Astaxanthin-antioxidant impact on excessive Reactive Oxygen Species generation induced by ischemia and reperfusion injury

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A B S T R A C T

Oxidative stress induced by Reactive Oxygen Species (ROS) was shown to be involved in the pathogenesis of chronic diseases such as cardiovascular pathologies. Particularly, oxidative stress has proved to mediate abnormal platelet function and dysfunctional endothelium-dependent vasodilatation representing a key factor in the progression of ischemic injuries. Antioxidants like carotenoids have been suggested to contribute in their prevention and treatment. Astaxanthin, a xanthophyll carotenoid produced naturally and synthetically, shows interesting antioxidant and anti-inflammatory properties. In vivo studies applying different models of induced ischemia and reperfusion (I/R) injury confirm astaxanthin’s protective action after oral or intravenous administration. However, some studies have shown some limitations after oral administration such as low stability, bioavailability and bioefficacy, revealing a need for the implementation of new biomaterials to act as astaxanthin vehicles in vivo. Here, a brief overview of the chemical characteristics of astaxanthin, the carrier systems developed for overcoming its delivery drawbacks and the animal studies showing its potential effect to treat I/R injury are presented.

1. Introduction

Reactive oxygen species (ROS) refers to a variety of highly reactive molecules and free radicals derived from molecular oxygen. ROS are formed as a normal byproducts of aerobic respiration and current cellular metabolism [1]. Moderate amounts of ROS have beneficial effects on several physiological processes like the reduction of malignant pathogens, wound healing, and tissue repair processes by acting as signaling molecules [2–4]. In contrast, ROS overproduction disrupts the body homeostasis inducing oxidative tissue damage [5]. Indeed, high ROS levels leads to decreased bioavailability of nitric oxide, impairing endothelium-dependent vasodilatation thus promoting vasoconstriction [6]. These alterations occur early in the development of vascular disease [7]. Moreover, overproduction of superoxide anion radical and hydroxyl radical have been considered causative agents of severe diseases, such as arteriosclerosis and I/R injury [8–10], pathologies currently linked to increased rates of lipids peroxidation [8,11].

In the cell, these reactions are counteracted by the action of enzymatic and non-enzymatic antioxidant defenses. Tissue damage takes place when these antioxidant defenses are not sufficient to control the radicals generation [12]. Recent studies suggest the use of exogenous antioxidant supplementation with carotenoids would enhance antioxidant defenses thanks to their potential scavenging capabilities [13–17]. Astaxanthin carotenoid is known to be a potent quencher of singlet oxygen and an efficient scavenger of superoxide anion [18], and hydroxyl radical [19,20] by acting as an antioxidant. Moreover, within the cell, it can effectively scavenge lipid radicals and effectively destroys peroxide chain reactions to protect fatty acids and sensitive membranes [21,22] reducing the risk of atherosclerotic plaque formation [23,24]. Furthermore, the astaxanthin effect in the prevention and treatment of I/R pathologies in vivo reveals its potent action as antioxidant molecule. However, astaxanthin as a highly unsaturated molecule decomposes easily when being exposed to heat, light and oxygen. Additionally, its poor water solubility, stability and bioavailability limits its appropriate oral administration and delivery in vivo. The implementation of new biomaterials to act as astaxanthin vectors has been attempted through various strategies. Here, a review of in vivo studies reporting the effect of astaxanthin supplementation to counteract ischemia/reperfusion injury will be presented, including a brief review of astaxanthin carrier’s system successfully developed for overcoming delivery challenges.

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2. Astaxanthin: A powerful antioxidant molecule

2.1. Astaxanthin sources

The carotenoid astaxanthin is found in various microorganisms and marine animals, such as yeast, microalgae, salmon, krill, shrimp, complex plants and some birds [25–29]. As in general with all carotenoids, astaxanthin is not synthesized by humans and therefore requires to be ingested in the diet, seafood being the main source [30,31].

Haematococcus pluvialis (H. pluvialis), a unicellular biflagellate green microalgae, is believed to have the highest capacity to accumulate astaxanthin in nature under environmental stresses such as starvation, high salt or pH, elevated temperature, or irradiation [25,32]. Under these unfavorable conditions, microalgae modify their cellular morphology, increasing their size to become red cysts charged with astaxanthin in nature under environmental stresses such as starvation, high salt or pH, elevated temperature, or irradiation [25,32]. Astaxanthin is found in various microorganisms and marine animals, such as yeast, microalgae, salmon, krill, shrimp, complex plants and some birds [25–29]. As in general with all carotenoids, astaxanthin is not synthesized by humans and therefore requires to be ingested in the diet, seafood being the main source [30,31].

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2.2. Chemical characteristics

Astaxanthin (3,3′-dihydroxy-β,β′-carotene-4,4′-dione) carotenoid is a fat-soluble orange-red color pigment with the molecular formula C40H52O4 and molar mass of 596.84 g/mol. Astaxanthin structure consists of 40 carbon atoms which contain two oxygenated β-ionone-type ring systems linked by a chain of conjugated double bonds (polyene chain). The oxygen presence in astaxanthin ionone rings in both hydroxyl (OH) and keto (C=O) groups, makes it a member of the xanthophyll carotenoid family and confers to astaxanthin a more polar nature than other carotenoids [41]. Additionally, the conjugated double bonds allow astaxanthin to act as a strong antioxidant by electron donation and by reacting with free radicals [42] (Fig. 1A).

In its free form, astaxanthin is considerably unstable and particularly susceptible to oxidation, therefore, this form is mainly produced synthetically or from yeast [43]. In nature, it is found either conjugated with proteins (e.g., salmon muscle or lobster exoskeleton) or esterified by hydroxyl reaction with one (monoester) or two (diester) fatty acids, which stabilize the molecule. Natural astaxanthin from H. pluvialis contains 70–90% of monoesters, about 8% of diester and 2% of free form [41,44,45] (Fig. 1B–C). A protective role against high light and oxygen radical has been attributed to astaxanthin accumulation in H. pluvialis [33]. The stereogenic carbons in the 3 and 3′ positions on the β-ionone moieties define astaxanthin conformation as chiral [(3S,3′S) or (3R,3′R)] or as meso form (3R,3′S), with the chiral conformation the most abundant in nature [27] (Fig. 1D–E). Astaxanthin from microalgae H. pluvialis biosynthesizes the (3S,3′S) isomer whereas yeast produces (3R,3′R) isomer [41]. The synthetic source consists of isomers (3S,3′S) (3R,3′S) and (3R,3′R) [27].

2.3. Extraction, storage, stability of astaxanthin

When the stress is induced, the microalgae H. pluvialis becomes encysted cells and accumulates high quantities of astaxanthin [46]. This growth stage is usually produced in either enclosed outdoor systems or closed indoor photo-bioreactors, which are preferred to avoid contamination by other microorganisms and to guarantee optimal and controlled growth conditions [36]. Different methods had been carried out to extract the greatest quantity of the carotenoid from H. pluvialis biomass by cracking the cell [33]. Some of them are based on the use of solvents [47], edible oils [48], enzymatic digestion [49], but
supercritical fluid extraction still represents the method most widely used in the agro-alimentary industry [50–52]. An innovative method for astaxanthin extraction from *H. pluvialis* using supramolecular solvents (SUPRAS) is currently under development [53]. Once astaxanthin is extracted from the biomass, its stability and storage must be assured to avoid degradation by environmental factors such as temperature, pH and light [26].

### 2.4. Pharmacokinetics and toxicity of astaxanthin

The low bioavailability of astaxanthin and all xanthophyll carotenoids after oral administration has been attributed to their poor water solubility/dispersibility. Particularly, the limited solubility in digestive fluids compromise the uptake of astaxanthin by intestinal epithelial cells and their final secretion to lymph as chylomicrons [30,54]. After ingestion, xanthophyll carotenoids are solubilized in the mixed micelles in the small intestine. These micelles represent a mixture of bile acids, phospholipids, cholesterol, fatty acids and monoacylglycerols surrounded by the bile acids [55]. Once degraded, carotenoids transfer from the micelles to the epithelial cells by simple and facilitated diffusion across the phospholipid bilayers of the cytoplasmic membrane [30]. Once degraded, carotenoids are stored in the liver and re-secreted as very low-density lipoproteins (VLDL), low density lipoproteins (LDL), and high-density lipoproteins (HDL) reaching a higher level of bioavailability, and eventually to be transported to the tissues via the circulation [56].

Due to the presence of polar ends in its structure, astaxanthin can be absorbed better than other non-polar carotenoids, such as lycopene and β-carotene [57–59]. In the case of esterified astaxanthin, before LDL transport, esters need to be hydrolyzed by cholesterol esterase [21,22]. Coral-Hinostroza et al. [58] showed that after oral administration, astaxanthin esters are hydrolyzed selectively during absorption, suggesting that unesterified astaxanthin may be preferentially absorbed or selectively transported through circulation in human. Additionally, astaxanthin blood levels have been reported as up to 0.19 μmol/L after 1–12 mg human intake for 1 year [60].

Conversely, animal studies showed a higher uptake of astaxanthin diesters than esters after oral administration [61]. H. D Choi et al. [62] evaluated the pharmacokinetics of astaxanthin in rats, reporting the elimination of an important portion of intravenous administered astaxanthin at doses up to 20 mg/kg via a non-renal route. Moreover, a longer astaxanthin half-life and a hepatic and gastrointestinal first-pass extraction ration of 0.490 and 0.901, respectively, were obtained when 200 mg/kg of astaxanthin was administered using an oral (1460 min) than intravenous (569 min) pathways. These results could indicate that bioavailability and a half-life of astaxanthin is influenced by its esterification status [34] and suggests that the lipophilic properties of the molecule require the use of additives and surfactants to incorporate it into carrier systems for use in foods, beverages and pharmaceutical products [63].

The safety of astaxanthin has been assessed in Sprague rats after receiving daily oral administration of astaxanthin-rich *H. pluvialis* biomass at concentrations up 500 mg astaxanthin/kg/day for 90 days [64], or synthetic astaxanthin in a range between 880 and 1240 mg/kg bw/day, for 13 weeks, [65]. No adverse effects were reported on the analyzed health-related parameters. The toxicity of synthetic astaxanthin was also tested in pregnant New Zealand white rabbits at concentrations up to 400 mg/kg bw/day without showing harmful effects on reproduction or fetal development [66]. Additionally, Katsumata et al. [67] performed a sub-chronic-toxicity evaluation of a natural astaxanthin-rich carotenoid extract produced from the natural bacteria *Paracoccus carotinifaciens* suspended in olive oil and administered daily to rats by oral gavage at doses of up to 1000 mg/kg/day for 13 weeks. The only result highlighted was the excretion of dark-red color feces without reporting any considerable adverse effect.

A. Satoh et al. [68] evaluated the human clinical toxicity and efficacy of long-term administration of soft capsules containing an oil based natural astaxanthin-rich product by measuring biochemical and hematological blood parameters and by analyzing brain function. The participants received an astaxanthin concentration up to 20 mg daily.

![Fig. 2. I/R injury enhance ROS levels and oxidative stress conditions. Adapted from Refs. [15,71,82].](image)
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<td>Gross and Lookwoo-d 2014 [98]</td>
<td>Disodium Disuccinate Astaxanthin (from Dr. Samuel F. Lockwood, Hawaii BioTech, Inc.) Sterile DI Water</td>
<td>Rat myocardial I/R</td>
<td>Intravenous injection</td>
<td>One of 3 doses (25, 50, and 75 mg/kg) for 4 days prior to I/R</td>
<td>Cardax at 50 and 75 mg/kg for 4 days significantly reduces infarct size at area at risk to 35 ± 3% (41% salvage) and 26 ± 2% (56% salvage), respectively.</td>
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<td>Gross and Lookwoo-d 2005 [99]</td>
<td>Dog myocardial I/R</td>
<td>Intravenous injection</td>
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<td>Lauver et al., 2005 [100]</td>
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<tr>
<td>Gross and Lookwoo-d 2006 [101]</td>
<td>Rat myocardial I/R</td>
<td>Oral administration as feed supplement</td>
<td>0.1 and 0.4%; ~125 and 500 mg/kg/day, respectively for seven days</td>
<td>CardaxTM at 0.1 and 0.4% in feed for 7 days resulted in a significant mean reduction in infarct size at area at risk to 45 ± 2.0% (26% salvage) and 39 ± 1.5% (36% salvage), respectively. Myocardial levels of Cardax achieved after 7-day supplementation at each of the two concentrations 400 ± 65 nM and 1634 ± 90 nM, respectively.</td>
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<td>Adluri et al., 2013 [102]</td>
<td>VitaePro (2% astaxanthin, 8.1% lutein and 1.23% zeaxanthin; VitaeLab AS, Eneshkveistr. Oslo, Norway)</td>
<td>Rat myocardial I/R</td>
<td>Oral gavage Dissolved in safflower oil</td>
<td>70 mg/kg body weight for 21 days</td>
<td>Increased left ventricular functional recovery after I/R Decrease infarct size (27.68 ± 1.7) Decrease apoptotic cardiomyocytes (61.7 ± 10.6) measured by TUNEL assay Decrease thiobarbituric acid reactive substances levels (80 ± 3)</td>
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<td>Wang et al., 2017 [96]</td>
<td>Astaxanthin (from Jianghe Biotech Co. Ltd. Jianghe, Hebei, China)</td>
<td>Mouse transvers aortic constriction</td>
<td>Oral gavage</td>
<td>200 mg/kg/day for 12 days prior to TAC</td>
<td>Mitigation of TAC induced cardiac dysfunction, myocardial fibrosis and myocardial disorder showing that SIRT1 participates in these protective functions by attenuating R-SMAD acetylation. Reduction in the expression of protein and transcript levels of TGF-β, α-SMA and COL I.</td>
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<td>Lu et al., 2010 [103]</td>
<td>Astaxanthin (from Sigma-Aldrich, St. Louis, MO, USA)</td>
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<td>Lee et al., 2010 [104]</td>
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<td>Li et al., 2015 [105]</td>
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<td>Mice renal I/R: 60 min R: 2 h, 8 h and 24 h Oral gavage Dissolved in olive oil</td>
<td>30 mg/kg or 60 mg/kg for 14 days</td>
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<td>Curek et al., 2010 [106]</td>
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<td>Qiu et al., 2015 [107]</td>
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<td>Mice renal I/R: 45 min R: 12 h and 24 h Oral gavage Dissolved in olive oil</td>
<td>5 mg/kg/day during 14 days prior to I/R</td>
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<td>Hussein et al., 2005 [24]</td>
<td>ASX-O, composed of 5.5% astaxanthin Fuji Chemical Industry Co., Ltd., Toyama, Japan</td>
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<td>ASX-O showed arterial blood pressure lowering effect from the first week at the dose of 50 mg/kg. No significant change in the heart rate after ASX-O treatment ASX-O (50 mg/kg) significantly delayed the incidence of stroke</td>
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<td>Polymeric systems</td>
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<td>Microencapsulation in calcium alginate</td>
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<td>Alga beads coating with multiple layer of chitosan fil</td>
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<td>Astaxanthin-calcium alginate gel (CAG) beads prepared by ionic gelation</td>
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<td>H. pluvialis cyst cells (Future Foods SA de CV, México) deoestrin</td>
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<td>Microencapsulation using lecithin as emulsifier and whey protein and gum Arabic as wall materials.</td>
<td>Not performed</td>
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<td>Co-polymer poly (hydroxybutyrate-co-hydroxyvalerate) (PHBV)</td>
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<td>Microencapsulation prepared by 2% sodium alginate and 3% calcium chloride using ionotropic gelation method.</td>
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<td>Barros et al., 2001 [138]</td>
<td>Astaxanthin from Sigma-Aldrich Sweden AB</td>
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<td>Peng et al., 2010 [139]</td>
<td>Astaxanthin from Sigma Chemical Co. St. Louis, MO, USA</td>
<td>Solvent: Chloroform/ methanol (2:1 v/v)</td>
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<td>Reduction of astaxanthin degradation after air and light exposure by twice.</td>
<td>Intra- and extracellular ROS reduction up to 74.49% and 47.7% respectively at 1000 mg/mL.</td>
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<td>Hama et al., 2012 [19,20] Kamezaki et al., 2016 [141]</td>
<td>Astaxanthin (from Sigma Aldrich Co.St. Louis, MO, USA).</td>
<td>Liposomes</td>
<td>Egg phosphatidylcholine (EPC) as based lipid</td>
<td>Lower degradation rate</td>
<td>High hydroxyl radical scavenging at concentration &lt; 20 μM</td>
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<td>Odeberg et al., 2003 [143]</td>
<td>Commercial formulation of algal meal and dextrin in formulation of algal meal and dextrin in hard gelatin capsules (Napro Pharma, Brattvaag, Norway).</td>
<td>Incorporation in three lipid based formulations containing polysorbate 80 and: 1.Long-chain triglyceride (palm oil) 2. glycerol mono- and dioleate 3. glycerol mono- and dioleate, and sorbitan monooleate</td>
<td>Enhanced bioavailability, ranging from 1.7 to 3.7 times Highest bioavailability using formulation B after a one dose human trial. Astaxanthin doses up to 40 mg were well tolerated.</td>
<td>Not performed</td>
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<td>Ribeiro et al., 2005 [144]</td>
<td>Crystalline astaxanthin (80% purity, BASF, Ludwigshafen, Germany)</td>
<td>O/W Emulsions prepared by repeated premix membrane emulsification</td>
<td>Stable suspension</td>
<td>Not performed</td>
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<td>Tachapruni et al., 2009 [145]</td>
<td>Astaxanthin (97% w/w purity, Acros Organics, Geel, Belgium) Solubilized in DMP//water</td>
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<td>Stable aqueous suspension</td>
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<td>Anaran et Tan 2013 [63,146,147]</td>
<td>Astaxanthin (&gt; 90%, from Kaihu Ever Brillance Biotechnology Co., Ltd. Beijing, China)</td>
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<td>Spherical-shaped with particle size of 88.9 nm for S2 and 114.6 nm using S1</td>
<td>Not performed</td>
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<tr>
<td>Tamjidi et al., 2014 [148]</td>
<td>H. Pluvialis oleoresin (astaxanthin content 40%; from Wuhan Erei Import &amp; Export Co. Ldt Wuhan, China) Extracted in dichloromethane</td>
<td>Nanostructured lipid carriers (NCL) using tween80 and lecithin as emulsifiers and oleic acid and glycerol behenate as lipids</td>
<td>Good storage stability for 25 days</td>
<td>Not performed</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
for 4 weeks. No safety concerns were reported and a positive effect on metabolic syndrome and cognitive function was suggested.

Astaxanthin has been approved by the United States Food and Drug Administration (US FDA) as well as the European Food Safety Authority (EFSA) for used as a food ingredient and feed additive. However, only astaxanthin from *H. pluvialis* and *P. carotinfaciens* have been approved as a human dietary supplement at dosages from 12 to 24 mg/day and 6 mg/day respectively, for no more than 30 days [28,43,69]. Although astaxanthin toxicity in humans.

3. Influence of oxidative stress in I/R: Astaxanthin antioxidant treatment

3.1. ROS production during I/R injury

Reperfusion injury is induced after blood flow is restored following an ischemic period. Recent studies shown that an oxidative stress could be a critical factor involved in the pathogenesis of this injury [70]. The induction of an ischemic state leads to an imbalance in the oxygen production and consumption. This lack of oxygen further restricts blood supply, inducing a hypoxic state which leads to microvascular dysfunction [71]. Restoration of blood flow and reoxygenation is frequently associated with an increased amount of tissue injury and an elevated inflammatory response [72], also called ‘reperfusion injury’ [73]. Reperfusion injury leads to the depression of the inner body defense mechanism, inducing an imbalance between a burst of ROS production and the inability of reoxygenated cells to handle this radical load [8]. Under these conditions, cell death programs including apoptosis, autophagy-associated cell death and necrosis [74] are activated, leading to a multi-organ failure, even if only one organ underwent I/R [75]. Here, extracellular ATP depletion from apoptotic cells acts as a ‘find-me’ signal that attracts phagocytes [76,77]. Additionally, limited oxygen availability is associated with the activation of inflammatory signals which control the stability of the transcription nuclear factor NF-κB [73] through a mechanism involving hypoxia-dependent inhibition of oxygen sensors [78], and adaptive immune responses that involves the infiltration of various types of inflammatory cells (neutrophils, T lymphocytes, monocyte/macrophages) [79,80].

In normal physiological conditions the undamaged endothelium prevents adhesion and activation of platelets and leukocytes by several mechanisms [81]. During reperfusion injury, adhesion of platelets and leukocytes to endothelial cells are enhanced leading a procoagulant state as well as platelet and leukocyte activation [83]. This activation results in the induction of proinflammatory cytokines and chemokines (TNF and IL-1B) [84] that are further released by activated leukocytes in the reperfused blood [85]. Under these circumstances, the endothelial cell barrier gets weak, increasing vascular permeability and leakage [86]. Endothelial damage is enhanced by the hydroxyl radical, superoxide and peroxynitrite overproduction that are formed following the reaction of NO with oxygen in the reperfused blood [82]. l-arginine is the main precursor of endothelial nitric oxide synthase, eNOS, which is in charge of NO synthesis which further enhances inducible NO synthase (iNOS) and iNOS [87]. Moreover, activation of NADPH oxidase in activated neutrophils, induces peroxynitrite which, then, in turn, generates more ROS by the increased availability of free iron during ischemia [88]. This excessive radical generation leads to lipid peroxidation of tissues within the subendothelial space. Accumulation of oxidized low-density lipoproteins (ox-LDL) within monocytes-derived macrophages generates foam cells that further amplify the inflammatory cascade [89], ultimately leading to the formation of thrombus and occlusion of the vessel [90] (Fig. 2).

3.2. Astaxanthin: An antioxidant ROS blocking agent

Natural carotenoids have shown particular abilities to entrap ROS and enhance the cellular capacity to block oxidative stress [91]. The effects of carotenoids vary depending on how they interact with cell membranes [92,93]. Astaxanthin carotenoid has been shown to reduce lipid peroxidation damages by the preservation of membranes structures using a polyunsaturated fatty acid enriched membrane model [94]. This action was attributed to its polar end groups which extended toward the polar regions of the membrane bilayer [95]. Astaxanthin has been currently studied in the cardiovascular field thanks to its antioxidants and anti-inflammatory properties [95]. Astaxanthin showed reduction of blood coagulation, platelet aggregation and promoted fibrinolytic activity in a high-fat diet-induced hyperlipidemic rats. These positive effects were correlated with decrease of serum lipid and lipoproteins levels, antioxidants production and protection of endothelial cells [96]. Moreover, the protective effect of astaxanthin has been studied on different in vivo models of I/R such as myocardial, cerebral, liver and renal (Table 1). In which animals received an oral or intravenous injection of astaxanthin dose ranging between 5 and 500 mg/kg/day. In these cases, astaxanthin was administered in both hydrophilic (solubilized on DI water and other organic solvents) and lipophilic (solubilized on oils) formulations before inducing the ischemic damage, thus acting as a preventive agent. A water soluble synthetic astaxanthin derivative or disodium disuccinate astaxanthin (Cardax Hawaii Biotech, Inc., USA) was studied on experimental myocardial I/R models in rat, rabbit and dogs (Table 1). After parental administration this derivative showed a potential efficacy to reduce infarct size and plasma lipid peroxidation levels attributed the direct scavenging of superoxide anion [97]. Similar results

### Table 3 (continued)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Astaxanthin source</th>
<th>System</th>
<th>Results</th>
<th>Antioxidant evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meor Mohd Afandi et al., 2011 [149]</td>
<td>Astareal 10% grade (an oil extract containing 10% w/w of standardized astaxanthin, from Fuji Chemical Industry, Nakaniiikawa, Toyama, Japan).</td>
<td>Nanoemulsion using Tween 80 and lecithin as emulsifiers (2.5% w/w)</td>
<td>Particles size at 5 cycles of homogenizing pressure 122.9 ± 1.55 nm. Conservation of stability and storage at 25 ± 2 °C/60% ± 5% relative humidity for 3 months.</td>
<td>Attenuation of nuclear levels of iNOS and NF-κB Hepatoprotective effects and completely alleviated the acute inflammatory status at a 10 mg/kg-day dosage.</td>
</tr>
<tr>
<td>Chun-Hung Chiu et al., 2016 [150]</td>
<td>Astaxanthin (&gt; 99%, from the Fuji Chemical Industry Co., Ltd. Toyama Prefecture, Japan).</td>
<td>Liposomes</td>
<td>Particles size distribution of 240 ± 58 nm Astaxanthin instantaneous pharmacokinetics release from the nanoliposome particles. Efficient and stable transport allowing a higher intrahepatic uptake.</td>
<td>-</td>
</tr>
</tbody>
</table>
Complex showed a DPPH radical activity lower than astaxanthin at same concentrations. High Fe

Table 4

Cyclodextrin inclusion complexes evaluated to protect and enhance astaxanthin properties.

<table>
<thead>
<tr>
<th>Cyclodextrin inclusion complex</th>
<th>System</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astaxanthin (purity &gt; 98%, from Dr. Ehrenstorfer Co. Ltd. Germany)</td>
<td>Cyclodextrin</td>
<td>Dong et al., 2014 [154]</td>
</tr>
<tr>
<td>Astaxanthin Sigma lot 71K1540 in Hydro-alcoholic solution (2:1 v/v) Solvent: Dichloromethane and Acetone</td>
<td>Cyclodextrin</td>
<td>Kim et al., 2010 [157]</td>
</tr>
<tr>
<td>Astaxanthin (from Shangyu NHU Bio-Chem, China) Solubilized in Hydro-alcoholic solution (2:1 v/v)</td>
<td>Cyclodextrin</td>
<td>Nalawade et al., 2015 [159]</td>
</tr>
</tbody>
</table>

Not performed

Astaxanthin (purchased from Sigma Chemical Co., St. Louis, MO, USA). Solvent: Dichloromethane and Acetone

Increased the apparent water solubility approximately 71-fold, to a concentration of 2 mg/mL

Increased stability against heat, light, and oxidation by over 7-9 fold

Improved stability at 120 °C

Improved stability < 0.5 mg/mL thermal stability

Increased stability enhanced 54 times over astaxanthin

Solubility enhanced 48.96%

A dissolution rate of 85% over 45 min

Increased bio-accessibility on HepG2 cell line.

Inclusion with Hydroxypropyl-β-cyclodextrin

Inclusion with β-cyclodextrin

Inclusion with methylated-β-cyclodextrin using spray drying technique

Inclusion with capto(β-cyclodextrin) Ether

Inclusion in capto(β-cyclodextrin)

Astaxanthin capacity to prevent the increasing levels after administration at doses of 12–18 mg/day during 12 weeks was also reported in another patient group [110]. In a clinical study, Park et al. [47] examined the action of dietary astaxanthin (2 and 8 mg/day for 8 days) in regulating immune response, oxidative damage and inflammation in humans. Results showed an enhancement of immune markers and reduction in DNA oxidative damage biomarker and inflammation.

Additionally, there is evidence of the effects of astaxanthin against oxidative damage in other disorders such as diabetes, obesity and neurodegenerative diseases.

Animal studies showed the astaxanthin potential to reduce the altered oxidative stress environment in diabetic and obese rats. Yeh et al. [111] studied the astaxanthin capacity to protect against oxidative damage in the ocular tissues of streptozotocin-induced diabetic Wistar rats receiving 3 mg/kg daily of astaxanthin for 8 weeks. Their results suggested a protective effect in the preservation and reduction of diabetic retinopathy mediated by downregulation of NF-kB activity, an increase of antioxidant enzymes, and reduction of downstream inflammatory mediators’ expression. Mounom-Benar et al. [112] studied the capacity of free-astaxanthin to reduce plasmatic triglycerides in obesity diet-induced dyslipidaemia mice, showing a positive effect in reducing triglycerides concentrations up to 45% but not cholesterol levels after astaxanthin supplementation for 8 weeks. Also, Al-Bulushi et al. [113] showed astaxanthin capacity to prevent the increasing oxidative stress biomarkers in rats presenting streptozotocin-induced hyperglycemia and pancreatic cell injury, after the animals received oral astaxanthin administration (20 mg/kg of body weight) for 12 weeks.

Human studies have also been conducted to identify the potential of using this antioxidant to reduce overweight and obesity problems linked to oxidative stress induction. Satoh et al. [68] showed the reduction of systolic blood pressure, triglyceride, and fasting glucose values after astaxanthin intake by patients with borderline diabetes mellitus or persons at risk for metabolic syndrome. Choi et al. [114] confirmed the capacity of astaxanthin to improve oxidative stress biomarkers by suppressing lipid peroxidation and stimulating the activity of the antioxidant defense system in overweight and obese adults in Korea, these patients daily received an oral administration of astaxanthin at concentrations up to 20 mg for 3 weeks.

Oxidative stress plays an important role in the induction of neurological diseases by damaging macromolecules and leading to neuronal dysfunction [115]. Astaxanthin has been evaluated as a potential neuroprotective agent due to its capacity to cross the brain blood barrier protecting the brain for acute injury and chronic neurodegeneration [116]. Grimming et al. [117] reviewed the potential of astaxanthin to promote or maintain neural plasticity, suggesting that astaxanthin could increase the cognitive function by promoting neurogenesis and behavioral performance on hippocampal-dependent tasks. Additionally, were obtained with natural astaxanthin and carotenoids mixtures (Vi-taePro, astaxanthin, lutein and zeaxanthin) in a rat model of I/R.

Oil-based astaxanthin formulations, administered mostly by oral gavage, showed a potential reduction of inflammatory cytokines expression, decreased organ infarct size area and reduction of arterial blood pressure lowering the risk of strokes. These studies are briefly summarized on Table 1.

Animal studies supports the potential preventive effect of astaxanthin supplementation to reduce the impact of cardiovascular diseases. The potential astaxanthin effects in the prevention and treatment of cardiovascular disease have been extensively studied [23,25,28]. Moreover, first preclinical studies support its antioxidant abilities to prevent oxidative processes. For instance, patients who received astaxanthin supplementation showed an increased resistance to LDL oxidation when administered at doses of 1.8–21.6 mg/day during 14 days [108] and a slight glucose-lowering effect at doses of 4–20 mg/day in other studies [109]. Additionally, the amelioration of triglyceride and HDL-cholesterol in correlation with increased serum adiponectin levels after administration at doses of 12–18 mg/day during 12 weeks was also reported in another patient group [110]. In a clinical study, Park et al. [47] examined the action of dietary astaxanthin (2 and 8 mg/day for 8 days) in regulating immune response, oxidative damage and inflammation in humans. Results showed an enhancement of immune markers and reduction in DNA oxidative damage biomarker and inflammation.

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Wu et al. [118] reviewed astaxanthin’s effect to act as a potential neuroprotective agent, based on its anti-oxidative, anti-inflammatory, and anti-apoptotic effects. In particular, Grimmig et al. studied [119] the potential of astaxanthin to attenuate the neurodegeneration process induced in Parkinson’s disease, while Lobos et al. [120] showed astaxanthin capacity to protect neurons from the oligomers’ noxious effects on mitochondrial ROS production on primary hippocampal cultures in vitro.

3.3. Encapsulation carrier’s systems

Despite the positive results described above there is still a lack in the understanding of astaxanthin’s therapeutic mode of action, uptake, distribution, pharmacokinetics, and metabolism. Furthermore, solving astaxanthin stability drawbacks and parenteral administration problems are of crucial interest for the development of astaxanthin-based therapies to prevent and treat oxidative stress-induced cardiovascular pathologies. Consequently, the implementation of new biomaterials to act as astaxanthin vectors in vivo is of vital interest. Tables 2–4 summarize some carrier’s systems successfully developed for overcoming astaxanthin delivery challenges. These systems were divided into three groups including polymeric systems, lipid-based carriers, and inclusion complex using cyclodextrins (Fig. 3).

3.3.1. Polymeric systems

The microencapsulation process with polymeric systems consists in the formation of a polymeric matrix or coating layer around a particular compound to provide a physical barrier between the core material and environmental conditions. These types of systems protect the compound’s biological activity and enhance its physicochemical stability.

Natural polymeric systems include polysaccharides like cellulose, starch, gum Arabic, alginate or chitosan [121] and the use of proteins like albumin, gelatin or soy proteins [122] (Table 2). Microencapsulation with polymer matrices controls the molecule release, reducing the core reactivity with environmental factors and facilitating molecular handling [123,124].

In polymeric nanosystems the absorption profile of the loaded molecules is driven by the particle size, shape and surface properties of the nanoparticles [54], which could be useful to control the drug release rate during oral administration until it reaches the systemic circulation [122]. Indeed, chitosan-alginate complexes have been shown to degrade slowly in phosphate buffer, avoiding the initial release of drugs occurring when using uncoated microspheres [31]. Conversely, polymeric micelles improve their steric stabilization and ability to interact with cells due to their hydrophilic shell [122].

Table 2, presents nine different studies using polymeric matrixes to improve astaxanthin solubility properties. Natural polysaccharides such as chitosan and alginate are currently being studied for astaxanthin microencapsulation due to their biocompatibility and biodegradability properties. For instance, chitosan showed to improve astaxanthin storage conditions and to preserve its antioxidant scavenging abilities, as confirmed by ABTS chemical method. A high astaxanthin loading efficiency was reported in studies using calcium-alginate, however microcapsules size distribution varied from 5.6 to 2041 μm between the studies. The preservation of the lipid peroxidation inhibitory activity was confirmed by two of four studies using the TBA method and only one study evaluated the in vitro cytotoxicity of the system. In general, all polymeric methods improved astaxanthin solubility but lack in the complete evaluation and verification of the antioxidant activity preservation after encapsulation.
3.3.2. Lipid based carriers

Lipid based carriers include micelles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), nanoemulsions and microemulsions. These systems had been used to encapsulate, protect, and deliver lipophilic bioactive components by enhancing their long-term stability while increasing bioavailability [132]. The system stabilization is achieved by surface charge or by surface adsorption of a layer of surfactant or polymer, or the combination of both methods [122].

O/W microemulsions and nanoemulsions differ according to their stability. Microemulsions are thermodynamically stable colloidal dispersions consisting of small spherical particles dispersed within an aqueous medium, O/W nanoemulsions refer to a thermodynamically unstable colloidal dispersion consisting of two immiscible liquids, being one of the liquids dispersed in the other liquid [132]. SLN are a mix of O/W nano/micro-emulsions in which the lipid phase is fully crystalized and has a highly-ordered crystalline structure at room/body temperature [133]. The low drug loading capacity and drug release after polymorphic transition of the lipid core during storage represents a disadvantage for the use of SLN [133,134]. Nanostructured lipid carriers (NLC) are modified SLN consisting of a lipid phase of a biocompatible mixture of solid and liquid lipids in a less-ordered crystalline structure [135,136]. The incorporation of oil into the core of a solid lipid leads to a higher loading capacity and controlled drug release. Here, the drug is dissolved in the oil and simultaneously encapsulated in the solid lipid [137]. Lipid based carriers size can range from around 10 nm for micelles to hundreds of nanometers for other systems [132].

Lipid based carrier systems presented in Table 3 showed the enhancement of astaxanthin properties. Five of twelve studies evaluated the in vitro interaction of the system after cellular supplementation without reporting toxicity problems. The in vitro antioxidant capacity of the system was assessed in four studies reporting the reduction of ROS levels and the attenuation of cellular inflammatory markers. Moreover, one human trial study revealed the improvement of astaxanthin bioavailability after incorporating into a lipid based formulation [143].

3.3.3. Inclusion complex using cyclodextrin

Cyclodextrins have been used extensively as additives to increase the solubility of poorly water-soluble organic compounds [122]. Cyclodextrins are natural macrocyclic oligosaccharides well known for having toroid-shaped structures with rigid lipophilic cavities and a hydrophilic outer surface. They are able to enclose highly hydrophobic molecules inside their hydrophobic cavity, constituting a true molecular encapsulation [151]. The resulting non-covalent inclusions or host–guest complexes are of current scientific and technological interest for their particular physical, chemical and biological properties. These non-covalent associations can improve the guests water solubility, bioavailability and stability [152], while regulating the release of the guest molecules [153,154].

Cyclodextrin systems highly increased the astaxanthin water solubility and its stability against heat, light and oxygen. Two of the six systems presented in Table 4 evaluated the chemical antioxidant activity of the inclusion system using the DPPH, the reduction power systems presented in Table 4 evaluated the chemical antioxidant activity of the inclusion system using the DPPH, the reduction power antioxidant capacity of the inclusion system using the DPPH, the reduction power of the included system. Regardless of the results reported using the different techniques, all of them require a deeper chemical and biological characterization to confirm their potential to be used as astaxanthin carrier systems in order to consider for future evaluations in clinical applications for the prevention and treatment of cardiovascular diseases.

4. Conclusion

Despite the influence of ROS to destabilize membrane and cell homeostasis, a regular production of these radicals is essential in the maintaining of redox signaling. Thus, antioxidant systems oversee ROS regulation without completely eliminating them. All antioxidants have different ways of action; their biological activity may also be conditioned by the cellular structure in which they act. Astaxanthin has shown potent antioxidant actions to stabilize ROS influx during oxidative stress related diseases such as I/R injury, as presented here. Indeed, astaxanthin showed a strong ability to reduce lipid oxidation thanks to its polar end groups which extend toward the polar regions of the membrane bilayer, thus contributing to the inhibition of thrombus and atherosclerotic plaque formation. However, a drawback of astaxanthin’s action has also been attributed to its structure, which renders it prone to oxidation and lowers its bioavailability. Protective encapsulation systems have been studied to solve these drawbacks. Additionally, new delivery systems may also contribute to limit potential untoward effects of in vivo antioxidant therapy that have been limited by antioxidant appropriate doses. Finally, the studies reviewed here show the interesting properties and potential medical use of astaxanthin to treat oxidative stress related pathologies, particularly in cardiovascular diseases such as I/R injury.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.jcbi.2017.11.012.

References


