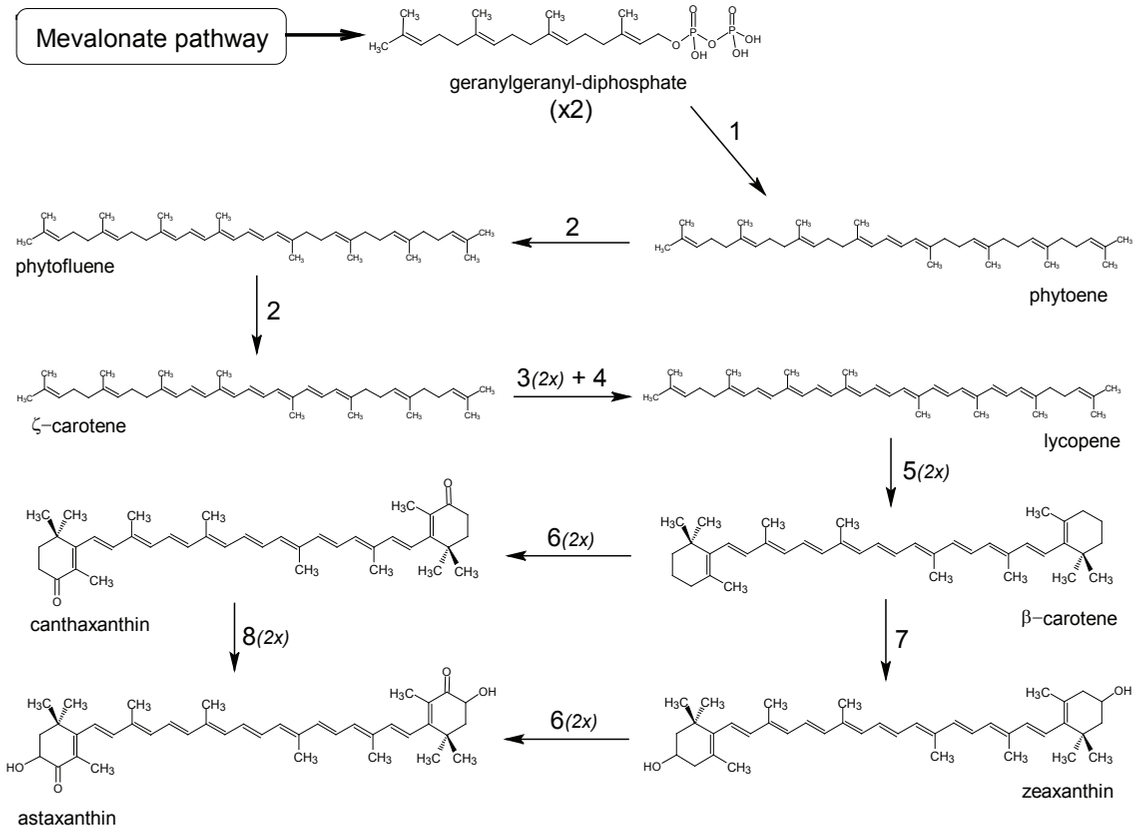
Carotenoids are widely distributed in both the plant and animal kingdoms and are ubiquitous in almost all living organisms. However, phytoplankton, bacteria, fungi, algae and plants are the only living organisms that produce carotenoids in significant quantities, whereas all other organisms obtain these pigments via their food chain. Astaxanthin (ASTA) is the most common carotenoid found in marine organisms and is particularly abundant in crustaceans and salmonid fishes (Christiansen et al., 1995). Some microalgal species like the freshwater alga *Haematococcus pluvialis* (Chlorophyceae) abundantly produce ASTA. In marine environments, ASTA is mainly produced by planktonic crustaceans such as copepods, but they are totally dependent on a constant supply of carbon backbone precursors - such as β-carotene and canthaxanthin - from algal food sources (Anderson et al., 2003). Scheme 1 depicts the major steps of ASTA biosynthesis in microalgal species.

The algal carotenoid ASTA is recognized as a powerful antioxidant both *in vitro* and *in vivo*, but is particularly efficient at scavenging peroxyl and alkoxyl radicals (ROO• and RO•, respectively) and quenching singlet oxygen [$O_2(^1\Delta_g)$] (Barros et al., 2001; Palozza & Krinsky, 1992). Recently, Polyakov et al. (2010) showed that ASTA and its mono- and dication forms can chelate Ca^{2+}, Zn^{2+}, and Fe^{2+} ions, although the lifetime of the radical ions formed electrochemically decreased in comparison to uncomplexed ASTA. Moreover, due to its spatial orientation perpendicular to the plane of lipid bilayers, ASTA increases the hydrophobicity in the central core of biological membranes, with several proposed biochemical/physiological consequences (Gabrielska & Gruszecki, 1996). It has been shown that the ASTA-induced rigidifying effect in membranes could provide a coadjutant mechanism for antioxidant protection, more precisely, by limiting the permeation of redox-active promoters of lipid oxidation such as Fe(II) ions and H_2O_2 (Barros et al., 2001). It is also noteworthy that, even at nanomolar concentrations, ASTA was able to rebalance the mitochondrial redox state by: i) sustaining a high mitochondrial membrane potential; ii) stimulating

the pH gradient; and iii) damping down the uncontrolled overproduction of reactive oxygen species (ROS), such as superoxide radical ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) (Wolf et al., 2010).

There is convincing scientific evidence in support of an inverse correlation between a healthy diet and the occurrence of chronic diseases. One of the most important paradigms of recommended dietary guidelines is the high consumption of fruits and vegetables, notably those that are natural sources of carotenoids. However, of the more than 600 carotenoids already characterized in nature, only twenty have been properly identified in human blood and tissues (Rao & Rao, 2007). The bioavailability of carotenoids in humans usually ranges from 10 to 50% of a given dose, due to their low solubility in gastrointestinal tract juices and poor absorption by the epithelial cells of the small intestine (Nagao, 2009). Stewart et al. (2008) suggested that the currently recommended doses of ASTA as a dietary supplement of 2-6 mg/day (0.07-0.1 mg/kg/day for an average individual weighing 60 kg) are ~800 fold lower than the no-observed-adverse-effect-level (NOAEL). The endogenous lipoproteins chylomicrons and VLDL - with a minor contribution from LDL - concentrate the major fractions of ASTA in the plasma after oral absorption (Odeberg et al., 2003). Petri & Lundebye (2007) showed that ASTA accumulates primarily in the spleen, kidneys, adrenals, skin, and eyes (> liver) of *Rattus norvegicus* rats after two weeks of oral administration. Interestingly, slight changes in the leucogram (especially of lymphocytes and neutrophils) were noted after seven days, but were restored after two weeks. Recent studies demonstrated that ASTA pharmacokinetic parameters were dose-dependent after its intravenous administration (5, 10 and 20 mg/kg), but dose-independent after higher oral administration, mainly due to the limited activity of hepatic cytochrome P-450, subclass 1A1/2 (Choi et al., 2010).

Regarding overall health properties, ASTA was proven to afford UV-photoprotection to skin/eyes (Cort et al., 2010), immune response enhancement (Bolin et al., 2010; Otton et al., 2010), protection against gastric ulcer induced by *Helicobacter pylori* (Kamath et al., 2008), and cardioprotective (Fassett & Coombes, 2009), antihypertensive (Hussein et al., 2006), and anti-tumorigenic effects in humans (Nakao et al., 2010). Recent findings have shown positive effects of ASTA in obese mice fed a high-fat diet by reducing total plasma cholesterol and plasma/liver triglyceride



Scheme 1. Biosynthetic pathway of astaxanthin in plants and microalgae. Enzymes: 1, phytoene synthase; 2, phytoene desaturase; 3, ζ-carotene desaturase; 4, carotene isomerase; 5, lycopene α-/β-cyclase; 6, β-carotene ketolase; 7, β-ring hydroxylase; 8, β-carotene 3',3-hydroxylase. Modified from Jin et al. (2003) and Cardozo et al. (2007).

levels (Ikeuchi et al., 2007). In a randomized, placebo-controlled human study of metabolic syndrome - a modern-life disease characterized by hypertension, impaired glucose tolerance, and dyslipidemia - ASTA consumption (12 and 18 mg/day; twelve weeks) efficiently restrained anomalous hyperlipidemia while HDL-cholesterol increased with 6 and 12 mg ASTA/day, in concert with measured levels of adiponectin (Yoshida et al., 2010).

The carotenoid ASTA has important applications in the nutraceutical, cosmetic, food and feed industries and, thus, has high economic value for biotechnology companies (Del Campo et al., 2007). Among the various ASTA-producing organisms present in nature, the green unicellular freshwater alga *H. pluvialis* is probably the source of ASTA most explored worldwide (Guerin et al., 2003). Adverse/stress growth conditions are imposed on *H. pluvialis* in order to exacerbate ASTA production in bioreactors, which can reach yields of ASTA (mono- and di-) esters of up to 98% of the total carotenoid content and around 4% of total dry cell weight (Jaime et al., 2010). Commercially grown *H. pluvialis* can accumulate more than 30g ASTA/kg of dry biomass (Li et al., 2010).

Exercise and oxidative stress

Moderate daily exercise is known to be beneficial to health, especially for reducing the risks of infections and of a large number of degenerative (age-related) disorders. Aerobic exercise is associated with a substantial increase in O_2 uptake by contractile muscles (up to 80-fold higher in oxygen volume), activation of oxidative mitochondrial metabolism and, thus, increased production of ROS (Powers et al., 2010). The biochemical mechanisms by which regular exercise exerts its beneficial effects are not fully understood. One of the most accepted theories refers to a retrograde response called mitohormesis: the constant but moderate increase in mitochondrial formation of ROS is chronically responded to by antioxidant adaptations that result in an upgraded stress resistance and ultimately limit the accumulation of oxidative damage within the intracellular environment. Hence, this mechanism should sustain longer periods of optimized mitochondrial function, described biochemically as a positive ATP-supply/oxidative damage ratio within cells (Ristow & Zarse, 2010). Based on the mitohormesis principle, it is likely that regular moderate exercise could upgrade overall antioxidant and repair systems - through redox-signaling pathways - offering an acquired protection against further ROS exposure provoked by opportunist infectious and chronic inflammation processes (Ji, 2008).

In contrast, prolonged and/or strenuous physical exertion is notably detrimental to health because massive amounts of ROS are abruptly produced under these circumstances (Banerjee et al., 2003). An overproduction of ROS that is not counterbalanced by an appropriate antioxidant capacity results in oxidative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA (Gomez-Cabrera et al., 2009). Contractile ischemia-reperfusion, thermal stress, dehydration, and osmotic imbalances can also exacerbate ROS formation during exercise (Martins et al., 2008). Taken together, redox imbalances during muscular contractions contribute significantly to the reduction of the contractility force, speed up the fatigue processes, and contribute to an increase in muscular injuries (Purvis et al., 2010).

In addition to the major role of mitochondrial electron leakage during aerobic exercise, it has been suggested that oxidative stress may be mediated through various other pathways: xanthine oxidase and NADPH oxidase activation, prostanoid metabolism, ischemia/reperfusion, phagocytic respiratory burst activity, disruption of iron-containing proteins, and alteration of Ca^{2+} homeostasis (Jackson, 2000). The production of ROS via these pathways is also attributed to anaerobic exercise (*e.g.*, isometric, eccentric, resistance, and sprint training) which may result in part from eccentric muscle actions, commonly followed by muscle injury (McHugh et al., 1999). Sprint exercise was and is still used as a form of anaerobic work to study oxidative stress responses. In the mid-1980's, Alessio et al. (1988) examined lipid peroxidation in rat skeletal muscle immediately following a 1-min sprint performed at 45m/min by using the classic TBARS method (Fraga et al., 1988) and measuring total lipid hydroperoxides (LOOH). More recently, Kayatekin et al. (2002) induced mice to perform fifteen sprints at 35m/min for 30 s each so that they could study oxidative stress in both skeletal muscle and the liver during the 24 h post-exercise period. While lipid oxidation increased acutely (*i.e.*, at 30 min and 3 h post-exercise) in skeletal muscle, no change was noted in the liver, suggesting a tissue-specific response. The majority of studies investigating dynamic resistance exercise-induced oxidative stress have utilized an exercise protocol consisting of two or more compound lifts (multiple joint exercises), occasionally performed in a circuit fashion (Ramel et al., 2004; McAnulty et al., 2005), usually $\geq$ 3 sets at an intensity of 60-95% of one repetition maximum (Rietjens et al., 2007). Intense acute resistance exercise is frequently followed by elevation in blood oxidative stress markers. Accordingly, partial occlusion imposes ischemia artificially and also results in increases in ROS production and protein/lipid modifications (Tsutsumi et al., 2007).

Muscle damage is characterized by ultrastructural changes to muscle architecture, increased muscle proteins and enzymes in the bloodstream (*e.g.*, creatine kinase and lactate dehydrogenase are classic biomarkers of muscle injury), loss of muscular strength and range of motion and muscle soreness. Post-exercise muscle injury is accompanied by: i) impaired/exhausted antioxidant defense systems; ii) release of pro-inflammatory arachidonic acid, prostaglandins, and other cytokines (*e.g.*, IL-6, IL-1β); iii) release of hemoglobin (from hemolysis) and myoglobin (from rhabdomyolysis) and related 'free' iron ions; iv) neutrophil migration, activation and, thus, subsequent late onset re-exposure to oxidative conditions (Peake & Suzuki, 2004). Nonetheless, much controversy has arisen as to whether strenuous exercise does, in fact, increase the need for additional antioxidants in the diet, as has been extensively recommended by scientists and companies involved in the marketing of dietary antioxidant supplements for athletes (Peake et al., 2007; Urso & Clarkson, 2003).

It had been sugested that ROS levels during exercise should be kept within an optimal range in order to trigger important ROS-mediated processes, such as muscle tissue acquired antioxidant adaptations and redox-sensitive gene expression, while simultaneously avoid extreme oxidative damage to cellular structures (Gomez-Cabrera et al., 2005). Teixeira et al. (2009) showed that antioxidant supplementation indeed resulted in higher plasma levels of α-tocopherol and β-carotene in athletes. After bouts of exercise, pro-inflammatory IL-6, TBARS, and uric acid also increased, regardless of the treatment group. Interestingly, cortisol levels increased more between the pre- and the post-supplementation periods in the placebo group. The authors reported that antioxidant supplementation did not offer protection against exercise-induced lipid peroxidation and inflammation and might even have hindered the recovery from muscle damage (Teixeira et al., 2009). Regarding antioxidant supplementation, key factors such as bioavailability, pharmacodynamic properties, and target-tissues are fundamental to establish the adequate oral dose for an antioxidant to match the narrow range of optimal *in situ* concentrations that sustain the redox balance in contractile skeletal muscles. A much more complicated system is expected when a combination of antioxidants is administered, since molecular interactions could occur within organs, tissues, cells, and intracellular compartments (Augustyniak et al., 2010).

Astaxanthin and exercise

Preliminary studies have found that ASTA can attenuate exercise-induced damage in mouse skeletal muscle and heart, in parallel with the modulation of post-exercise neutrophil infiltration and attenuation of delayed-onset muscular soreness in trained individuals (Aoi et al., 2003). On the other hand, other controversial results in resistance-trained men indicate that ASTA supplementation does not favorably affect indirect markers of skeletal muscle injury following eccentric loading (Bloomer et al., 2005). Regarding metabolic responses, Aoi et al. (2008) showed that ASTA: i) stimulated lipid oxidation as an energy-supplying substrate for extended exercise in detriment to glucose utilization; ii) inhibited the elevation of plasma lactate and reduced muscle glycogen catabolism during physical activity; and iii) increased the co-localization of fatty-acid translocase (FAT/CD36) with carnitine-palmitoyltransferase I (CPT I), enhancing its lipolytic effect associated with exercise. Ikeuchi et al. (2006) showed that the increase in plasma creatine kinase activity (a biomarker of muscle injury) was inhibited by treatment with ASTA, in parallel with the observed delay in muscle fatigue and endurance enhancement. Furthermore, a whole blood transit time evaluation performed in humans after administration of 6 mg ASTA/daily for ten days showed a significant decrease of 10% in the rheological properties of blood with putative implications of a lower risk of thrombosis and atherosclerotic plaque formation (Miyawaki et al., 2008).

Two decades ago, elegant immunological studies carried out by Jyonouchi et al. (1991) showed that ASTA enhances *in vitro* antibody production by mouse spleen cells when stimulated by sheep erythrocytes. The authors assumed that the main targets of ASTA action were T-cells, especially T-helper cells (Jyonouchi et al., 1993; Jyonouchi et al., 1995). Significantly, such immunomodulating properties are retinol-independent since ASTA, unlike β-carotene, does not exhibit provitamin A activity (Jyonouchi et al., 1994). Despite several works directly link ASTA to immunecompetence, information on the pharmacological mechanisms by which ASTA might improve immune functions is still scarce.

Astaxanthin and cognitive properties

Recent findings have associated ASTA with putative benefits in exercise practice and eventually athletic performance, which also includes improvement of cognitive capacity. However, it is still unclear whether ASTA directly crosses the brain-blood barrier (BBB) or not (Tso & Lam, 1996). Liu & Osawa (2009) claim that ASTA not only crosses the BBB but also develops neuroprotective effects to dopaminergic SH-SY5Y cells against oxidative damage provoked by neurotoxic 6-hydroxydopamine. Furthermore, ferritin-aggregates

in mutant neuroblastoma cells - a cellular model for degenerative neuroferritinopathies – were inhibited by in vitro treatment with 20 μM ASTA (Cozzi et al., 2010).

Concluding remarks

Based on recently published literature, we conclude that consumption of ASTA obtained from natural sources (salmon, shrimp, krill oil etc) or via dietary supplements (from biotechnologically manufactured *H. pluvialis* biomass) might be a practical and beneficial strategy in exercise practice and health management. This is based on a consideration of the high antioxidant and anti-inflammatory activities of ASTA, although additional biological properties, like amelioration of cognitive capacity, have also been recently suggested. Further mechanistic studies focusing on the role of ASTA in exercise and physiopathological processes, especially neurodegenerative and modern-life diseases (diabetes, obesity, occupational stress), remain an open field for researchers involved in the Free Radical field.

Acknowledgements

The authors are indebted to the Fundação de Amparo a Pesquisa do Estado de São Paulo (Projects n. 2002/09405-9 and 2009/12342-8, FAPESP, Brazil), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil, International Foundation for Science (Project F/3618-1, IFS, Sweden) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Bolsa Produtividade em Pesquisa, Nivel 2, n. 312404/2009-3, CNPq, Brazil,) for research funding and financial support.

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