proceedings

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Proceeding Paper

Chemical Features and Biological Effects of Astaxanthin Extracted from *Haematococcus pluvialis* Flotow: Focus on Gastrointestinal System †

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† Presented at the 2nd International Electronic Conference on Nutrients, 15–31 March 2022; Available online: https://iecn2022.sciforum.net/.

Abstract: The main purpose of this review is to analyze published data concerning the antioxidant properties of astaxanthin, a xanthophyll, produced by the microalga *Haematococcus pluvialis* in response to specific conditions of "environmental stress" and characterized by the typical deep red color. Natural astaxanthin establishes effective protection against oxidative stress, neutralizing free radicals in both the inner and outer layer of cell membranes, especially in mitochondria. The most recent preclinical and clinical studies that have investigated the beneficial properties of this molecule towards the gastrointestinal tract were included.

Keywords: natural astaxanthin; xanthophyll; *Haematococcus pluvialis*; antioxidant activity; anti-inflammatory activity; microbiota; gastrointestinal inflammation

Citation: Budriesi, R.; Micucci, M.; Daglia, M.; Corazza, I.; Biotti, G.; Mattioli, L.B. Chemical Features and Biological Effects of Astaxanthin Extracted from *Haematococcus pluvialis* Flotow: Focus on Gastrointestinal System. *Proceedings* **2022**, *69*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Torsten Bohn

Published: date: 15th March 2022

1. Introduction

Astaxanthin is a xanthophyll of the antioxidant group of carotenoids; widely present in the aquatic kingdom, it is produced by the microalga *Haematococcus pluvialis* as a natural reaction to specific environmental stress conditions, such as solar irradiation or prolonged absence of nutrients; it has a typical intense red coloration, characteristic, for example, of krill, shrimps, lobsters, flamingos, crabs and salmon, species that feed directly or indirectly on the alga.

2. Astaxanthin: "the Red Gold"

2.1. Main Sources of Astaxanthin

Astaxanthin is a natural carotenoid, with red color, belonging to the class of xanthophylls [1]. The biosynthesis of astaxanthin occurs exclusively in plant organisms, bacteria and fungi, from which it reaches, through the food chain, crustaceans and fish [2]; it is responsible for the pigmentation—which turns from deep red-blue to pale pink—of the internal tissues and tegument of aquatic species (such as salmonids, shrimp, lobsters and krill) and the color of the feathers and skin of some birds, such as flamingos [3–5].

The primary source of astaxanthin is the microalga *H. pluvialis*, a unicellular, biciliate, class Chlorophyceae, order Volvocales, whose habitat is found in freshwater lakes, rivers, natural pools or puddles (which dry out regularly), widespread in the islands of the Stockholm archipelago (Stockholms skärgård), one of the largest in the Baltic Sea [6,7].

H. pluvialis has greater biosynthetic and accumulation capacity for astaxanthin than other organisms that synthesize it, and that results in 6% of its dry weight [8].

2.2. Chemical Structure of Astaxanthin

Astaxanthin (3,3′-dihydroxy-β-carotene-4,4′-dione) is part of the xanthophylls family, carotenoids oxygenated derivatives. The basic skeleton is an unsaturated hydrocarbon chain with 40 carbon atoms, with thirteen conjugated double bonds, perfectly symmetrical with respect to the positions 15-15′ (Figure 1).

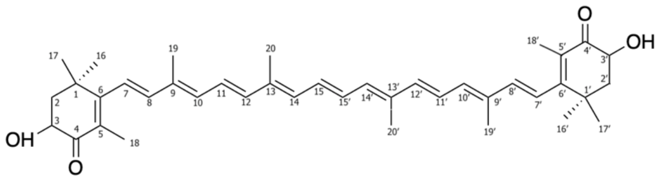

Figure 1. Natural astaxanthin chemical structure.

The presence of oxygen atoms in the tetraterpenic molecule makes the "small-big" difference in terms of functional capacity: these atoms give the molecule strong antioxidant properties. The chain of conjugated double bonds is also responsible for the antioxidant function because it produces a molecular region where electrons can be donated to reduce the number of ROS (Reactive Oxygen Species), oxidizing more reactive molecules.

The terminal rings contribute strongly to the antioxidant ability of astaxanthin, while the oxygen atoms on both sides of the terpenoid chain gives the molecule a remarkable polarity, which allows it to fit symmetrically from one side to the other of the plasma membranes, stabilizing and protecting them more effectively than other antioxidants.

3. Astaxanthin, the "Supernutrient"

Astaxanthin has only recently obtained the status of "supernutrient", becoming the subject of an increasing number of scientific studies [9,10]. Since our organism is not able to synthesize this precious molecule, the presence of astaxanthin at systemic level has always been exclusively correlated with food intake, also because astaxanthin is characterized by discrete solubility in aqueous environment and presents a good intestinal absorption [11]. The critical aspect related to the intake of astaxanthin from food is represented by the very high quantity of fish and crustaceans needed to reach the useful dosage (it would be necessary to consume from 600 g to 2 kg of salmon per day to obtain the optimal dosage) [12]. As this is practically impossible—also considering the problem of contamination with chemicals and heavy metals—it is essential to use astaxanthin as a food supplement (with a concentration useful for its functional effect). Compared to other carotenoids, such as β-carotene and lycopene, astaxanthin is more bioavailable being a lipophilic compound, endowed with polarity, and therefore with amphipathic peculiarities (Figure 2) [11]. Probably this molecule represents one of the few cases of phytochemical that, administered at low dosages (typically between 4 and 20 mg/day) reaches in vivo concentrations similar to those used in in vitro experiments This fact means that many of the in vitro experiments are really indicative of the potential efficacy of this substance also in vivo.

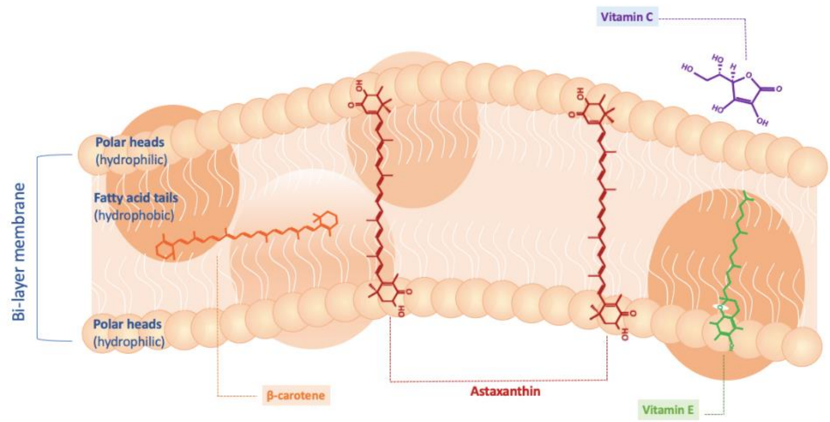

Figure 2. Location of astaxanthin and other antioxidants in the cell membrane.

4. Areas of Action and Use of Astaxanthin

Astaxanthin features make it an extraordinarily versatile nutraceutical, able to play significant antioxidant and anti-inflammatory activities on skin, brain system, visual and cardiovascular system. It also seems to act as an anti-aging agent, as extensively described in the literature. We chose to turn our attention mainly on the antioxidant and anti-inflammatory effect, focusing on the gastrointestinal tract.

4.1. Antioxidant Action

An antioxidant is a molecule able to inhibits oxidation and thus to prevent oxidative damages: free radicals are produced by normal aerobic metabolism, in living organisms, to support vital processes. However, when excessive amounts of oxidative species react with cellular components, such as proteins, lipids and DNA through a chain reaction, they cause excessive oxidation leading to damage [13]. These cellular biochemical reactions that occur physiologically and produce free radicals can also be abnormally induced by external factors such as pollution, smoking, UV rays, prolonged stress, too much physical activity, or the use of additives [13–15]. Oxidative stress can be inhibited by endogenous and exogenous antioxidants: some foods represent great sources, as they are able to boost endogenous antioxidant systems. Carotenoids are endowed with very strong antioxidant ability: by extinguishing singlet oxygen (quenching) and eliminating radicals to end chain reactions they can be considered excellent scavengers of peroxyl radicals, able to interrupt the reactions that lead to oxidative damage of lipophilic compartments. The potential benefits of astaxanthin, administered as a dietary supplement, are explicated by several studies that show how its antioxidant activity is almost 5 times greater than β-carotene, 3 thousand times more powerful than resveratrol and even 6 thousand times more effective than vitamin C [16–18]. By virtue of the unique characteristics of its chemical structure, astaxanthin is much more stable than other antioxidants: while most other molecules lose their antioxidant status after capturing a free radical (becoming pro-oxidant) astaxanthin retains only the antioxidant capacity and not the pro-oxidant [19–21]. Astaxanthin has the ability to establish an effective protection against oxidative stress neutralizing free radicals in both the inner and outer layer of cell membranes: in particular, it exerts antioxidant and anti-inflammatory properties in the mitochondria, here it neutralizes free radicals and protects the two membranes from oxidative stress [22].

4.2. Anti-Inflammatory and Gastrointestinal Protective Action

An efficient digestive system plays a key role in the physical and mental well-being: several studies have shown that the administration of astaxanthin promotes the health of the gastrointestinal system for its ability to lower inflammatory markers and decreasing clinical symptoms in patients. The gastrointestinal system can undergo acute and chronic inflammatory diseases, including those related to *Helicobacter pylori* infection that can lead to more severe diseases such as chronic type B gastritis, peptic ulcer and gastric carcinoma: data suggest the administration of astaxanthin decreases inflammation and provides protections towards gastric mucosa [23–25]. It was observed that the treatment with astaxanthin in patients with functional dyspepsia increased the expression of IFN-γ, IL-10, IL-2, IL-8; decreased gastric inflammation, up-regulated CD4 and down-regulated CD8 [26]. Thus, it is evident that astaxanthin significantly reduces oxidative stress, inflammation, and cell proliferation in the colon through inhibition of inflammatory markers such as IL-1β, IL-6, TNF-α, IL-36α, and IL-36γ, and inhibition of NF-κB, AP-1, and MAPK [27,28]. Furthermore, the use of astaxanthin seems to be associated to a protective action of mitochondria, which are significantly damaged (resulting in increased ROS) by *H. pylori* infection [29]. A clinical study, evaluating the antioxidant activity in patients with functional dyspepsia, showed that, in the group that was given the highest amount of astaxanthin (40 mg/*die*) reflux was reduced, especially in patients with *H. pylori* [30]. The treatment of human macrophages, with krill oil—rich in PUFAs and astaxanthin—resulted in a reduction of LPS-induced, IL-1β and TNF-α expression in vitro in a concentration-dependent manner. Astaxanthin also decreased the amount of *Rickettsiales* and several *Lactobacillus* species and, at the same time, appeared to increase the presence of *Firmicutes* and *Lactobacillaceae* in the bowel [31–33]. In two recent studies, astaxanthin has been shown to provide important protection towards the intestinal mucosa decreasing oxidative stress, stimulating calyciform cells and increasing IgA secretion. In addition, it decreased the loss of beneficial bacteria such as *Lactobacillus* and *Bifidobacteria* and affected *Clostridium coccoides* and *Enterobacteriaceae*: as a result, key metabolites of the gut microbiota, including acetic acid, propionic acid, butyric acid, and other short-chain fatty acids, were indirectly increased, thereby improving gut function and immunity [33,34]. Further studies confirm that astaxanthin positively modulates the composition of the gut microbiota by optimizing the ratio *Bacteroides*/*Firmicutes* while improving the abundance of *Akkermansia* and *Verrucomicrobia* species, which protect the gut from pathogens [35–37]. In addition, it is noteworthy that, in a recent study in 2021, astaxanthin treatment was shown to effectively reduce intestinal damage even in necrotizing enterocolitis [38].

5. Conclusions

In conclusion, the feature of natural astaxanthin make it a nutraceutical with a broad spectrum of potential clinical applications, in particular due to its powerful antioxidant and anti-inflammatory activities, even at low doses, and to its excellent bioavailability. In the gastrointestinal tract, this molecule may be used as nutraceutical approach, even in combination with other nutraceuticals, to help restoring the physiological balance and inhibiting degenerative events associated with infections, inflammation and various syndromes, related to genetic, environmental, psychological and aging factors. Scientific research is opening new perspectives to the uses of this antioxidant and it is evaluating a possible use concerning protection and improvement of the intestinal microbiota, improving the general state of health and the possible onset of dangerous pathologies.

Author Contributions: Conceptualization, L.B.M. and R.B.; methodology, L.B.M. and G.B.; validation, R.B., M.M. and M.D.; writing—original draft preparation, L.B.M., R.B.; writing—review and editing, L.B.M., R.B., M.M., M.D., I.C.; visualization, R.B., M.M., I.C., G.B.; supervision, R.B., M.M., M.D.; funding acquisition, L.B.M., R.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study did not require ethical approval.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest

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