

Chapter

Bioactive Properties of the Pigment Astaxanthin from *Haematococcus pluvialis* in Human Health

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Abstract

Astaxanthin is a carotenoid with the most reported cellular antioxidant effect, providing significant protection. It is evident that various diseases related to oxidative stress are increasing in the population. Therefore, there is an interest in searching for new sources of bioactive compounds that can be applied to improve human health. The information presented here is based on a review of the most relevant scientific articles that have shed light on the current state of the potential effects of astaxanthin, both in mammalian cell lines and in humans. The model organism studied was the freshwater microalga *Haematococcus pluvialis*, which accumulates high concentrations of astaxanthin under stress conditions. The biological activity of astaxanthin described in this review demonstrates that it is a potent antioxidant without adverse effects. Therefore, natural astaxanthin derived from *Haematococcus pluvialis* could be safely used as a nutraceutical and for preventive and therapeutic purposes in human health.

Keywords: microalgae, astaxanthin, antioxidant power, carotenoid, *Haematococcus pluvialis*

1. Introduction

Astaxanthin (3,3'-dihydroxy-diketo- β,β' -carotene-4,4-dione) is a secondary carotenoid, which belongs to the xanthophyll family, it is naturally synthesized by photosynthetic organisms mainly microalgae, but it can also be found in a limited number of fungi, bacteria, and plants [1, 2]. It has been reported that the freshwater microalgae *Haematococcus pluvialis* under conditions of environmental stress protects its photosynthetic apparatus by transforming its vegetative state into an astaxanthin-rich aplanospore state. To date, it is the only microorganism with the greatest capacity to produce astaxanthin [3, 4].

Several studies reveal that astaxanthin obtained from natural sources is the most effective carotenoid with antioxidant and cell protective properties. It has been reported to have anti-aging, anti-carcinogenic, and anti-inflammatory effects, and the ability to protect against exposure to solar radiation booster of the immune system, prevents

gastrointestinal, neurodegenerative, and ocular diseases, which is why it is considered the most promising natural antioxidant that has been reported to date [5, 6]. Other carotenoids such as B-carotene, canthaxanthin, zeaxanthin, lutein, act in synergy and make natural astaxanthin a more effective antioxidant than synthetic astaxanthin, making it more effective in the treatment of various diseases and of greater benefit to human health [6, 7]. So, it is necessary to consume it through a food diet [5, 8].

Worldwide, economic, technological, cultural, and scientific development has had an impact on eating habits that are usually risky and a disordered lifestyle. As a consequence, heart disease has increased, diabetes, hypertension, obesity, and metabolic syndrome [9, 10].

In addition to the current economic, social, and environmental crisis that the world is facing, there is also a rise in the occurrence and spread of various diseases among humans. Recognizing this problem, both the FAO and UN have called upon researchers, entrepreneurs, and economic and industrial sectors to explore new sources of healthy and sustainable natural foods that can cater to the vulnerable population of nations [11]. In this context, the natural pigment astaxanthin produced by the *Haematococcus pluvialis* microalgae is gaining and increasing attention due to its potent bioactivity and potential benefits for human health. Consequently, several researchers have dedicated their efforts to the cultivation and biotechnological applications of this microalgae [4].

However, despite synthetic astaxanthin being the most commonly form for sale worldwide, it should not be used as a nutritional supplement due to its petrochemical origin. Consequently, the Food and Drug Administration (FDA) has not authorized its use in human nutrition [12, 13]. Additionally, in 2008, the Food and Agriculture Organization of the United Nations (FAO) issued restrictive regulations on the use of synthetic dyes in the food and feed industry. These regulations have contributed to the increasing utilization of natural astaxanthin as a food coloring agent [14, 15].

Thus, this literature review highlights the consumption of natural astaxanthin produced by the microalgae *H. pluvialis* and its potential beneficial effects on human health.

2. General information about astaxanthin

2.1 Definition and sources of production of astaxanthin

Astaxanthin is a naturally occurring fat-soluble pigment synthesized by the photosynthetic organisms and is found in various natural environments, particularly aquatic environments. The red pigmentation observed in salmon, shrimp, lobster, and crab tissue is attributed to the presence of ataxanthin [16, 17]. Although astaxanthin can be synthesized by different microorganisms, its productivity is generally too low for commercial exploitation (**Table 1**). However, *H. pluvialis* stands out among these microorganisms, with a productivity of 2.64% in relation to its dry weight, making it the most important microalgal species in the world [20, 21, 26].

Additionally, astaxanthin is a secondary carotenoid, from the xanthophyll group, it has unique chemical properties based on its molecular structure, it has 2 carbonyl groups, 2 hydroxyl groups, and 11 conjugated ethylenic double bonds. The polyene character gives it a distinctive molecular structure, chemical properties, and light absorption characteristics. The presence of a keto group and a hydroxyl group at the cyclic ends of the molecule, gives it great reactive power (**Figure 1**). This explains some of its unique characteristics such as the ability to be esterified, the high antioxidant activity, and its amphipathic nature over other carotenoids [27, 28].

Microorganisms	Astaxanthin (% dry weight)	Reference
<i>Chlorella zofingiensis</i>	0.7	[18]
<i>Chlorococcum</i> sp	0.7	[19]
<i>Haematococcus pluvialis</i>	2.4	[20]
<i>Haematococcus pluvialis</i>	2.03	[21]
<i>Neochloris wimmeri</i>	1.9	[22]
<i>Protosiphon botryoides</i>	1.4	[22]
<i>Phaffia rhodozyma</i>	0.4–0.8	[23, 24]
<i>Scotiellopsis oocystiformis</i>	1.1	[22]
<i>Xanthophyllomyces dendrorhous</i>	0.09	[25]

Table 1.
Content of Astaxanthin produced by different microorganisms.

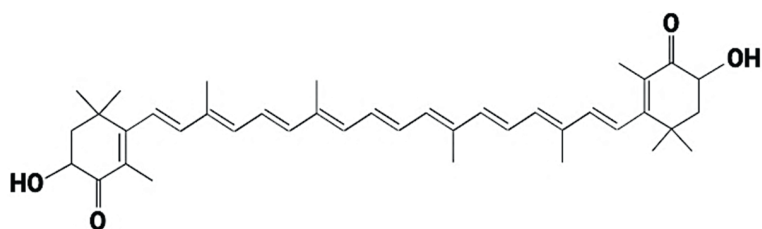


Figure 1.
Molecular structure of astaxanthin.

2.2 Biological role of astaxanthin in *Haematococcus pluvialis*

Haematococcus pluvialis is a unicellular microalga that thrives in freshwater environments. It belongs to the Chlorophyta division and exhibits a fascinating life cycle that undergoes transformations depending on environmental factors. The life cycle stages include: (A) Vegetative State: This is the green bi-flagellated oval cell stage, where the microalgae are actively growing and reproducing. (B) Initial Palmella State: When the cell experiences stress, it transitions into a non-flagellated spherical cell with a green coloration. This stage is also known as the palmella state. (C) Red Palmella State: Under stressful conditions, the cell undergoes a transition and develops a reddish coloration. (D) Aplanospore or Cyst: This stage is characterized by a

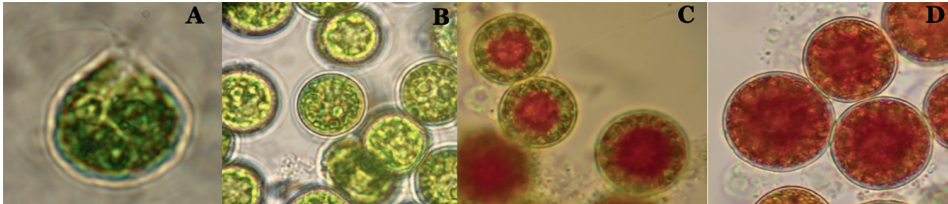


Figure 2.
Different cell forms of the microalga *Haematococcus pluvialis*. (A) Green vegetative cell; (B) initial palmella; (C) Palmella under stress conditions; (D) Aplanospore predominantly red under stressful conditions. Source: Authors.

predominantly red, spherical shape with a rigid cell wall. The cyst serves as a protective mechanism for the genetic material and photosynthetic machinery of the cell (as shown in **Figure 2**) [2, 29].

During the aplanospore/cyst stage, *Haematococcus pluvialis* experiences intense environmental stress. To safeguard its essential components, the microalgae produces astaxanthin, which accumulates in lipid vesicles and forms cytoplasmic globules, giving the cells their distinctive red coloration. Astaxanthin plays a crucial role in protecting the microalgae's genetic material and photosynthetic machinery during this critical stage [26, 30, 31].

2.3 Metabolic pathway of astaxanthin synthesis in *Haematococcus pluvialis*

In *Haematococcus pluvialis*, numerous genes have been identified that are responsible for the synthesis of carotenoids, particularly in relation to astaxanthin biosynthesis. The study of these genes has provided valuable insights into the regulation of astaxanthin biosynthesis and a deeper understanding of its biological role in response to stress [20, 27, 32, 33].

The precursor for carotenoid synthesis is isopentenyl pyrophosphate (IPP) [34]. In higher plants, two distinct pathways have been identified for IPP biosynthesis: the mevalonate pathway in the cytosol and the non-mevalonate pathway in the chloroplast [35]. However, in unicellular green microalgae like *Haematococcus pluvialis* and *Chlamydomonas reinhardtii*, it is believed that IPP is synthesized exclusively through the non-mevalonate pathway. This is supported by the presence of the enzyme IPI (isomerase), which catalyzes the conversion of IPP to dimethylallyl diphosphate (DMAPP) within the plastids [27, 36, 37].

In the chloroplast of microalgae, the enzyme phytoene synthase (PSY) catalyzes the first step of carotenoid biosynthesis, which involves the condensation of two molecules of 20-carbon geranylgeranyl pyrophosphate (GGPP) to form a 40-carbon phytoene molecule, which serves as the precursor for all carotenoids, as shown in **Figure 3**. The subsequent desaturation reactions of PSY are catalyzed by two structurally similar enzymes, phytoene desaturase (PDS) and ζ -carotene desaturase (ZDS), converting the colorless phytoene into colored lycopene. The subsequent steps of the pathway lead to the synthesis of colored carotenoids, carried out by membrane-bound enzymes such as PDS and lycopene β -cyclase (LCY). The biosynthesis of astaxanthin in *H. pluvialis* follows the general carotenoid pathway up to the formation of β -carotene [4, 27, 30].

Studies using carotenogenic inhibitors and *in vitro* and *in vivo* analysis of astaxanthin synthesis in *H. pluvialis* have revealed the involvement of two enzymes, β -carotene ketolase (BKT) and β -carotene hydroxylase (CHY), in the conversion of β -carotene to astaxanthin. BKT converts β -carotene to canthaxanthin via an equinone intermediate, where CHYB participates in the formation of astaxanthin [39]. The genes for ZDS and carotenoid isomerase (CRTISO) have not yet been well studied in *H. pluvialis* [9, 36]. Although the specific steps of astaxanthin biosynthesis occur in the cytoplasm, the enzymes of the general carotenoid pathway are localized in the chloroplast [9, 32, 40].

2.4 Extraction and quantification methods of astaxanthin from *Haematococcus pluvialis*

Various extraction methods have been employed to extract astaxanthin from *Haematococcus pluvialis*. These methods involve the use of organic solvents such

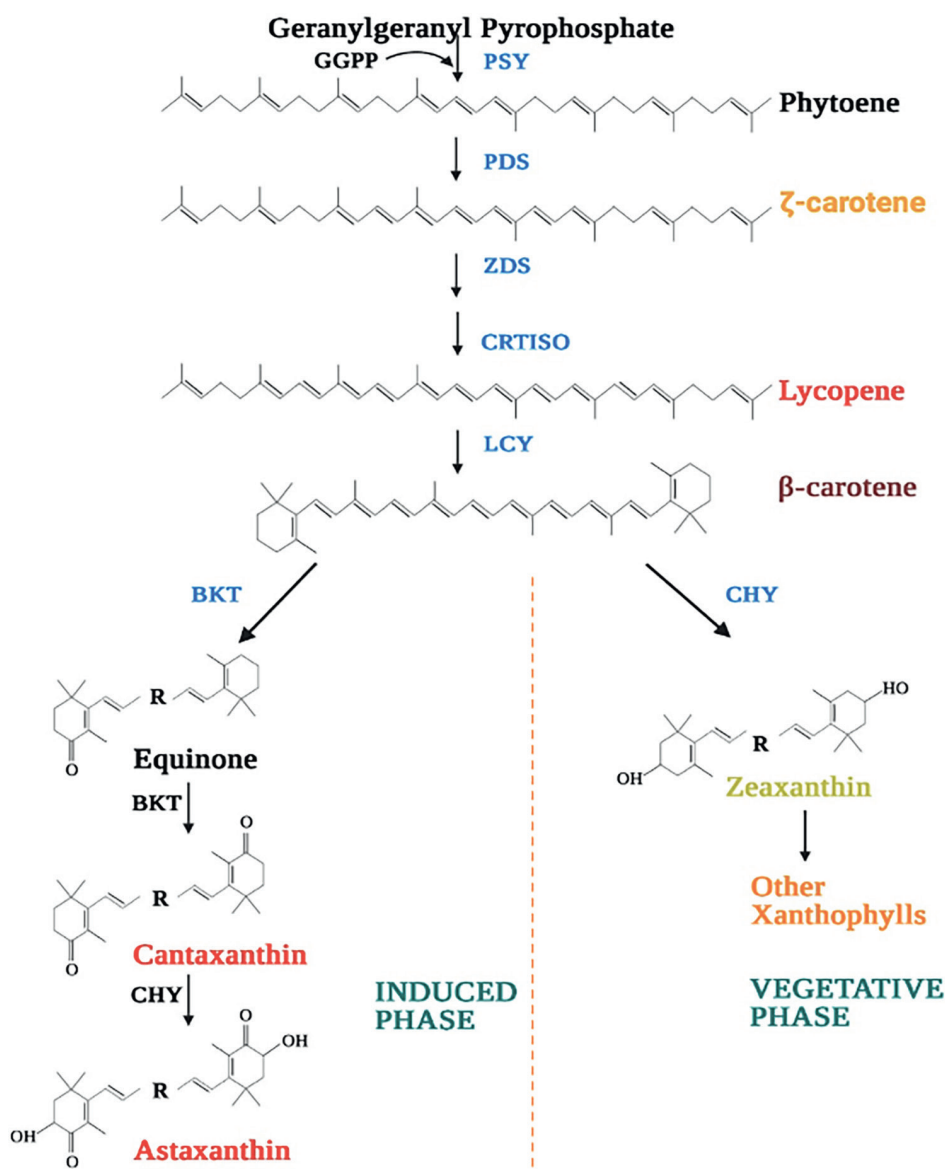


Figure 3.
 Metabolic pathway of astaxanthin synthesis in *H. pluvialis*. Adapted from Bhosal, P. Bertein, P 2005 [38].

as acetone, ethanol, ethyl acetate, n-hexane, dichloromethane, and methanol, as well as hydrophobic deep eutectic solvents (DES) based on oleic acid and terpenes [20, 41, 42]. Prior to extraction, the cysts of *H. pluvialis* need to be lysed. The extraction of total carotenoids is typically initiated through a series of sonication and centrifugation cycles until the sample becomes colorless [21].

Following the extraction of total carotenoids, the isolation of astaxanthin is facilitated by a de-esterification process. This can be achieved through saponification using KOH or NaOH [41], enzymatic hydrolysis with alkaline lipase [43], or cholesterol esterase treatment, which aids in chromatographic analysis, concentration and pigment yield. Astaxanthin extracts are then analyzed using high-performance liquid

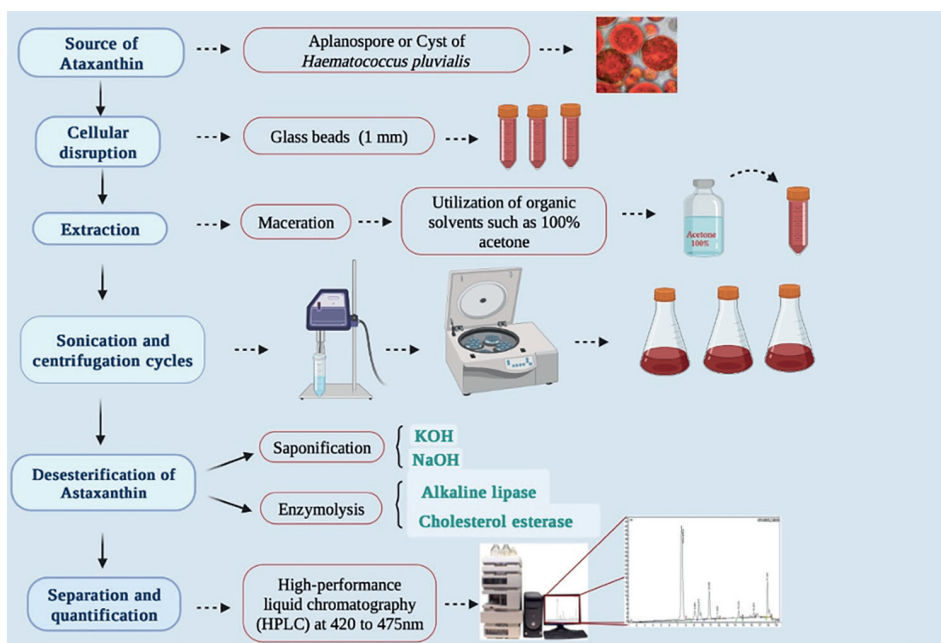


Figure 4. Schematic diagram illustrating the astaxanthin extraction process using 100% acetone. The diagram showcases the various steps involved in the extraction procedure. Source: The authors.

chromatography (HPLC) at a wavelength between 440 and 475 nm. The retention time and absorption spectrum are compared with known standards to identify and quantify astaxanthin [41, 44]. **Figure 4** provides a general overview of the astaxanthin extraction process.

3. Bioactivity of astaxanthin in human health

Various studies have demonstrated that astaxanthin is a carotenoid of considerable interest due to its potent bioactivity in human health. Below is a detailed overview of its potential.

3.1 Antioxidant activity

Oxygen is known to be an essential element for life. However, reactive oxygen species (ROS) and singlet oxygen are generated during cellular metabolism as a result of an imbalance between the production of free radicals and the cell's antioxidant mechanisms, leading to oxidative stress [45, 46]. ROS are highly unstable molecules that accumulate in cells in response to physiological stress, air pollution, tobacco smoke, exposure to chemicals, or ultraviolet (UV) radiation, causing severe damage to DNA, proteins, and lipid membranes [26, 47]. When DNA is damaged, cells fail to function normally, leading to numerous problems and diseases. To address these issues, the human body is designed to neutralize free radicals and singlet oxygen at a normal level by producing its own antioxidants. For example, it produces the enzyme superoxide dismutase, which is highly effective in eliminating free radical molecules, and other enzymes that quench singlet oxygen activity, thus protecting the cell from oxidative damage [46].

Currently, the amount of antioxidants produced by our bodies is insufficient to counteract the production of free radicals and singlet oxygen caused by stress. Therefore, it is necessary to enhance the levels of antioxidants through a healthy diet [7]. Consequently, nutritionists recommend incorporating natural antioxidants into our diets as a means of protection against our hectic lifestyles [48, 49]. Extensive research has demonstrated the efficacy of carotenoids such as astaxanthin and β -carotene as potent antioxidants that effectively hinder the activity of singlet oxygen. These compounds not only scavenge free radicals but also neutralize them, thereby safeguarding our body's cells from oxidation and degradation [10, 50–52].

3.2 Anti-inflammatory effects

The initial immune response to infection or irritation is inflammation, also known as the innate defense mechanism. However, certain inflammatory reactions can have detrimental effects on host cells or tissues, leading to various diseases including arthritis, hepatitis, gastritis, colitis, atherosclerosis, pneumonia, among others [9, 45]. Both *in vitro* and *in vivo* studies have demonstrated that astaxanthin exhibits superior anti-inflammatory effects compared to common medications [16]. Consequently, natural anti-inflammatory substances such as astaxanthin are extensively utilized for the prevention and management of inflammatory conditions due to their ability to inhibit the production of nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokines [1, 47]. Furthermore, research has shown that astaxanthin derived from the microalga *H. pluvialis* is effective in alleviating symptoms of ulcers caused by *Helicobacter pylori* and reducing gastric inflammation [48]. Based on these findings, it can be concluded that astaxanthin serves as an anti-inflammatory agent, and its consumption may contribute to the reduction of DNA damage, the modulation of acute-phase protein levels, and the improvement of the immune response [8, 46, 49].

3.3 Hepatoprotective effects

The liver is a vital organ responsible for cellular catabolism and anabolism. It plays a crucial role in various functions, including the oxidation of lipids to generate energy, detoxification of harmful substances, and elimination of viruses, pathogenic bacteria, and damaged red blood cells [53]. These functions result in the production of substantial amounts of free radicals and oxidative byproducts, necessitating protective mechanisms to safeguard liver cells from oxidative damage [13]. Astaxanthin has demonstrated remarkable efficacy in protecting mammalian liver cells against lipid peroxidation, surpassing the cellular protection provided by vitamin E [16]. Additionally, astaxanthin and β -carotene have been shown to exhibit hepatoprotective properties by inhibiting oval cell proliferation and promoting cellular differentiation in hepatocytes and bile duct epithelial cells during liver regeneration. This is particularly significant in preventing liver cancer resulting from the inhibition of normal cellular differentiation in hepatocytes [10, 54]. Moreover, astaxanthin offers hepatic protection in cases of hepatic ischemia–reperfusion injury by reducing the formation of oxidant-induced protein carbonyls and the conversion of xanthine dehydrogenase to xanthine oxidase. The remarkable effects of astaxanthin observed in mammalian cells have led scientists to recommend its use as an antioxidant therapy for patients with chronic hepatitis C, aiming to prevent obesity, metabolic syndrome, and liver diseases associated with insulin resistance [7, 48].

3.4 Antidiabetic activity

Studies conducted on humans have consistently demonstrated that carotenoids play a crucial role in reducing the risk of developing type 2 diabetes mellitus (T2DM). Increased intake of carotenoids has been found to be associated with lower levels of glycated hemoglobin (HbA1c) [13, 45]. These findings establish a clear connection between carotenoid consumption and the reduction of T2DM risk. Thus, it is imperative to include natural carotenoids in the human diet as a preventive and therapeutic measure against T2DM [55, 56].

Among the various carotenoids investigated, astaxanthin stands out as one of the most extensively studied compounds. Astaxanthin has demonstrated significant potential in the management of diabetic patients by effectively reducing oxidative stress induced by hyperglycemia, enhancing insulin levels, and lowering blood glucose levels [49, 57]. Notably, astaxanthin exhibits superior antioxidant activity compared to other carotenoids such as lutein, β -carotene, and zeaxanthin, making it a safe and viable option for human consumption [15, 48].

3.5 Cardiovascular activity

Astaxanthin, among other carotenoids, exhibits remarkable therapeutic benefits in the management of cardiovascular diseases. This can be attributed to its unique physicochemical structure, which enables it to interact effectively with cell membranes and possesses distinct properties [13, 47]. A study conducted on hypertensive mice treated with natural astaxanthin revealed its ability to prevent atherosclerosis, significantly reduce blood pressure, and delay the occurrence of stroke. These findings indicate that astaxanthin holds the potential in safeguarding against hypertension and stroke [1]. Furthermore, in patients at risk of cardiovascular disease, astaxanthin has shown promise in the treatment of myocardial injuries, thrombolysis, and other heart-related conditions. In a separate study involving individuals from different age groups who consumed astaxanthin, elevated adiponectin levels, improved triglyceride levels, and enhanced high-density lipoprotein cholesterol levels were observed, irrespective of age [53, 55].

3.6 Anticancer activity

Scientific evidence supports the potent cancer chemopreventive properties of carotenoids, which are independent of their antioxidant activity or their potential to convert to retinoids [13]. Among these carotenoids, astaxanthin exhibits exceptional anticancer activity, distinguishing it from β -carotene and canthaxanthin. Astaxanthin has demonstrated significant inhibitory effects on the growth of various tumor cells, including oral fibrosarcoma, breast cancer cells, prostate cells, and embryonic fibroblasts, suggesting its potential application in cancer treatment and prevention [45, 53]. Moreover, studies have shown that astaxanthin possesses notable preventive effects on colon carcinogenesis and bladder carcinogenesis. It also exhibits the ability to suppress fibrosarcoma cell growth and enhance immunity against tumor antigens, indicating its potential for greater anti-tumor activity through immune response enhancement [58, 59].

Furthermore, several studies utilizing extracts from the microalga *H. pluvialis*, which contains astaxanthin, have demonstrated the inhibition of human colon cancer cell growth, including HCT-116, HT-29, LS-174, WiDr, and SW-480. This inhibition

is achieved by arresting cell cycle progression and promoting apoptosis or cell death [16, 49]. These findings suggest that *H. pluvialis* extracts may also exhibit equal or superior effects in the treatment and prevention of cancer.

3.7 Neuroprotective effects

The nervous system, characterized by its high content of unsaturated fats and iron (which possesses prooxidant properties), is susceptible to oxidative damage due to aerobic metabolism and blood supply. Oxidative stress has been identified as a causal factor in the pathogenesis of various neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Diets rich in antioxidants have shown significant potential in reducing the associated risks of these diseases [5, 12, 51].

Notably, natural astaxanthin has been found to possess the ability to traverse the blood–brain barrier in mammals, thereby extending its antioxidant benefits to brain tissue. By inhibiting oxidative stress, this antioxidant pigment has the potential to reduce free radical-induced damage caused by ischemia, cell death, neurodegeneration, and cerebral infarction. As a result, astaxanthin holds clinical promise in the treatment of vulnerable or susceptible patients to ischemic events. Its potent bioactivity is attributed to its intracellular inhibition of ROS and its neuroprotective effects observed in human neuroblastoma SH-SY5Y cells. Additionally, astaxanthin has been found to enhance the proliferation of neural stem cells and promote their neural osteogenic and adipogenic differentiation [60]. These findings collectively indicate that astaxanthin possesses potential antioxidant and mitochondria-protective effects, making it a promising candidate for the prevention and treatment of neurodegenerative diseases.

3.8 Eye protective effects

Recent human studies have provided compelling evidence regarding the ocular protective effects of astaxanthin extracted from the microalgae *H. pluvialis*. These studies have shown that astaxanthin supplementation significantly improves deep vision, critical flicker fusion, and eye fatigue [48]. Furthermore, it has been found to exert a substantial inhibitory effect on the development of choroidal neovascularization, a condition that can lead to severe vision problems and even blindness [9, 45].

Animal trials investigating the effects of astaxanthin on ocular health have also yielded promising results. Astaxanthin has demonstrated potential as a therapeutic agent for ocular inflammation, as it can interact with selenite, thereby delaying its precipitation in the crystalline lens and attenuating cataract formation. Moreover, in cases of high intraocular pressure, astaxanthin has been associated with a significant decrease in the percentage of apoptotic cells in the retina, highlighting its protective effect in ocular hypertension [16, 51]. Additionally, rats fed with astaxanthin have shown reduced damage to their retinal photoreceptors from ultraviolet radiation and faster recovery compared to animals that did not receive astaxanthin supplementation [60, 61].

3.9 Skin protective effects

The skin possesses inherent antioxidant agents that can effectively neutralize the harmful impacts of ROS and mitigate cellular damage. However, when the production of ROS reaches excessive levels as a result of exposure to ultraviolet (UV) radiation, these natural defenses become inadequate [62]. The accumulation of ROS within

cells leads to cell death, and an excessive level of cell death can manifest as wrinkles, skin dryness, and photoaging conditions such as skin inflammation, melanoma, and skin cancer [1, 14]. Previous studies have demonstrated the therapeutic potential of natural pigments in protecting the skin [62, 63]. Consequently, consumers show a preference for naturally derived compounds in their cosmetic products rather than chemically synthesized pigments [63].

In a study involving women aged over 40, which investigated the relationship between skin roughness and aging, a clear correlation was observed between the concentration of carotenoids and individuals with elevated antioxidant levels. These individuals exhibited noticeable improvements in wrinkles and skin roughness [5, 64]. Another trial assessed the systemic photoprotective effects against UV radiation-induced damage in human dermal fibroblasts using various carotenoids such as astaxanthin, canthaxanthin, and β -carotene. The findings indicated that astaxanthin exhibited a significantly high level of photoprotection, effectively mitigating UV-induced alterations. Furthermore, the uptake of astaxanthin by fibroblasts was found to be greater than that of other carotenoids. These results suggest that astaxanthin possesses superior preventive properties against photooxidative changes in dermal cells [9, 55].

3.10 Effects on fertility

Astaxanthin has also exhibited notable effects on fertility. Evidence in humans indicates that a nutritious diet featuring a high intake of antioxidants, such as astaxanthin, can serve as an affordable and safe means to enhance sperm quality and fertility [65]. Pilot trials conducted on infertile men, who received astaxanthin according to the guidelines set by the World Health Organization (WHO), revealed that this carotenoid significantly decreased levels of ROS and improved the secretion of inhibin B hormone by Sertoli cells. These findings suggest a positive impact of astaxanthin on sperm characteristics and fertility in infertile patients [51].

3.11 Effects on the immune system

Immune cells are highly susceptible to oxidative stress due to the high concentration of polyunsaturated fatty acids present in their plasma membranes. However, the use of astaxanthin can counteract this sensitivity, as it has been shown to decrease markers of oxidative DNA damage and inflammation, thereby enhancing immune response [64, 66, 67]. In *in vitro* immunology studies utilizing human blood cells, astaxanthin has also demonstrated immunomodulatory effects, exhibiting an enhancement in the production of immunoglobulins in response to T-cell-dependent stimuli [53].

Considering the close association between oxidative stress and impaired immune response in individuals with diabetes, an animal study demonstrated that astaxanthin could serve as a beneficial adjunct in the prophylaxis and recovery of lymphocyte dysfunctions associated with diabetes. This carotenoid was shown to restore redox balance and potentially exert an anti-apoptotic effect on lymphocytes [8, 16].

4. Conclusions and outlook

This review highlights the potential impact of astaxanthin, a pigment, on human health, particularly in the treatment and prevention of diseases associated with

oxidative stress. Among various carotenoids, astaxanthin stands out for its remarkable protective efficiency, attributed to its ability to penetrate the cell membrane and its unique chemical structure. *Haematococcus pluvialis*, a microalga, has been identified as the microorganism with the highest capacity for producing and accumulating astaxanthin under environmentally stressful conditions.

Having recognized the valuable properties of astaxanthin and its natural sourcing from *H. pluvialis*, it is recommended that researchers in the healthcare field conduct clinical trials involving human subjects. Such trials would provide insights into the functions of the pigment, the appropriate patient population, and the optimal dosage for disease prevention, treatment, and control. Furthermore, in less developed countries, it is essential to establish parameters for large-scale cultivation and stress conditions to achieve high astaxanthin production. Additionally, there is a need to explore cost-effective and environmentally friendly methods for pigment extraction, ensuring its suitability for human consumption.

Acknowledgements

The authors would like to thank the contribution of the projects INCYT-PNF-2017 M3112 and CUP 91870000.0000.384095- Peninsula de Santa Elena State University- Ecuador. And it has the permission of the Ministry of Environment, Water and Ecological Transition MAATE-DBI-CM-2022-0264.

Conflict of interest

The authors declare no conflict of interest.

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