Handbook of Food Bioactive Ingredients

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Editors

Handbook of Food Bioactive Ingredients

Properties and Applications

With 301 Figures and 131 Tables

Springer

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Preface

In recent years, the field of food science and nutrition has witnessed a remarkable growth in understanding the importance of bioactive ingredients in promoting human health and well-being. Bioactive compounds found in various foods have been extensively studied for their potential health benefits and therapeutic properties. These compounds possess a wide range of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardiovascular-protective effects. The significance of bioactive ingredients in preventive medicine and the development of functional foods has sparked great interest among researchers, food technologists, nutritionists, and health professionals.

The *Handbook of Food Bioactive Ingredients: Properties and Applications* aims to provide a comprehensive and up-to-date resource that encompasses the diverse aspects of bioactive ingredients in food. This handbook serves as a valuable tool for scientists, professionals, and students seeking an in-depth understanding of the properties and applications of various bioactive compounds. It presents a compilation of the latest research and knowledge in the field, including insights into their chemical composition, extraction techniques, bioavailability, and mechanisms of action.

This comprehensive handbook is divided into several sections to cover the major classes of bioactive ingredients found in food. Each section provides a detailed exploration of the properties, sources, bioactivity, and potential applications of the specific bioactive compounds. The handbook covers a wide range of bioactive ingredients, including polyphenols, flavonoids, carotenoids, fatty acids, fiber, peptides, prebiotics, vitamins, and minerals, among others. Additionally, it delves into the latest advances in the identification and characterization of novel bioactive compounds from both traditional and unconventional sources.

In order to ensure the relevance and currency of the information presented, this handbook incorporates corresponding references and citations from recent years. The cited research represents the most recent advancements in the field, offering readers an up-to-date perspective on the properties and applications of food bioactive ingredients. These references encompass a wide range of scientific publications, including peer-reviewed articles, books, and conference proceedings, authored by esteemed researchers and experts in the field.

We think that this handbook will serve as a valuable resource for professionals and researchers working in the fields of food science, nutrition, pharmaceuticals, and preventive medicine. It offers a comprehensive overview of the properties and applications of bioactive ingredients, bridging the gap between scientific research and practical applications in the development of functional foods and dietary interventions. By harnessing the potential of bioactive ingredients, we can pave the way for a healthier and more sustainable future.

Finally, we extend our sincere gratitude to all the contributors who have dedicated their expertise and time to enrich this handbook with their valuable insights. We hope that this comprehensive collection will inspire further research and innovation in the field of food bioactive ingredients and contribute to the advancement of human health and well-being.

Gorgan, Iran — Seid Mahdi Jafari
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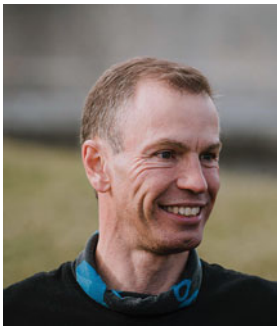
Seid Mahdi Jafari received his PhD in Food Process Engineering from the University of Queensland (Australia), in 2006. Now, he is a full-time Professor in GUASNR (Iran). He has published >550 papers in International Journals (h-index = 90 in Scopus) and 100 book chapters/36 books with Elsevier, Springer, and Taylor & Francis. Selected achievements: (1) one of the top national researchers by the Iranian Ministry of Science, Research, and Technology (2017); (2) one of the world's highly cited researchers by Clarivate Analytics (Web of Science), in 2018, 2019, and 2020; (3) a top reviewer in the field of agricultural and biological sciences by Publons (2018 and 2019). **Personal Website**: www.smjafari.com

Ali Rashidinejad is an accomplished scholar and expert in the field of Food Science, with a special focus on phytochemicals and bioactive compounds. He obtained his PhD in Food Science from the prestigious University of Otago in New Zealand, solidifying his foundation of knowledge and expertise. He is currently a senior scientist and an academic member of Riddet Institute, Massey University (Palmerston North, New Zealand).

On the field of bioactive ingredients, Dr. Rashidinejad has published numerous impactful papers in top-ranked international food science and nutrition journals, as well as co-authoring books and book chapters on various topics related to his field, further solidifying his authority in the subject matter. He is the primary investigator and first inventor of "FlavoPlus," a new a groundbreaking method for

delivery of hydrophobic flavonoids in functional foods. His research and contributions have not only expanded scientific knowledge but also hold promise for practical applications that can positively impact the food industry and public health.



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Astaxanthin

Sources, Properties and Benefits

Chi-Ching Lee

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Abstract

Astaxanthin is a lipid-soluble orange-red pigment in the family of the xanthophylls, which are the oxygenated derivatives of carotenoids, including β-cryptoxanthin, zeaxanthin, canthaxanthin, and lutein. Its molecular structure is similar to β-carotene and other carotenoids, but it does not have the biological activity of pro-vitamin A in the human body. Astaxanthin can be found in microalgae, yeast, bacteria, phytoplankton, a few fungi, and marine animals, such as *Haematococcus pluvialis*, *Xanthophyllomyces dendrorhous, Agrobacterium aurantiacum, Chlorococcum* sp., salmon, lobster, shrimp, crustacean, and red sea bream. The main application of astaxanthin in the aquaculture industry is used as a food colorant in fish feed to provide the desirable reddish-orange pigmentation in crustacean and farmed fish. Many studies demonstrated that astaxanthin had shown a variety of its biological activities and health benefits, such as antioxidant, anti-inflammatory, anti-apoptosis, anticancer, anti-obesity, anti-diabetes, and cardioprotection. The special structure of astaxanthin not only shows potential antioxidant capacity but also allows it to pass through the cell membrane to display potent antioxidant activity inside and outside the cell. This chapter will discuss the physical and chemical properties of astaxanthin, the sources of astaxanthin, extraction and isolation of astaxanthin, its aquaculture application, astaxanthin biological activities in human health, and its benefits in mammals and chickens.

Keywords

Astaxanthin · Carotenoids · Biological activities · Human health · Antioxidant · Aquaculture applications

1 Introduction

Astaxanthin is an orange-reddish pigment with a similar structure to β-carotene and lycopene. It is a secondary metabolite produced by microalgae under stress conditions such as strong light, high salinity, high carbon-nitrogen ratio, and low nutrient utilization. It has a protective mechanism for microalgae themselves. The most common source and the highest production of astaxanthin are from freshwater unicellular green microalgae *Haematococcus pluvialis*. Other sources of astaxanthin can also be produced by bacteria and yeast. Some marine or terrestrial organisms feed on microalgae, such as shrimp, crab, lobster, trout, krill, salmon, red sea bream, flamingo, and quail. Astaxanthin accumulates in their body tissues and displays a bright pink or orange color. Most animals do not produce astaxanthin on their own but accumulate it from food. Shrimp feed on red algae and consequently accumulate

astaxanthin in the body. Only a few species of shrimps can metabolize other carotenes into astaxanthin by themselves. Since astaxanthin contains two oxygenated groups in each end ring on its chemical structure, it has significant antioxidant capacity. Its ability to scavenge reactive oxygen species and capture free radicals is ten times more than β-carotene and 500 times more than α-tocopherol (Duffose 2009). Astaxanthin has been widely recognized for its biological activities, such as antioxidant activity, anti-lipid peroxidation activity, anti-inflammation, antiaging, antitumor, anticancer, and immuno-modulation. Astaxanthin also can provide the prevention of cardiovascular and cerebrovascular diseases due to passing the blood-brain barrier easily. In addition, it has a high tinctorial property as a food colorant or a feed additive in the human food and animal feed industry. In this chapter, the properties of astaxanthin will be interpreted for its physical and chemical characteristics. The sources and analysis of astaxanthin will also be mentioned. The application of astaxanthin will be broadly discussed in a variety of business areas such as human food, animal feed, nutraceutical, and pharmaceutical industry.

2 Physical and Chemical Properties of Astaxanthin

2.1 Chemical Structure and Isomerism

Astaxanthin is a reddish-orange pigment in carotenoids that contain more than seven hundred fifty naturally occurring pigments that can be generated and synthesized by bacteria, fungi, algae, mosses, and higher plants. Carotenoids are classified into two classes depending on the chemical components found in their molecules. One class of carotenoids is carotenes, including only hydrogen and carbon. The common bioactive compound of carotenes is lycopene which is symmetrical tetraterpene with eight isoprene units. The chemical structure of lycopene is comprised of 40-carbon hydrocarbons with a long and straight structure containing a chain of conjugated double bonds. The other class of carotenoids is xanthophylls, including hydrogen, carbon, and also oxygen. In the molecule structure of xanthophylls, oxygen can be found as hydroxyl (OH) groups in zeaxanthin, carbonyl (C=O) groups in canthaxanthin, or a combination of hydroxyl and carbonyl groups located in each ionone ring of astaxanthin (Fig. 1). This feature of the chemical structure can provide an excessive polar nature, significant antioxidant activity, and the ability to be esterified. The molecular formula of astaxanthin $C_{40}H_{52}O_4$ and its molar mass is 596.84 g/mol. Astaxanthin is comprised of two terminal ionone rings joined by a polyene chain which provides its light-absorption features and chemical properties. This molecule can be derived from 3-hydroxylation and 4-ketolation of β-carotene at both β-ionone end rings, which include two asymmetric carbon centers at the 3, 3′ positions. Hydroxylation is catalyzed by β-carotene hydroxylase and can be found in higher plants. However, ketolation is catalyzed by β-carotene ketolase and can only be observed in a few unicellular green algae, fungi, and some bacteria.

In the natural sources of astaxanthin, there are a variety of chemical structures, such as free forms, esterified forms, stereoisomers, and geometric isomers (Higuera-

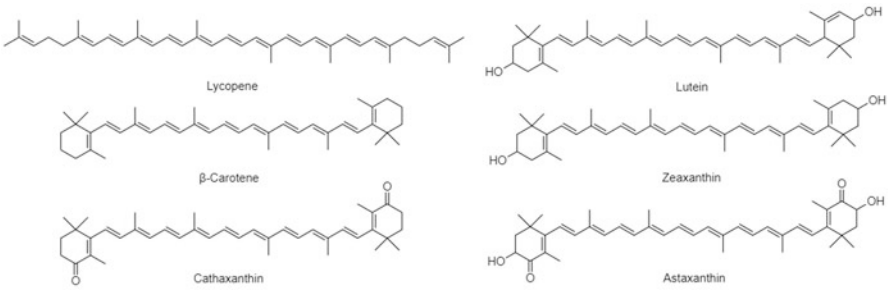

Fig. 1 Chemical structure of astaxanthin and other carotenoids

Ciapara et al. 2006). The hydroxyl group in the two terminal β rings can react with fatty acid under esterification to have the monoester form or the diester form when both hydroxyl groups are esterified. One or both hydroxyl groups of astaxanthin may be esterified with different fatty acids such as linoleic acid, palmitic acid, or stearic acid. Sometimes astaxanthin also can associate with other proteins or lipoproteins to form carotenoproteins and carotenolipoproteins, respectively. In addition, there may exist in the free form of astaxanthin when both hydroxyl groups are not esterified (Johnson and Echavarri-Erasun 2011). Each double bond in the long polyene chain may offer two configurations as *cis* or *trans* forms in geometric isomers. *Trans* isomers are usually more stable than cis isomers because *trans* isomers have more favorable steric interaction of the substituents, a lower heat exothermic energy of combustion, and thermodynamically higher stability than cis isomers. Besides, *trans* isomers can be found primarily among the most carotenoids in nature. Because there are two chiral centers in C-3 and C-3′ at both β-ionone terminal rings, it makes that all-*trans* configuration of astaxanthin in the long chain may exist in three configurational stereoisomers: one meso form (3R, 3′S; 3S, 3′R) and two enantiomers (3R, 3′R and 3S, 3′S) (Fig. 2). These three types of stereoisomers can be found in microalgae, yeast, and crustacean. Synthetic astaxanthin also comprises a racemic mixture of these three isomers (Moretti et al. 2006). Among all these optical isomers, the two enantiomers (3S, 3′S) and (3R, 3′R) are the most abundant in nature. The unicellular biflagellate microalga *Haematococcus* can produce the enantiomers (3S, 3′S), and this isomer can also be found in wild Atlantic salmon as in the free form. The yeast *Xanthophyllomyces dendrorhous* can biosynthesize the enantiomer (3R, 3′R), and this isomer is also the main astaxanthin configurational stereoisomer in the Antarctic krill *Euphausia superba* as commonly in the esterified form (Hussein et al. 2006).

2.2 Physicochemical Characteristics

Crystalline astaxanthin is a red or pink solid powder with a melting point of 215–216 °C and a boiling point of 774 °C. It is insoluble in water resulting in fat-soluble and easily soluble in most organic solvents such as dichloromethane,

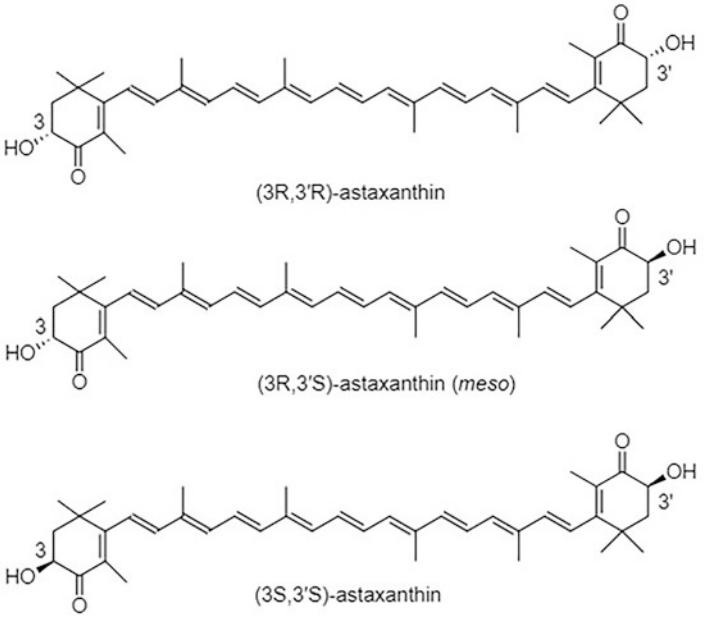

Fig. 2 Optical isomers of astaxanthin

benzene, chloroform, acetone, and dimethyl sulfoxide. The ketone group and the hydroxyl group at both end rings of the molecular structure of astaxanthin, as well as the conjugated double bond in a polyene long chain, can trap unpaired electrons of free radicals or donate an electron to a free radical for the neutralization purpose. Therefore, astaxanthin has high antioxidant activity to scavenge free radicals in reactive oxygen species. The molecule structure of astaxanthin is also susceptible to light, heat, acids, alkalis, and oxide compounds. All these factors cause the degradation of astaxanthin to trigger serial chemical reactions, remarkably ultraviolet light providing a significant influence. Continuous irradiation for about 4 h will entirely cause astaxanthin degradation. On the contrary, astaxanthin is relatively stable in the range of pH 4–7 and below 70 °C. Astaxanthin basically is not affected by many metal ions, such as calcium, magnesium, potassium, sodium, and zinc. Instead, iron and copper ions provide evident destructive effects (Zhou et al. 2018). The chromophore in the molecular structure of astaxanthin has a unique absorption region in the ultraviolet and visible light region so that its crystalline or solution is purple-red color under visible light. Astaxanthin exists mainly in free and esterified forms. Free astaxanthin is extremely unstable and easily oxidized. Typically synthetic astaxanthin is in free form. The esterified form of astaxanthin is stable because of the presence of hydroxyl groups in the terminal ring structure of astaxanthin, which tends to form esters with fatty acids. In comparison with esterified astaxanthin, free astaxanthin is more susceptible to temperature changes and photochemical effects, such as photolysis or photosensitized oxidation.

The esterified form of astaxanthin is mainly found on the skin and shell of fish and crustaceans, and the free form could be observed in their meat and internal organs. The astaxanthin in red yeast *Xanthophyllomyces dendrorhous* and green microalgae *Haematococcus pluvialis* primarily exists in the esterified form. Astaxanthin can be classified into astaxanthin monoester and astaxanthin diester according to the fatty acid it binds. After astaxanthin is esterified, its hydrophobicity is increased, and diesters are significantly more hydrophobic than monoesters. The esterified astaxanthin forms complex molecules with various proteins resulting in different colors.

3 Sources of Astaxanthin

There are a variety of natural sources of astaxanthin, including microalgae, yeasts, shrimps, crabs, crayfishes, salmons, trout, lobsters, and krill. Astaxanthin was first discovered and isolated from lobster in 1938. Microalgae living in the aquatic environment can synthesize astaxanthin. Then they are consumed by insects, zooplankton, or crustaceans. Afterward, they are eaten by fishes and large crustaceans by this means offering them their reddish-orange color. The commercial value and the application of astaxanthin for reusable sources is developing rapidly as a substitute for synthetic manufacture. Commercial astaxanthin is predominantly from the red yeast *Xanthophyllomyces dendrorhous* and the green microalgae *Haematococcus pluvialis* because both microorganisms can synthesize astaxanthin mainly for the application of the pharmaceutical industry. A large number of studies have indicated the optimum experimental conditions for the extraction and synthesis of astaxanthin from these microorganisms (Ni et al. 2008; Kang and Sim 2008).

3.1 Synthetic Astaxanthin

Synthetic astaxanthin comprises a mixture 1:2:1 of isomers (3S, 3S'), (3R, 3S'), and (3R, 3R) that is similar to that formed in live organisms (Higuera-Ciapara et al. 2006). Chemical synthesis produces stereoisomers that vary from those occurring naturally (3S, 3'S) astaxanthin form. In 1981, Widmer et al. synthesized astaxanthin from the educt 6-oxo-isophorone. A Wittig reaction of two C15-phosphonium salts with a C10-dialdehyde is the earliest and most extensively utilized strategy for astaxanthin synthesis. Subsequently, the hydroxylation of canthaxanthin is another approach. In 1993, double Wittig condensation of an appropriate C15 phosphonium salt with the symmetrical C10 dialdehyde 2,7-dimethyl-2,4,6-octatriene-1,8-dial was developed, and this is the primary astaxanthin production commercially on the current market (Ernst et al. 1993). Dienolether condensation for astaxanthin synthesis is also another method. Lastly, the isomerization of marigold flower lutein to zeaxanthin, followed by oxidation to astaxanthin, was developed. Hence, the examination of the astaxanthin structure and content may distinguish between wild and

farmed fish since farmed fish received the synthetic astaxanthin form (Nguyen 2013).

3.2 Microalgae

A great number of research studies have reported that microalgae are the main natural sources of astaxanthin, especially *Haematococcus pluvialis*. It is a freshwater microorganism of the phylum Chlorophyta and the family Haematococcaceae. High amounts of ketocarotenoids can be found in cytoplasmic lipid vesicles of this microalgae. Astaxanthin may exist in the resting cells, particularly under undesirable environmental situations for normal cells growth, because these cells can be produced and accumulated rapidly. The Astaxanthin productivity of *Haematococcus pluvialis* for maximal values ranged from 290 to 428 μg/g cell per day depending on the environmental conditions of the light intensity, culture media, aeration, and so on. The commercial production of astaxanthin from *Haematococcus pluvialis* has become possible because of the recent designs in photobioreactor technology. The Aquasearch Growth Module (AGM), a 25,000 L enclosed and controlled outdoor photobioreactor, was used for astaxanthin manufacturing. Three AGMs with a total capacity of 75,000 L are utilized to generate vast volumes of clean, rapidly growing *Haematococcus pluvialis*, and the biomass of this microalga generated in AGMs is transferred daily to a pond culture system for the purpose of carotenogenesis and astaxanthin accumulation. The photobioreactor can significantly improve astaxanthin production in AGMs for the viability of large-scale manufacturing and high-quality products from *Haematococcus pluvialis* (Domínguez-Bocanegra et al. 2007).

Entirely enclosed photobioreactors with artificial light are utilized in Sweden, and a mix of closed photobioreactors with open culture ponds is effectively used in Hawaii for economically producing *Haematococcus*. The photobioreactors usually provide a two-step procedure in a large-scale, outdoor system. First, vegetative cells must be cultivated under near-optimal growth circumstances, with pH, temperature, and nutrient levels carefully controlled. pH regulation can be automated using metered solenoids and carbon dioxide under demand. Metered solenoids and thermocouples can also be used to maintain temperature control. The culture is exposed to environmental and nutritional stress when a sufficient number of vegetative cells have been produced. By providing inadequate nitrate and phosphate, increasing light intensity and cultural temperature, or enhancing salinity to the growth media in commercial systems stimulate astaxanthin production. Haematocysts develop and begin collecting astaxanthin about 2 to 3 days after the culture is stressed. They are suitable for collection between 3 to 5 days after the formation of haematocysts with 1.5–3.0% astaxanthin content (Lorenz and Cysewski 2000).

Astaxanthin production from *Haematococcus pluvialis* is developed by Cyanotech Corporation, the main and oldest world manufacturer in microalgae cultivation since 1988. Cyanotech Corporation is located in Kailua-Kona, HI, USA. BioAstin® is the trade name of the Hawaiian astaxanthin product and contains

4 ml of astaxanthin per gel cap in a supercritical extract 5% oil. Natural astaxanthin derived from microalgae was industrialized to replace synthetic astaxanthin. The biomass is dried to produce a fine reddish powder. These products may include 1.5–2.0% of astaxanthin and are used as pigments and nutrients for aquatic animals and in the poultry business for broiler and egg yolk coloration. In 2014, Cyanotech Corporation installed a 684 KW photovoltaic system, lowering greenhouse gas emissions by 791 metric tons per year and saving the company a total of 2.5 million dollars for the next 20 years. For the manufacturing of astaxanthin, Cyanotech installed an onsite supercritical carbon dioxide extraction unit in 2015. Cyanotech is the only microalgae firm in the world that can cultivate and generate *Haematococcus* biomass, as well as extract it to make a natural astaxanthin-rich oleoresin. In the Hawaiian astaxanthin manufacturing process, extraction technology is uniquely 1000 bar (14,700 psi) supercritical carbon dioxide extraction facility more quickly and efficiently on a commercial scale globally (Cyanotech 2018).

3.3 Yeasts

The red yeast *Phaffia rhodozyma* has been studied as the natural source of astaxanthin for many decades. Therefore, plenty of scientific research has reported on the extraction of this red yeast under optimum conditions. The modification of the culture media on different carbon sources and nutrients was also studied for the maximum production of astaxanthin and yeast biomass. Astaxanthin extracted from microalgae needs to be absorbed by the human body if there are esters in the structure chain. The astaxanthin produced by the red yeast *Phaffia rhodozyma* is a free form that is easier to be absorbed by the human body. At present, gene transfer in biotechnology has been used to produce a red yeast variant strain *Xanthophyllomyces dendrorhous* to produce a large amount of astaxanthin. The basidiomycetous yeast *Xanthophyllomyces dendrorhous* generates the high-amount carotenoid astaxanthin. Astaxanthin is generated by a few species of bacteria, microalgae, thraustochytrids, and fungi. It is one of the most prevalent carotenoids in the biosphere, especially in marine environments. *Phaffia rhodozyma* is the sexual form of *Xanthophyllomyces dendrorhous* is found in tree exudates at high elevations and latitudes in the Northern Hemisphere (Johnson and Echavarri-Erasun 2011).

Two strategies of glucose feeding were investigated to maximize biomass and carotenoid production by *Phaffia rhodozyma* in pH-stat cultures. The glucose feeding set point (pH 5.02) was higher than the culture pH (5.00) in the first approach, and *Phaffia rhodozyma* grew at a low specific growth rate. The glucose feeding set point (pH 4.98) in the second approach was lower than the culture pH (5.00), and the yeast grew at a high specific growth rate. In the second way of glucose feeding, a "time interval" was added to the glucose pump's control strategy and allowed to expire before the next dose of glucose was added to avoid overfeeding glucose. Carotenoid production was impacted by the length of the time interval, which was established as a crucial time period. The yeast did not develop in pH-stat cultures of *Phaffia rhodozyma* if the time interval was set longer than the crucial time interval.

In addition, the growth of *Phaffia rhodozyma* and its carotenoid production in fed-batch cultures with various feeding strategies and cultivated at particular growth rates were investigated. The dissolved oxygen-stat fed-batch culture produced the highest biomass and the lowest carotenoid content of *Phaffia rhodozyma* compared to continuous feeding, exponential feeding, dissolved oxygen-stat, and pH-stat fed-batch cultures of *Phaffia rhodozyma*. The exponential fed-batch culture produced the lowest biomass and the maximum carotenoid content (Chan and Ho 1999).

The effects of copper and iron on the growth of *Phaffia rhodozyma* and astaxanthin production were investigated. Copper concentrations below 3.2 M enhanced astaxanthin levels within the cells, although growth was slightly reduced. Iron concentrations below 1 mM, on the other hand, reduced cell proliferation and astaxanthin levels. Copper restriction rather than harmful respiratory inhibitors to increase astaxanthin synthesis offers apparent benefits in product quality, environmental impact, and process efficiency. Some research results also demonstrated the optimum conditions for the growth of the red yeast *Phaffia rhodozyma* and astaxanthin production (Ni et al. 2008). The substantial inhibitory impact of high glucose concentration on astaxanthin synthesis of the yeast *Phaffia rhodozyma* is the main hindrance to industrial-scale astaxanthin production. The influence of high glucose on metabolic mechanisms and transcription was determined. Derepression of carotenogenic *pbs* genes increases astaxanthin production in MK19 yeast strain at high glucose (Miao et al. 2019). Moreover, in a pigmentation experiment, Atlantic salmon *Salmo salar* were fed diets treated with the red yeast *Phaffia rhodozyma*, a control diet containing synthetic astaxanthin, and a non-pigmented control diet in ocean pens. The nutritional status of the test fish remained nearly unchanged throughout the study. The application of modified red yeast had no nutritional benefits or drawbacks for the fish (Whyte and Sherry 2001). Ultrasound was used to improve astaxanthin synthesis in batch fermentation with the wild strain of *Phaffia rhodozyma* MTCC 7536. The medium and fermentation conditions were optimized on this wild strain. The maximum astaxanthin production was the sonication of 8.6 mg/L or 1728 μg/g DCW with sonication. The high micro-turbulence induced by sonication is associated with increasing yield (Batghare et al. 2018). Other studies have focused on increasing astaxanthin yields by using metabolic-engineered strains of this yeast. The yield of astaxanthin increased significantly in *Phaffia rhodozyma* PR106 under titanium dioxide stress, as did the yields of lycopene and β-carotene. In addition, titanium dioxide stress enhanced cell division and modified PR106 cell morphology. To enhance astaxanthin production in PR106 cells, additional carbon flux was moved to the astaxanthin synthesis pathway, which decreased carotenoid formation in the astaxanthin branch pathway (Zhang et al. 2021). Furthermore, the effects of atmospheric and room temperature plasma, as well as UV mutagenesis on astaxanthin overproducing mutants, were investigated. A high-production astaxanthin mutant was produced by combined mutagenesis. The carbon source of astaxanthin production is from sugarcane bagasse hydrolysate. In the mutagenized *Xanthophyllomyces dendrorhous* strains, the increase of β-carotene and echinone after overexpression of crtYB implies that the oxygenation processes are rate-

limiting in these transgenic strains. Overexpression of the phytoene desaturase-encoding gene resulted in a rise in monocyclic carotenoids like torulene and HDCO (3-hydroxy-3′,4′-didehydro-β,ψ-carotene-4-one) and a reduction in bicyclic carotenoids like echinone, β-carotene, and astaxanthin (Zhuang et al. 2020).

3.4 Crustaceans

Crustacean by-products have the potential to provide high-quality carotenoids and lipids for application in the pharmaceutical, cosmetic, food, and biomaterial sectors. Carotenoids and lipids have traditionally been extracted utilizing energy/waste rigorous processes that can degrade the product and by-products. Crustacean byproducts can be produced during the recovery and conditioning of the edible section of crabs, shrimp, lobsters, and krill. Mineral salts, proteins, chitin, lipids, and pigments are the most common components of byproducts. There are different carotenoid contents in the different body components of crustaceans. Astaxanthin can be discovered in complexes with lipids and proteins in nature. A vibrant blue astaxanthin complex with a protein, crustacyanin, is found in the shells of shrimp, crabs, lobsters, and other crustaceans. Astaxanthin is only produced following thermal treatment with protein denaturation, and the characteristic pink-reddish hue may be observed. Astaxanthin lipoglycoprotein, found in lobster ovaries and eggs, is responsible for the deep green pigment (Ahmadkelayeh and Hawboldt 2020). When four shrimp species from the Indian coast were examined for their carotenoid content, the head and carapace of *Parapenaeopsis stylifera* contained the highest total carotenoid content, and the body components of *Pangasius indicus* contained the lowest carotenoid concentration. The predominant carotenoids found in the carotenoid extracts from the shrimps were astaxanthin and its mono- and diesters which are 63–92% of total carotenoids, with modest amounts of β-carotene and zeaxanthin. The same authors also extracted astaxanthin from different Indian shrimps under optimum conditions by using a variety of edible vegetable oil, including sunflower, groundnut, gingelly, mustard, soybean, coconut, palm, and rice oils (Sachindra and Mahendrakar 2005). At various temperatures, the extraction of astaxanthin from giant tiger shrimp *Penaeus monodon* waste was investigated. The extraction of astaxanthin from shrimp waste using palm oil was shown to be mediated by both mass transfer and reaction kinetics. The astaxanthin yield with palm oil is from 48.5 to 131.7 (μg/g waste) at 70 °C under freeze-dried and different mesh parameters (Handayani et al. 2008).

Other sources of astaxanthin are exoskeleton crawfish *Procambarus clarkia,* including 153 μg/g waste consisting of 40% astaxanthin, 50% astaxanthin ester, and 10% astacene (Meyers and Bligh 1981). Another study also used flaxseed oil for astaxanthin extraction on the crawfish *Procambarus clarkia* at 60 °C and 60 min to obtain an astaxanthin yield of 30.2 μg/g waste. First-order reaction kinetics might be used to characterize the breakdown of astaxanthin. At 30 °C and 40 °C, astaxanthin remained stable in flaxseed oil, but at 50 °C and 60 °C, it deteriorated dramatically (Pu and Sathivel 2011). On a dry basis, by-products from various portions of

Canadian back snow crab *Chinoecetes opilio* and shrimp *Pandalus borealis* included between 17 and 32% of chitin and 3.4 to 14.7 mg/100 g of carotenoid pigments, primarily 119.6 (μg/g waste) of astaxanthin and its esters. Chitin was recovered from cod liver oil at a yield of up to 74%, while carotenoids were extracted at a yield of up to 86% (Sahidi and Synowiecki 1991). The esterified and unesterified astaxanthin fractions were extracted from the meal of the pelagic red crab langostilla *Pleuroncodes planipes*. Among total carotenoids, there are approximately 70% astaxanthin diesters, 12% astaxanthin monoesters, and 10% unesterified astaxanthin (Coral-Hinostroza and Bjerkeng 2002). The industrial waste of the South African West Coast rock lobster *Jasus lalandii* was investigated on simultaneous extraction of chitin and astaxanthin. To obtain intact chitin and astaxanthin, it is necessary to remove proteins from waste. We examined partial proteolysis with enzyme papain followed by centrifugation to remove adherent tissue or protein because typical chemical techniques degrade astaxanthin and chitin. The astaxanthin yield is 3.1 mg from 56.8 g crushed lobster waste under the optimum extraction condition with 24 h incubation, 0.5% papain, 1:10 ratio of waste:medium, and 5 min centrifugation with 5 mm holes. Astaxanthin was extracted in methanol from the deproteinized exoskeleton, and transferred to different vegetable oils, and its content was determined using spectrophotometry. The maximum stable astaxanthin content in oils was around 80 mg/ml (Auerswald and Gäde 2008). The effects of processing techniques on astaxanthin concentration, structural isomers, and composition containing free astaxanthin and astaxanthin esters were investigated in Antarctic krill *Euphausia superba* by using three different drying strategies, including freeze-drying, microwave drying, and hot-air drying. Free astaxanthin, astaxanthin monoesters, and astaxanthin diesters in boiling krill and dried krill were isolated and examined by using high-resolution mass spectrometry with ultraviolet detection. Total astaxanthin loss varied from 8.6% to 65% after three treatments. Besides, astaxanthin monoesters and astaxanthin diesters contents were also lost, ranging from 78 to 17 μg/g and 169 to 91 μg/g, respectively. According to the findings, freeze-drying, low-power microwave drying ($\leq$1 kW), and low-temperature hot-air drying ($\leq$60 °C) are the optimal drying techniques for Antarctic krill production (Cong et al. 2019).

3.5 Plants

Except for the major source of astaxanthin mentioned above, there are other sources of astaxanthin, including some vegetables, fruits, and flowers. Species of the *Adonis* genus, i.e., *A. aestivalis* and *A. annua*, contain the richest astaxanthin. *Adonis annua* or *Adonis autumnalis* L., also known as pheasant's-eye, is a decorative plant of the family Ranunculaceae. A rich orange-red carotenoid is produced in significant amounts when dried petals of *Adonis* annua are extracted with light petroleum or methanol. This pigment has 90% of esterified astaxanthin. However, this plant is not a profitable source of astaxanthin because of the growing area's poor yield of floral biomass. A higher number of petals in this flower head was used as commercial

sources of astaxanthin. To obtain a source of natural astaxanthin, a unique strain of *Adonis aestivalis* with an average of 18–22 petals per flower head was harvested. An average of 200–350 μg of astaxanthin pigment per flowerhead can be produced. The genes encoding the astaxanthin biosynthesis pathway from *Adonis* plants were isolated and transferred into other plants, such as marigolds, to ensure a high production of biomass containing carotenoids. The high content of β-carotene can be produced by a variety of plants, including marigolds, rapeseed, maize, sweet potatoes, and various palm species. The DNA fragment encoding the astaxanthin biosynthesis pathway from *Adonis* plants can be inserted into the genome of these plants for β-carotene conversion into astaxanthin (Cunningham 2007). Tobacco *Nicotiana tabacum* with a red pigment has been used for astaxanthin production by altering the carotenoid biosynthesis pathway in chromoplasts under engineered metabolic procedures. The cDNA of gene CrtO of green microalgae *Haematococcus pluvialis* was transferred and inserted into the genome of this plant regulated by tomato promoter *pds*, which can produce phytoene desaturase. The result showed that tobacco could be a highly potential source of carotenoid and astaxanthin pigments under the genetic modification of the different plants (Mann et al. 2000). The development of a highly nutritious tomato *Solanum lycopersicum* by converting the intrinsic carotenes to astaxanthin was studied. The two particular enzymes, the β-carotene hydroxylase from *Haematococcus pluvialis* and the algae β-carotene ketolase from *Chlamydomonas reinhardtii*, were co-expressed together to convert β-carotene to astaxanthin in *Escherichia coli* under functional complementation. The regulation and expression of β-carotene hydroxylase and ketolase in the intrinsic carotenogenic genes of tomatoes can make carbon flux extensively into carotenoids. The result exhibited that approximately 3.1 mg/g of free astaxanthin accumulated in leaves and 16.1 mg/g of esterified astaxanthin in fruits. Besides, a 16-fold increase in total carotenoid content was observed in the genetic engineering tomatoes (Huang et al. 2013). In Table 1, free and esterified forms of astaxanthin and its configurational isomers from various natural sources are discussed.

4 Extraction, Isolation, and Analysis of Astaxanthin

Astaxanthin (3,3′-dihydroxy β, β-carotene-4,4′-dione) has high lipophilicity to allow this compound to dissolve easily in oils and different solvents. Currently, astaxanthin is primarily extracted from *Haematococcus pluvialis* for commercial availability. Nevertheless, its large-scale production is difficult. In addition, the extraction of astaxanthin from crustaceans is rapidly developed because it can have prodigious social and economic profits.

Various methods of astaxanthin extraction have been reported, such as solvent extraction, acid extraction, edible oils extraction, ultrasound or microwave-assisted extraction, and enzymatic extraction. Astaxanthin can be found in the thick-walled cyst cells of *Haematococcus pluvialis*. The thick encysted cell wall consists of algaenan that is sporopollenin-like material to be able to impede solvent extraction and bioavailability of astaxanthin. The evaluation of astaxanthin extractability from

Table 1 Free and esterified forms of astaxanthin and its configurational isomers in various natural sources

Natural sources	Total astaxanthin content (mg/kg)	Astaxanthin esters form (%)			Ratio configuration isomers (%)			Reference
		Free	Monoester	Diester	3R, 3'R	3S, 3′S	3R, 3′S and 3S, 3′R (meso form)	
Haematococcus pluvialis (Microalgae)	27,000–38,000	5	22	59	4	88	8	Ambati et al. 2014; European Food Safety Authority (EFSA) 2005
Phaffia rhodozyma (Red yeast)	5000	100	0	0	100	0	0	Ambati et al. 2014
Adonis aestivalis, (Plant), Follower petals	11,000	1.4	13.8	72.2	0	100	0	Maoka et al. 2011
Pandalus borealis (Caridean shrimp)	1200	3.95	19.72	74.29	0	12–25	50–53	Jackson et al. 2008
Pandalus borealis (Caridean shrimp)	1200	8	22.5	69.5	0	12–25	50–53	Torrissen et al. 1981
Pandalus clarkii (Red swamp crayfish)	153	40.3	49.4		–[a]	–	–	Meyers and Bligh 1981
Homarus gammarus (Lobster), Shell crustacyanine	54–295	–	–	–	39	33	28	Jackson et al. 2008
Euphausia superba (Antarctic krill)	120	5	31	64	9	70	21	European Food Safety Authority (EFSA) 2005
Thysanoessa inermis (Antarctic krill)	120	4	35	61	55	38	7	European Food Safety Authority (EFSA) 2005
Salmo salar/Salmo (Atlantic/Pacific salmon)	1–38	–	–	–	12–17	2–6	78–85	European Food Safety Authority (EFSA) 2005; Jackson et al. 2008

(continued)

Table 1 (continued)

Natural sources	Total astaxanthin content (mg/kg)	Astaxanthin esters form (%)			Ratio configuration isomers (%)			Reference
		Free	Monoester	Diester	3R, 3'R	3S, 3′S	3R, 3′S and 3S, 3′R (meso form)	
Calanus finmarchicus (Marine Planktonic Copepods)	60	11	43	46	83	14	3	European Food Safety Authority (EFSA) 2005
Acanthephyra purpurea (Deep sea shrimp)	–	20	37	43	20	15	44	European Food Safety Authority (EFSA) 2005
Cancer pagurus (Brown crab), Shell	–	58	13	22	20	56	24	European Food Safety Authority (EFSA) 2005
Chionoecetes opilio (Snow crab)	119.6	21.16	5.11	56.57	–	–	–	Shahidi and Synowiecki, 1991

[a]Not available

cyst cells was determined by treating cells with a different solvent, such as acetone for 1 h, acetone for 24 h, methanol for 24 h, and dimethyl sulfoxide (DMSO) with five drops of glacial acetic acid. Besides, acid extraction was examined at 70 °C under the cell pretreatment with different concentrations of hydrochloric acid (HCl), 2 N formic acid, citric acid, acetic acid, and tartaric acid, followed by acetone extraction. The result showed that 1–4 N hydrochloric acid treatment has the highest potential for 86–96% extractability of astaxanthin (Ashaolu et al. 2021). In another study, four hydrochloric acid treatments also offered a significantly high yield in astaxanthin extraction. Four different methods for extracting astaxanthin from *Haematococcus pluvialis* were thoroughly evaluated: hydrochloric acid pretreatment followed by acetone extraction (HCl-ACE), hexane/isopropanol (6: 4, v/v) mixture solvents extraction, methanol extraction followed by acetone extraction (2-step extraction), and soy-oil extraction. The results exhibited that HCl-ACE extraction produced the maximum oil content (33.3 ± 1.1%) and astaxanthin yield (19.8 ± 1.1%) (Dong et al. 2014). Cells were lyophilized or treated with some particular lytic enzymes after being kept in 40% (v/v) acetone for 2 min at 80 °C. The result indicated that 70% of the astaxanthin was extracted from the cells. The effectiveness of astaxanthin recovery with different methods was evaluated, which was determined by measuring how much astaxanthin was leached into an organic solvent. Autoclave treatments and mechanical disruption (homogenization) were reported as the most effective extraction and bioavailability compared to the other methods using HCl solvent, sodium hydroxide solvent, enzymatic treatment, and spray drying (Kang and Sim 2008).

The astaxanthin extraction from *Haematococcus pluvialis* was studied using solvent, ultrasound, and microwave for extraction. Acetone provided the maximum astaxanthin recovery in all circumstances compared to other solvents, such as methanol, ethanol, and acetonitrile. The maximum astaxanthin recovery (74 ± 4%) was achieved with microwave-assisted extraction at 75 °C for 5 min (Ruen-ngam et al. 2010). The extraction of astaxanthin from *Haematococcus pluvialis* was used supercritical carbon dioxide without and with ethanol as an entrainer. The astaxanthin extraction could be more than twice increased in supercritical carbon dioxide extraction with ethanol entrainer at lower pressures (40 MPa). The astaxanthin extraction increased as the entrainer concentration was increased up to 5% (v/v) ethanol. Furthermore, the carbon dioxide flow rate had a significant impact on the astaxanthin extraction with an entrainer. The astaxanthin recovery increased when the carbon dioxide flow rate declined (Machmudah et al. 2006). By using a bench-scale reactor in a semi-batch conformation, astaxanthin was extracted from disturbed biomass of the *Haematococcus pluvialis* using carbon dioxide in supercritical fluid extraction conditions. At 50 °C and 550 bars, the greatest recovery of astaxanthin attained was 98.6% (Sanzo et al. 2018). Astaxanthin was extracted from *Haematococcus pluvialis* using a supercritical fluid extraction process with ethanol and sunflower oil as cosolvent. The yield of astaxanthin was 87.42% when the conditions were under pressure 43.5 MPa, the temperature of 65 °C, and a cosolvent 2.3 mL/g sample (Wang et al. 2012). The astaxanthin from *Haematococcus* was extracted with common vegetable oils, including grapeseed,

soybean, olive, and corn oil. The procedure involves extracting astaxanthin using a single integrated unit and then separating the astaxanthin-containing oil extract. The culture broth was combined immediately with the vegetable oils without a cell harvesting step, and the astaxanthin inside the cell was extracted into the vegetable oil phase via hydrophobic interactions. The highest recovery is 93% with olive oil, and the other three types of vegetable oil also exhibited over 87% recovery yield (Kang and Sim 2008).

The red yeast *Xanthophyllomyces dendrorhous* (formerly *Phaffia rhodozyma*) can synthesize astaxanthin in its cytoplasm membrane. Several extraction parameters, such as acids, organic solvents, temperature, and time, were examined in order to optimize a procedure for extracting astaxanthin from *Phaffia rhodozyma* by acidic methods. For yeast cell disruption, lactic acid is better than ether hydrochloric acid or acetic acid. The optimal conditions were determined as follows: ratio of ethanol to yeast dry weight at 20.25 mL/g, the concentration of lactic acid at 5.55 mol/L, extraction time of 3 min, and the temperature for cell disruption at 30 °C. With these conditions, the extraction levels of astaxanthin and total carotenoids are 1294.7 μg/g and 1516.0 μg/g, respectively (Ni et al. 2008). The influences of enzymatic cell wall disruption and feed extrusion temperature were investigated on the utilization of astaxanthin from red yeast *Xanthophyllomyces dendrorhous* for experimental diets of rainbow trout (Storebakken et al. 2004). There are a tremendous amount of shrimp or crab shells discarded during the food process in the seafood industry, and they are well-known for containing abundant astaxanthin. The extraction and purification of astaxanthin from shrimp and crab shells were established. The effects of cool-ventilated, sun-dried, and cooked conditions on the concentration of astaxanthin in shrimp shells were investigated. The result revealed that the astaxanthin content in the red swamp crayfish *Procambarus clarkii* shell was 239.96 μg/g. Fresh shrimp shells were the best raw material for extraction of astaxanthin with ethanol under the optimum experimental condition with 20 min of extraction time, a solid-liquid ratio of 1:7, and a temperature of 50 °C to provide the maximum reproducibility and recovery of astaxanthin. Besides, the purity of astaxanthin improved around 250 times from 0.34% to 85.1% by silica gel column chromatography for purification of the crude astaxanthin extraction (Hu et al. 2019).

The high-performance liquid chromatography (HPLC) method for the analysis of astaxanthin is commonly used because it can determine astaxanthin content rapidly and precisely. During HPLC identification and quantification of astaxanthin, the C18 chromatographic column is also generally used under different elute conditions. A methanol-water (95:5 v/v) mobile phase at a flow rate of 1 ml/min was used, and the absorbance of the extract was detected at wavelength 475 nm to analyze astaxanthin content (Ruen-ngam et al. 2010). Under the HPLC method, the eluants were acetone and methanol: H_2O (9: 1 v/v) at a column temperature of 40 °C with a flow rate of 0.8 ml/min. The mixture of methanol and H_2O for a gradient concentration program was 80 to 20% for 25 min, 20% for 10 min, and 20% to 80% for 5 min. The astaxanthin extract was measured at a wavelength of 460 nm (Dong et al. 2014). The maximum absorption wavelength of astaxanthin is 492 nm in dimethyl sulfoxide, 477 nm in acetone and methanol, and 486 nm in dimethylformamide and

chloroform. The C18 chromatographic column also is used for the separation of astaxanthin under the following condition: 1 ml/min of the flow rate, 25 °C of the column temperature, 20 μl of the injection volume, and 474 nm of the detection wavelength. The mixture solvent acetonitrile/methanol/dichloromethane (80:15:5, v/v/v) was used as the mobile phase (Hu et al. 2019). Furthermore, the astaxanthin esters in extracts of dried microalga *Haematococcus pluvialis* and commercial shrimp *Pandalus borealis* were identified by negative ion liquid chromatography-atmospheric pressure chemical ionization mass spectrometry (LC – APCI – MS). The quantification of astaxanthin esters was also determined by HPLC equipment coupled to a diode array detector (Ranga et al. 2009).

5 Biological Activities of Astaxanthin and Human Health

Astaxanthin is widely commercially used in aquaculture, food, cosmetics, functional foods, and nutraceuticals due to its potential antioxidant and natural pigment properties. A variety of studies have been reported on the relationship between astaxanthin and human health, including antioxidants, anti-inflammatory, anti-diabetic, prevention of cardiovascular disease, anticancer activity, anti-lipid peroxidation, skin health, liver health, immune regulation, improvement of exercise performance, and so on. The possible physiological effects of astaxanthin were also studied on protecting the retina, improving eye fatigue, enhancing mitochondrial function, promoting the use of fat as an energy source, controlling arteriosclerosis, and inhibiting hypertensive states (Guerin et al. 2003; Higuera-Ciapara et al. 2006). Various health benefits of astaxanthin in vivo are described in Table 2.

5.1 Antioxidant and Antiaging Activity

Potent antioxidant activity effects of carotenoids have been discovered and broadly used in the pharmaceutical, cosmetic, medical, and food industries. Carotenoids effectively scavenge both reactive oxygen species and free radicals. Many studies have reported that carotenoid compounds like β-carotene, astaxanthin, and lycopene have much stronger antioxidant capability against singlet oxygen than other antioxidants like vitamins C and E. The antioxidant capacity of astaxanthin is 54 times that of β-carotene, 14 times that of vitamin E, and 65 times that of vitamin C. Astaxanthin is one of the few compounds that can enter the blood-brain barrier and cross both sides of the cell membrane, providing a complete antioxidant activity from the inside out and not producing peroxides or pro-oxidants. Astaxanthin, as a xanthophyll carotenoid, can provide distinct cell membrane activities and a wide range of therapeutic applications. By absorbing or donating electrons, free radicals or other reactive oxygen species can be neutralized by this molecular without being destroyed or becoming a pro-oxidant. Common antioxidants such as carotenoids or vitamin C can only exist on the outside or in the middle of the cell wall and can only unilaterally prevent the damage of free radicals. However, the molecular

Table 2 Health benefits of astaxanthin in vivo

Health benefit	Model	Subjects	Duration	Dosage	Significant result	Reference
Prevention of cardiovascular diseases	Human	30 middle-aged and senior volunteers	12 weeks	6 or 12 mg daily	The level of phospholipid hydroperoxides was decreased in the plasma and red blood cells	Nakagawa et al. 2011
	Animal	Sprague Dawley rats with age 14 to 16 weeks, weighing 250–300 g	2 weeks	40 mg per kg weight daily	Astaxanthin can improve cardiac insufficiency by inhibiting oxidative stress and preventing cardiomyocyte apoptosis and myocardial infarction	Xue et al. 2019
Modulation of the immunological response	Human	Free-living healthy 42 female native Korean college students with an age of 20.2–22.8 years old and BMI of 16.3–27.5	8 weeks	0, 2, or 8 mg daily	The enhancement of cytotoxic activity in natural killer cells and the total subpopulation of T and B cells by promoting mitogen-induced lymphocyte proliferation were significantly observed	Park et al. 2010
	Animal	Adult Wistar male rats, weighing 225.6 ± 17.1 g with 3 months old	45 days	1 mg per kg weight mg daily, 5 days per week	The proliferation capacity of activated T and B lymphocytes were decreased by reducing the generation of reactive oxygen species and nitric oxide, GSSG content, and GSH/GSSG ratio under fish oil with astaxanthin supplementation	Otton et al. 2012
Antiaging activity	Human	31 volunteers including 17 men and 14 women over the age of 40	29 days	4 mg daily	Malondialdehyde levels were reduced by 11.2% on day 15 and 21.7% on day 29	Chalyk et al. 2017

Prevention of complications of diabetes mellitus	Human	29 nondiabetic mellitus subjects	12 weeks	12 mg daily	Glucose and hemoglobin A1c concentration of the astaxanthin-administrated group at 30 min by 75 g oral glucose tolerance test were significantly reduced. Astaxanthin may help prevent diabetes in subjects with prediabetes whose hemoglobin A1c levels from 5.6% to 6.4%	Urakaze et al. 2018
Prevention of neurodegenerative disorders	Animal	75 adult male Wistar rats, weighing 230–270 g	28 days	10 μl of 0.2 mM, Intrathecal	Aastaxanthin could potentially improve the sensory and motor function of male rats in a severe spinal cord injury model by reducing glutamate-induced signaling pathways and inflammation	Fakhri et al. 2018
	Animal	144 healthy male and female adult Sprague-Dawley rats, weighing 280 ± 20 g	4 weeks	75 mg per kg weight, twice per day	Astaxanthin could significantly protect spinal cord tissues from neuroapoptosis and enhance motor function in rats with spinal cord injury	Li et al. 2021
Antihypertensive activity	Animal	Male rats of Wistar Kyoto (7 weeks), Wistar standard breed (20–40 weeks), neously hypertensive rat (7 weeks), and stroke-prone SHR-SP strains (10 weeks)	14 days and 5 weeks	50 mg per kg body weight	Arterial blood pressure and the occurrence of stroke were reduced significantly. The antihypertensive mechanism of astaxanthin may be associated with the vasorelaxation induction mediated by nitric oxide	Hussein et al. 2005

(continued)

Table 2 (continued)

Health benefit	Model	Subjects	Duration	Dosage	Significant result	Reference
	Animal	Spontaneously hypertensive rats with age 12 weeks	8 weeks	75 or 200 mg per kg body weight daily	Endothelial function in the resistance artery and the bioavailability of nitric oxide was boosted, and oxidative stress was also reduced	Monroy-Ruiz et al. 2011
Improvement of exercise performance and recovery	Human	40 male students aged 17–19 years old	6 months	4 mg daily	The number of knee bending times in the group taking astaxanthin increased significantly to indicate the improvement of strength endurance	Monroy-Ruiz et al. 2011
	Animal	40 male C57BL/6 mice with 7 weeks weighing from 20 ~ 25 g	4 weeks	5, 15, and 30 mg per kg body weight	High-dose astaxanthin treatment could downregulate the mRNA transcription of nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and Nrf2-dependent enzymes, reduce antioxidant enzyme activity, as well as lower plasma and muscle malondialdehyde	Zhou et al. 2019

Eye health	Animal	Male albino ddY mice with age 8–10 weeks	4 days	100 mg per kg body weight, twice per day	Inhibition ischemia-induced retinal cell death, the production of reactive oxygen species and electroretinogram reduction were observed	Otsuka et al. 2016
Treatment of *Helicobacter pylori* infections	Animal	BALB/cA mice with age 6–8 weeks	10 days	10, 50, and 100 mg per kg body weight, Daily	Lipid peroxidation and inflammatory response were significantly decreased	Wang et al. 2000
Skin protection	Human	65 healthy female adult aged 35–60 years	16 weeks	6 or 12 mg daily	Long-term astaxanthin intake may prevent age-related skin degradation and preserve skin conditions linked with environmental exposure by acting as an anti-inflammatory	Tominaga et al. 2017
	Animal	Female hairless Hos:HR-1 mice with age 6 weeks	70 days	0.1 and 0.01% astaxanthin extraction daily	Dietary astaxanthin inhibited photoaging such as transepidermal liquid loss and wrinkle development in the dorsal skin to prevent desquamation mechanism in the epidermis, the dermal extracellular matrix, and filaggrin formation.	Komatsu et al. 2017

arrangement direction of astaxanthin across the cell wall can protect cells with double layers and effectively protect cells from the damage of free radicals (Kidd 2011). The evaluation of oxidative injury under astaxanthin treatment was examined. The protection of astaxanthin on the damaged mitochondria of tocopherol-deficient rats under Fe^{2+}-catalyzed lipid peroxidation was observed in vitro and in vivo. In addition, mitochondrial lipid peroxidation also was much more inhibited significantly by astaxanthin in comparison with α-tocopherol because of the suppression of $Fe^{2+}$and Fe^{3+}-xanthine oxidase system by astaxanthin. The other study also indicated that the damage of phosphatidylcholine multilamellar liposome was decreased under the treatment of the lipoperoxidation promoters containing H_2O_2, tert-butyl hydroperoxide, or ascorbate, and Fe^{2+}-EDTA. The antioxidant capability of astaxanthin in oxidative damage of iron-liposomes might be attributed to its recognized rigidifying influence and innate scavenging activity. The antiaging activities and antioxidative ability of astaxanthin configurational stereoisomers were examined in the roundworm *Caenorhabditis elegans.* When the roundworm was fed with 9-cis, 13-cis, and all-trans *astaxanthin* isomers, their median lifespan was enhanced from 25% to 60%. These stereoisomers could alleviate the functional senility process physiologically and reduce the intracellular accumulation of reactive oxygen species involved in the lifespan. Based on the RNA sequence analysis, different isomers resulted in changes in antiaging processes via the modulation of certain differentially expressed genes involved in the regulation of the longevity pathway (Liu et al. 2018).

5.2 Prevention of Cardiovascular Diseases

The concentration of cholesterol linked to low-density lipoprotein (LDL), or "bad cholesterol," increases the risk of arteriosclerosis in humans. High levels of LDL have been linked to cardiovascular diseases such as myocardial infarction, coronary artery disease, peripheral artery disease, and cerebral thrombosis. Astaxanthin can reduce LDL cholesterol content and increase high-density lipoprotein (HDL) cholesterol and adiponectin content in the human body. The effects of astaxanthin in vitro and ex vivo on LDL oxidation were investigated. Twenty-four adults with an average age of 28.2 were administered 1.8, 3.6, 14.4, and 21.6 mg astaxanthin per day. After 14 days, their fasting venous blood samples were tested. The result revealed that astaxanthin consumption can inhibit LDL oxidation and may potentially prevent atherosclerosis (Iwamoto et al. 2000). A mouse model of arterial thrombosis was used to evaluate a proprietary astaxanthin prodrug on thrombus development. The mechanisms of free astaxanthin on human endothelial cells and rat platelets were also examined. The results revealed that free astaxanthin could inhibit lipid oxidation in blood vessels and reduce occlusive thrombus formation through a significant increase in nitric oxide (NO) levels and a significant decrease in peroxynitrite (ONOO-) levels in human endothelial cells and rat platelet. Hence

astaxanthin has the potential to alleviate or prevent thrombotic cardiovascular complications (Khan et al. 2010). The concentration of phospholipid hydroperoxides is peculiarly high in the red blood cells of dementia patients. The effect of 6 or 12 mg per day of astaxanthin supplementation was estimated in a human trial in the erythrocytes of 30 middle-aged and senior volunteers. After 12 weeks of astaxanthin administration, the level of phospholipid hydroperoxides was decreased in the plasma and red blood cells. It supported that astaxanthin supplementation may be a potential treatment for human dementia by enhancing antioxidant capacity and reducing phospholipid hydroperoxides concentration (Nakagawa et al. 2011). In a Sprague-Dawley rat and dog infarct model, animals pretreated with astaxanthin remarkably reduced the risk of myocardial infarction. The result also indicated that infarct size and myocardial salvage versus plasma concentration of disodium disuccinate astaxanthin at the end of reperfusion were correlated significantly. These findings showed that astaxanthin might be valuable in clinical treatment where individuals at risk of myocardial infarction are pretreated. Besides, astaxanthin may be an innovative approach to avoid myocardial injury and necrosis related to cardiac surgical treatment, including coronary artery bypass surgery or coronary angioplasty and stenting (Gross and Lockwood 2005). The activation of nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling pathway and the prevention of coronary micro-embolization on cardiovascular functions were investigated in Sprague Dawley rats with age 14 to 16 weeks under astaxanthin treatment. The result presented that astaxanthin can alleviate cardiomyocyte apoptosis after coronary microembolization and cardiac dysfunction under the suppression of reactive oxygen species by the activation of the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling pathway. Astaxanthin can improve cardiac insufficiency by inhibiting oxidative stress and preventing cardiomyocyte apoptosis and myocardial infarction. Therefore, astaxanthin played a key role in cardiovascular protection in rats (Xue et al. 2019).

5.3 Modulation of the Immunological Response

Due to its high antioxidant capability, astaxanthin is beneficial to the human immune system and plays a major role in regulating the immune response with the enhancement of antibody production. The study disclosed that after 45 days of treatment of fish oil with astaxanthin supplementation on adult Wistar male rats, the assessment includes lymphocyte proliferation capacity, reactive oxygen species and nitric oxide production, oxidative stress to lipids and proteins, and the concentration of reduced glutathione (GSH)/oxidized glutathione (GSSG). The results suggested that the proliferation capacity of activated T and B lymphocytes were decreased by reducing the generation of reactive oxygen species and nitric oxide, GSSG content, and GSH/GSSG ratio. Therefore, fish oil with astaxanthin supplementation may offer a potential approach to modulating and improving the immunological system by

preventing oxidative stress (Otton et al. 2012). Forty-two female young and healthy adults with an average age of 21.5 years old were administrated 0, 2, or 8 mg astaxanthin per day for 8 weeks. The modulation of inflammatory, oxidative responses and immunological effects were measured under a randomized placebo-controlled and double-blind method. The result displayed that the enhancement of cytotoxic activity in natural killer cells and the total subpopulation of T and B cells by promoting mitogen-induced lymphocyte proliferation were significantly observed under dietary astaxanthin treatment. Astaxanthin can reduce oxidative stress and inflammation in the human body while enhancing the immune response (Park et al. 2010). The influence of astaxanthin on immune response and cytokine production was determined in primary cultured lymphocytes in ex vivo and in vitro. The study exhibited that astaxanthin could potentially modulate the immune response of lymphocytes in vitro, mainly by improving the production of interferon (INF-γ) and interleukin (IL-2) and moderately utilizing its immunomodulation without any cytotoxicity induction (Lin et al. 2015).

5.4 Anticancer Activity

The chemopreventive effects of astaxanthin have been reported to associate with a variety of bioactivity functions, including antioxidation, antiproliferation of cells, anti-inflammation, apoptosis promotion, the prevention of cancer cell invasion and metastasis, and the improvement of gap junctional intracellular communication. A novel disodium salt disuccinate astaxanthin compound with high aqueous dispersibility was synthesized to examine mouse embryonic fibroblast 10 T1/2 cells in an aqueous or aqueous/ethanol solution. The findings presented that disodium salt disuccinate astaxanthin can upregulate the expression of connexin 43 protein, enhance the development of connexin 43 immunoreactive plaques in plasma membrane areas associated with gap junction localization, and considerably increase gap junctional intercellular communication. Hence, this novel astaxanthin agent demonstrated a potential strategy to reduce the growth of human tumors in xenografts (Hix et al. 2004). Later, another novel tetrasodium diphosphate astaxanthin derivative that possesses high aqueous dispersibility was synthesized to examine the same 10 T1/2 cell line in an aqueous and ethanol solution in comparison with nonesterified astaxanthin in tetrahydrofuran. The finding supported that tetrasodium diphosphate astaxanthin 100% inhibited methylcholanthrene-induced neoplastic transformation by upregulating gap junctional intercellular communication, increasing connexin 43 protein expression, and promoting the production of connexin 43 immunoreactive plaques. In all of these tests, tetrasodium diphosphate astaxanthin outperformed nonesterified astaxanthin and all other carotenoids tested in the same model previously. The water dispersibility and enhanced potency of tetrasodium diphosphate astaxanthin should be tremendously important for the design of cancer chemopreventive treatments (Hix et al. 2005).

5.5 Prevention of Complications of Diabetes Mellitus

Oxidative stress levels in diabetic mellitus patients are induced by hyperglycemia and are generally relatively high due to tissue deterioration and pancreatic β-cell dysfunction. Diabetes reduced superoxide dismutase, glutathione peroxidase, and reductase activity in the dental pulp tissue and the submandibular gland. Diabetes mellitus also improved thiol content in the parotid gland without any effect in the presence of antioxidants). Diabetes mellitus causes hyperglycemia, hyperlipidemia, abnormal liver and kidney function, oxidative stress, inflammation, and the formation of blood clots. A thrombosis in the blood vessel blocks the blood vessel to allow the blood to flow slowly, resulting in clinical symptoms such as myocardial infarction and cerebral apoplexy. In several studies on animal models, the diabetic rats after supplementing astaxanthin, except for not able to lower glucose levels in the blood, all the metabolic abnormalities described above could be improved. Many clinical studies also demonstrated that astaxanthin could reduce metabolic abnormalities in diabetic patients, including hyperlipidemia, oxidative stress, inflammation, liver, kidney dysfunction, and blood coagulation. All the results supported that astaxanthin can evidently alleviate the complications of diabetes (Urakaze et al. 2018). A meta-analysis of retrospective studies examined the effect of oral astaxanthin supplements on plasma lipid profile and fasting glucose concentrations. The researchers primarily selected randomized controlled trials and investigated the effects of astaxanthin supplementation on plasma lipid and glucose concentrations. Seven eligible studies were selected, including a total of 280 subjects, of which 163 were administered with astaxanthin supplement, and the other 117 were controls. The results of the review did not find a significant effect of astaxanthin supplementation on blood lipids, but a slight hypoglycemic effect was observed (Ursoniu et al. 2015). In another clinical study, the effect of astaxanthin on 29 non-diabetic mellitus subjects was examined for their glucose tolerance. At the beginning of the study, their hemoglobin A1c ranged from 5.6% to 6.4% at baseline which this range would be considered in the prediabetic period. Sixteen participants were randomly assigned to receive 12 mg of astaxanthin per day, and 13 participants received a placebo for 12 consecutive weeks. Subjects were required to have a 75 g oral glucose tolerance test before they started taking astaxanthin or a placebo and then had this test again after 12 weeks of supplementation. The result displayed that the glucose and hemoglobin A1c concentrations in the astaxanthin-administrated group at 30 min by 75 g oral glucose tolerance test were significantly reduced in comparison with the first trial 12 weeks ago. The results of this study supported that astaxanthin may help prevent diabetes in subjects with prediabetes whose hemoglobin A1c levels are from 5.6% to 6.4% (Urakaze et al. 2018). Insulin is the enzyme that primarily metabolizes blood sugar. When this enzyme is deficient or unable to function, glucose cannot be efficiently entered into tissues for utilization, resulting in hyperglycemia, which is called diabetes. Clinical symptoms include eating more, drinking more, urinating more, weight loss, blurred vision, fatigue, wounds that do not heal quickly, etc. The influence of astaxanthin on glucose metabolism and insulin

signaling was determined in the liver of mice that received high fructose and high fat dietary. The result demonstrated that astaxanthin could stimulate the insulin receptor substrate–PI3K–Akt pathway in insulin signaling under the reduction of serine phosphorylation of insulin receptor substrate proteins. Glucose metabolism in insulin-resistant mice also can be improved by astaxanthin with the regulation of metabolic enzymes (Bhuvaneswari and Anuradha 2012).

5.6 Astaxanthin Effect Against Neurodegenerative Disorders

Both unsaturated lipids and iron are abundant in the nervous system, and they are prooxidative compounds and susceptible to oxidation. Meanwhile, nervous system tissues contain plentiful blood vessels with high metabolic oxidative activity, which makes them particularly vulnerable to oxidative injury. Many studies reported that oxidative stress is a fundamental or at least secondary role in the pathophysiological etiology of major neurodegenerative illnesses, such as amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease. Some antioxidants have been studied for the alleviation of these neurodegenerative diseases. Alzheimer's disease is a comparatively serious chronic neurodegenerative disease characterized by memory impairment and cognitive dysfunction, mainly due to neuronal death. Oxidative stress inside mitochondrion occurs in the early stages of Alzheimer's disease. Therefore, various natural compounds with antioxidant and anti-inflammatory properties are recommended to prevent or reduce the progression of this specific neurodegeneration. Astaxanthin can significantly inhibit oxidative damage through various mechanisms by deactivating singlet oxygen, scavenging free radicals, inhibiting lipid peroxidation, and regulating gene expression related to oxidative response. As a result, it can be used as an alternative therapy for Alzheimer's disease. On the other hand, similar to Alzheimer's disease, Parkinson's disease is currently incurable, astaxanthin has been reported as a potential effect against Parkinson's disease, possibly preventing or at least slowing its disease progression. Mitochondrial protein turnover plays a fundamental role in granulosa gland-mediated pathways, and several genes related to mitochondrion function may be the main cause of Parkinson's disease. Thus, astaxanthin can provide a critical neuroprotective treatment in various neurodegenerative diseases because the health benefits of astaxanthin are high anti-inflammatory, high antioxidant activity, and mitochondrial protective properties (Guerin et al. 2003; Ambati et al. 2014). Astaxanthin can significantly accelerate recovery from traumatic brain injury in brain tissue and reduce post-injury brain swelling to promote critical brain function. The mechanism may be caused by the amelioration of aquaporin 4/ Na^+–K^+–$2Cl^-$ co-transporter 1-mediated cerebral edema. Aquaporin 4 can be upregulated by Na^+–K^+–$2Cl^-$ co-transporter one after traumatic brain injury in mice (Zhang et al. 2016). When astaxanthin is investigated in mice to evaluate their resilience preceding traumatic brain injury in a closed head injury model, the pretreatment of astaxanthin can be a beneficial strategy to enhance recovery from post-traumatic brain injury in mice (Fleischmann et al. 2020). The protein kinase signaling pathway activated by

glutamatergic-phospho p38 mitogen was investigated for astaxanthin's potential to reduce spinal cord injury. In a rigorous compression model of SCI in male rats, the inflammatory response, histopathological alterations, and sensory-motor function were also studied. The results demonstrated that astaxanthin could potentially improve the sensory and motor function of male rats in a severe spinal cord injury model by reducing glutamate-induced signaling pathways and inflammation (Fakhri et al. 2018). The influence of astaxanthin on 144 healthy adult Sprague-Dawley rats was estimated on neuronal cell apoptosis after spinal cord injury. The experimental group of rats has administered a dose of 75 mg of astaxanthin per kg body weight compared to other groups fed with the same amount of olive oil. The founding also revealed that astaxanthin could significantly protect spinal cord tissues from neuroapoptosis and enhance motor function in rats with spinal cord injury. Astaxanthin is a promising treatment to ameliorate the recovery of neural function after spinal cord injury (Li et al. 2021).

5.7 Antihypertensive Activity

Astaxanthin can reduce high blood pressure in several ways by regulating nitric oxide and relaxing blood vascular. Astaxanthin can continue to dilate microvessels after effectively administrating for a long time, but it is different from the general mechanism of reducing blood pressure by dilating blood vessels by relaxing vascular smooth muscle. Nonetheless, common antihypertensive drugs containing angiotensin-converting enzyme inhibitors are fast and short-term. Astaxanthin dilates blood vascular slowly, long-term, and sustainably. Therefore, after taking astaxanthin for about 2–4 months, the dosage or frequency of antihypertensive drugs can generally be decreased. But astaxanthin does not lastingly lower normal blood pressure, and it is not simply to have vasodilation function but to reduce blood pressure by treating atherosclerosis. As a result, there is no risk of causing hypotension (Hussein et al. 2006). Spontaneously hypertensive rats were orally administrated with astaxanthin for 14 days. The arterial blood pressure of these rates was significantly decreased compared with normotensive Wistar Kyoto rats. When stroke-prone spontaneously hypertensive rats were administrated with 50 mg astaxanthin per kg body weight for 5 weeks in the long term, arterial blood pressure and the occurrence of stroke were reduced significantly. The antihypertensive mechanism of astaxanthin may be associated with the vasorelaxation induction mediated by nitric oxide. Besides, astaxanthin also exhibited substantial neuroprotective effects in mice (Hussein et al. 2005). The influence of dietary astaxanthin in 12-week-old spontaneously hypertensive rats was determined on cardiac hypertrophy, superoxide production, blood pressure, and vascular conditions. After eight-week administration of dietary astaxanthin at a dose of 75 or 200 mg per kg body weight each day, endothelial function in the resistance artery and the bioavailability of nitric oxide was boosted, and oxidative stress was also reduced. A diet with astaxanthin supplementation is a potential strategy for treating hypertension and improving cardiac remodeling (Monroy-Ruiz et al. 2011).

5.8 Improvement of Exercise Performance and Recovery

During strenuous exercise, training can induce reactive oxygen and nitrogen species to elevate oxidative stress in the body and then cause muscle damage and prolong recovery time. Many clinical studies on the relationship between astaxanthin and exercise have suggested that astaxanthin is a potent antioxidant to provide a defense mechanism against muscle injury and oxidative stress by reducing cell membrane damage, muscle cell DNA damage, and inflammation after heavy training. Astaxanthin has a potential benefit in the improvement of physical activity, enhancement of muscular endurance and explosiveness, and muscle fatigue mitigation (Brown et al. 2018). The 4-week-old male mice were treated orally with 1.2 mg, 6 mg, and 30 mg of astaxanthin per kilogram of body weight by stomach intubation. After 5 weeks, the result indicated that the administration of astaxanthin could increase the swimming time, and the lactic acid concentration in the body was significantly decreased. The accumulation of lactic acid has a positive relationship with exercise fatigue. Astaxanthin can also effectively reduce blood sugar and adipose tissue. The body can convert blood sugar into energy during sports training to allow blood sugar to decrease. The result displayed that astaxanthin reduces the use of blood sugar and instead consumes fat to generate energy. This mechanism can enhance the utilization of fatty acids and stimulate fat-burning during sports training. The results showed that astaxanthin could improve endurance capacity and reduce fatigue in swimming, and this situation may be triggered by increasing the use of fatty acids as an energy source (Ikeuchi et al. 2006). The 7-week-old male mice were treated orally with 5 mg, 15 mg, and 30 mg of astaxanthin per kilogram of body weight and 45 min of moderate-intensity swimming training each day for 4 weeks. Malondialdehyde, glutathione peroxidase, creatine kinase, and catalase levels in plasma or muscle were declined when these male mice were under 15 mg and 30 mg/kg of astaxanthin treatment. Nevertheless, superoxide dismutase and nitric oxidase synthase were enhanced instead for the same groups of mice administrated with 15 and 30 mg/kg of astaxanthin. The finding showed that high-dose astaxanthin treatment could downregulate the mRNA transcription of nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and Nrf2-dependent enzymes, reduce antioxidant enzyme activity, as well as lower plasma and muscle malondialdehyde (Zhou et al. 2019). A double-blind study was conducted on 40 male students administered by astaxanthin supplementation for 6 months. The performance of the knee bending was evaluated when the subjects carried a 42.5 kg barbell weight. It was observed that the number of knee bending times in the group taking astaxanthin increased significantly to determine that astaxanthin can increase exercise strength and endurance performance (Malmsten and Lignell 2008).

5.9 Eye Health

Astaxanthin has many eye health benefits, including protection against macular degradation and inflammatory eye disease because of its high potential antioxidant effect on the macula. Astaxanthin reduces eye tiredness, enhances visual activity and

depth perception, relaxes the ciliary muscle of the eye, and promotes choroidal blood flow in ocular tissues. In recent years, astaxanthin has been added to many functional foods and nutraceuticals for eye protection. Sometimes other carotenoids like lutein or zeaxanthin are added too. The structure of astaxanthin is quite similar to that of lutein and zeaxanthin. Furthermore, astaxanthin can provide higher antioxidant capacity, and it is also possibly associated with protection against ultraviolet light. On the contrary, several recent studies reported that astaxanthin has never been found in human eyes (Guerin et al. 2003). This result might be uncertain because astaxanthin may not accumulate in ocular tissue, or the daily intake of astaxanthin may not be enough in the diet. This is unlike the study of lutein and zeaxanthin, which is clearly found in retinal tissue. However, an animal study supported that astaxanthin has the ability to cross the blood-brain barrier and possibly deposit in the mammalian retina like lutein. Astaxanthin (100 mg/kg) dissolved in olive oil was administrated on mice orally 1 hour before retinal ischemia induction, immediately after reperfusion, at 6 or 12 h after reperfusion, and the control group was fed with olives oil only. These mice were treated with astaxanthin supplementation twice a day for the next 4 days and observed tissue damage and death on the fifth day. It was found that during retinal ischemia in mice, a large amount of astaxanthin could inhibit ischemia-induced retinal cell death and the production of reactive oxygen species. Besides, astaxanthin noticeably decreased retinal ischemic damage and electroretinogram reduction under histological analysis (Otsuka et al. 2016).

5.10 Treatment of *Helicobacter pylori* Infections

Microaerophilic *Helicobacter pylori* (formerly *Campylobacter pylori*) is a spiral gram-negative bacterium regularly found in the lining of the stomach. Due to its helical shape, it can infiltrate the mucoid lining of the stomach to cause infection. The complications of *H. pylori* infection may include gastric ulcer, duodenal ulcer, inflammation of the stomach lining, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. Contaminated foods or drinking water can spread pathogens quickly to cause foodborne illness (Lee et al. 2015). Bacteria can attach or form biofilm on the food surface, resulting in food contamination (Lee et al. 2016). Recent research suggests that the antioxidant and anti-inflammatory properties of astaxanthin may help prevent *H. pylori*-induced stomach inflammation. In infected tissues, astaxanthin alters the *H. pylori*-induced activation of T helper cell type 1 response to T helper cell type 2. *H. pylori* growth is inhibited, and *H. pylori*-induced stomach inflammation is reduced by astaxanthin without decreasing cytokine levels (Kang and Kim 2017). The influence of antioxidant astaxanthin on *H. pylori*-infected mice was estimated for the activity of cytokines produced by the T lymphocyte of *H. pylori*. The result presented that the antioxidant astaxanthin diminished bacterial population and gastrointestinal inflammation in *H. pylori*-infected mice. These modifications are linked to a transfer in the T-lymphocyte reaction from a mostly T-helper-2 response driven by interferon γ to a T-helper-1 and -2 response dominated by interferon γ and interleukin 4. The astaxanthin inhibition of *H. pylori* infection in 6-week-old BALB/cA mice was investigated.

These mice infected with the *H. pylori* strain 119/95 were treated orally with the astaxanthin content at 10, 50, and 100 mg/kg of body weight per day for 10 days. The *H. pylori* growth, lipid peroxidation, and inflammatory response were significantly decreased in the mice treated with astaxanthin compared to those not treated or treated with the control diet. Hence, astaxanthin could provide a potential new treatment for human *H. pylori* infection (Wang et al. 2000).

5.11 Skin Protection

The dermal extracellular matrix includes collagen, elastin, and glycosaminoglycans. Both intrinsic and extrinsic aging factors are associated with these structures, which may be involved in wrinkle development, tensile properties, poor wound healing, rebound capability, and dryness of the skin. Astaxanthin also prevents UV-induced skin photoaging, as demonstrated in animals and humans (Guerin et al. 2003). Both matrix-metalloproteinase-1 and skin fibroblast elastase were induced by ultraviolet (UVA) treatment on cultured human dermal fibroblasts to evaluate astaxanthin antioxidant capability. These findings demonstrated that astaxanthin effectively inhibited skin cell damage caused by reactive oxygen species-directed signaling cascade and induced matrix-metalloproteinase-1 in vitro after UVA irradiation (Suganuma et al. 2010). The hairless mice under UVA treatment were induced skin photoaging to estimate the effect of dietary astaxanthin. The results showed that dietary astaxanthin inhibited photoaging such as transepidermal liquid loss and wrinkle development in the dorsal skin to prevent desquamation mechanism in the epidermis, the dermal extracellular matrix, and filaggrin formation (Komatsu et al. 2017). Sixty-five healthy female adult subjects aged 35–60 years were administered 6 or 12 mg astaxanthin supplement orally or a placebo for 16 weeks. Long-term preventive healthcare astaxanthin intake may prevent age-related skin degradation and preserve skin conditions linked with environmental exposure by acting as an anti-inflammatory (Tominaga et al. 2017).

6 Astaxanthin in the Aquaculture Industry

Astaxanthin has been used as aquatic feed legally in Europe, America, Japan, and other countries for a long time. It belongs to one group of carotenoids, especially widely used in crustacean and salmon farming. This pigment carotenoid is well recognized as an important aquaculture feed ingredient for providing and increasing the pinkish-red color of the meat of salmons, trout, ornamental fish, shrimp, lobsters, and crayfish, resulting in higher quality and customer acceptability. Astaxanthin diesters were dominant in natural mesozooplankton populations during the winter cold season, whereas Astaxanthin monoesters were dominant during the summer hot season in the Baltic Sea. Astaxanthin is largely employed as a pigment in aquaculture and nutritional supplements in the food industry, but it also uses nutraceuticals and medicines. The sources of astaxanthin used in the feed may vary. It may be that

the cultured red algae are not purified, or it may come from yeast or bacterial fermentation. Astaxanthin has been approved as a food colorant in animal and aquaculture feeds by the United States Food and Drug Administration. Besides, it also specifically requires that if astaxanthin is added to the feed for farmed salmon, it must be marked as "Color Added" when it is sold in the market to distinguish it from natural wild-caught salmon. The ongoing expansion of the aquaculture industry has resulted in an enormous need for astaxanthin pigment (Stachowiak and Szulc 2021). Many aquatic animals like sea urchins *Pseudocentrotus depressus*, guppies *Poecilia reticulate* (Karino and Haijima 2004), crustaceans, and salmonids all have astaxanthin as a favorable impact on their growth and reproduction. There is possible differential utilization of astaxanthin in fish fed with different configurational isomers. The fish feeds containing all-*E*-astaxanthin were fed to freshwater rainbow trout *Oncorhynchus mykiss* in comparison with the other group of trout fed with a mixture of all-*E*-astaxanthin and primarily 9*Z*-, 13*Z*-, and 15*Z*-astaxanthin. The mixture includes 64% of all-*E*-astaxanthin and 36% of *Z*-astaxanthin. After 69 days, both groups of rainbow touts grew from 0.4 to 1.0 kg per fish, with a growth rate of 1.2% each day. The result demonstrated that there was higher retention of digestible total astaxanthin content in the trout flesh when a mixture of geometric isomers of astaxanthin was fed to the rainbow trout. It determined that the bioavailability and absorption capacity of total astaxanthin could be affected by the configurational isomer composition of the astaxanthin in their diet (Bjerkeng et al. 1997).

Many studies found that astaxanthin provided the best prevention from reactive oxygen species. While fish or crustaceans were fed a diet containing natural astaxanthin from microalgae *Haematococcus pluvialis* or other natural sources, the growth performance and immune capability were improved compared to fish or crustaceans fed with synthetic astaxanthin or basal diets. The antioxidative ability of astaxanthin is significantly related to stress resistance ability to improve various stress tolerance, including pH temperature, salinity, and oxidation in fish and crustaceans (Stachowiak and Szulc 2021). The influence of astaxanthin supplementation was investigated *on various* stress tolerance abilities, including antioxidative capacity, low salinity tolerance ability, growth performance, survival, and immune activity. The post-larval white shrimps *Litopenaeus vannamei* were fed with experimental diets containing *Haematococcus pluvialis* as the main source of astaxanthin for 25 days. The results revealed that dietary *Haematococcus pluvialis* significantly enhanced the salinity stress resistance, survival rate, immune ability, antioxidative activity of post-larval whiteleg shrimp *Litopenaeus vannamei*. The optimal concentration of astaxanthin and *Haematococcus pluvialis* in the supplement was 100 to 200 mg per kilogram diet and 3.3–6.7 g per kilogram diet, respectively (Xie et al. 2018). On the other hand, the application of modified dietary red yeast *Phaffia Rhodozyma* on Atlantic salmon did not have any nutritional benefits significantly. However, the pigmentation of Atlantic salmon was affected considerately by feeding with untreated, heat-treated, and commercially available synthetic astaxanthin from *Phaffia Rhodozyma* (Whyte and Sherry 2001). Scallops are popular bivalve mollusks in aquaculture across the world because of their high commercial value and

nutritional significance. Scallop production is based on seeds received from hatcheries, and its broodstock is a critical phase during the spat generation. The scallop *Nodipecten nodosus* was fed with dietary astaxanthin to investigate the astaxanthin accumulated content and the gonads of female scallop in the sexual phase during the pre-spawning and post-spawning period. The survival conditions of scallop larvae were also estimated. The result indicated that an astaxanthin-containing diet could significantly enhance the accumulated content of astaxanthin at approximately 18.7 ± 1.4 μg mL^{-1} in the gonad of female scallops before spawning and improve the production of scallop spawning. Besides, the survival of pediveliger and D-larvae was also increased under astaxanthin supplementation considerately (Sühnel et al. 2015).

7 Benefits of Astaxanthin in Livestock and Poultry

Astaxanthin is not only broadly used in the fishery industry but also in the poultry and livestock business. A number of studies have reported using Astaxanthin esters in poultry and livestock to provide their health benefit and the high-quality of their product. The effect of astaxanthin was demonstrated in the breeding and production of mammals, such as bovine, horses, porcine, dogs, and sheep. When astaxanthin is administered in animal feed, their breeding rate and production can be significantly enhanced. Besides, for preventative and therapeutic purposes, astaxanthin can be a potential medication for improving the length of mammalian muscle function or treating mammalian muscle illnesses, such as equine exertional rhabdomyolysis (Lignell 2001). Astaxanthin provides a number of therapeutic benefits in animals, including improvement of immunological response, disease prevention by scavenging free radicals, and cell protection from oxidative stress. Astaxanthin-rich red yeast *Phaffia rhodozyma* supplementation in broiler diets at doses of 10 and 20 mg/kg boosted weight gain by 4.1 and 6.4%, respectively. T-cell proliferation and immunoglobulin G production were enhanced by 111.1 and 34.6%, respectively, while dietary *Phaffia rhodozyma* at a dose of 100 mg/kg was added to broiler feeds for 14 days. All results disclosed that *Phaffia rhodozyma* in broiler diets could increase poultry production and the immune response of broilers (Ebeid et al. 2021). The addition of astaxanthin to the diet of layer hens enhanced their reproduction and health condition by diminishing poultry mortality. Chicken meat also can obtain highly desirable pigmentation under dietary astaxanthin supplementation. Egg production and yolk coloring have both improved. Besides, *Salmonella* contamination has decreased considerably because of a stronger membrane development in eggs. The effect of astaxanthin extracted from *Phaffia rhodozyma* on 1440 female 1-day-old Pekin ducklings was examined on their antioxidant capacity, relative organ weight, meat quality, and growth performance. After 6-week dietary astaxanthin with soybean and corn-containing supplementation at a 3.46 or 6.92 mg astaxanthin per kilogram diet, there is a positive influence on antioxidant activities, meat quality, and body weight gain (Ao and Kim 2019).

8 Micro- and Nano-encapsulation of Astaxanthin

Microencapsulation is a technology used to preserve food components from degradation during food preparation. It requires the generation of a wall structure to contain the core material's droplets or particles. Using a chitosan matrix has been used to increase astaxanthin solubility and stability (Demirci et al. 2020). Other matrixes have also been reported, such as β-cyclodextrin and hydroxypropyl-β-cyclodextrin (Chen et al. 2007), liposomes, and emulsions (Wackerbarth et al. 2009). The spray drying technology was used to encapsulate astaxanthin in order to improve its stability and applicability in food production (Lee et al. 2020). The wall components were a mixture of milk protein and carbohydrates with soluble corn fiber. The findings indicate that spray drying might be used to alter stable astaxanthin emulsions into powders with desirable attributes such as surface morphology, water activity, and oxidative stability. The microencapsulation efficiency was significantly high up to 95%, confirming that wall structures are adequate for encapsulation of the hydrophobic astaxanthin (Shen and Quek 2014). The protection of astaxanthin from photodegradation was investigated by the formulation of biocompatible hierarchically assembled nano- and microstructures. Astaxanthin is significantly protected against photodegradation by nanocarriers. The sequence from high to low protection is nanoemulsion, carrageenan-coated nanoemulsions, and chitosan-coated nanoemulsions. Hydrogels/microgels with nanocarriers were fed to adult *Danio rerio* and juvenile *Eleginops maclovinus.* Both fish species captured the hydrogels in the water column at high rates, demonstrating that the formulations appeal to fish in a diet (Alarcón-Alarcón et al. 2018). Carboxymethyl cellulose sodium and microcrystalline cellulose were used for the encapsulation of astaxanthin extracted from *Phaffia rhodozyma* under the freeze-drying method. The stability of microencapsulated astaxanthin was noticeably enhanced as compared to nonencapsulated astaxanthin. The yogurt with the addition of astaxanthin exhibited desirable orange-red color and considerably increased free radical scavenging activity and product stability in comparison to plain yogurt (Feng et al. 2018).

9 Safety and Recommended Dosage of Astaxanthin

Shrimps, crabs, lobsters, fish, and other aquatic animals humans eat daily contain abundant natural astaxanthin. There are no adverse reactions and poisoning symptoms found during daily human consumption. Thus, natural astaxanthin is safe and has no pathogenic effect on humans and animals. For toxicity evaluation of astaxanthin derived from green microalgae *Haematococcus pluvialis*, a biotechnology company Mera Pharmaceuticals Inc. conducted a safety study on participants received orally either a low dosage of 3.85 mg astaxanthin or at a high dose at 19.25 mg astaxanthin for 29 days. After comprehensive toxicological analysis, clinical examinations on the patients revealed that they were free of side-effect symptoms or intoxication at these levels of ingestion (Higuera-Ciapara et al. 2006). Astaxanthin is entirely safe because it cannot be converted to vitamin A or

synthesized in the human body and mammals. Unlike β-carotene, astaxanthin has found no provitamin activity in animals. However, chemical synthetic astaxanthin may be contaminated by other harmful substances during the synthesis process, and the product also contains a large number of *cis* isomers, which may reduce the safety of bioavailability. Therefore, chemically synthesized astaxanthin in the application of human food, animal feed, pharmaceuticals, and cosmetics might be critically restricted. Recommended daily intake or approved doses of astaxanthin is between 2 and 24 mg varied in different regulations and countries. Astaxanthin is recommended to be taken with omega-3-rich seed and fish oils, including chia, flaxseed, hazelnuts, walnuts, almonds, and salmon. There are nutraceuticals like soft gels, capsules, and ointments that contain astaxanthin on the market (Brendler and Williamson 2019).

10 Globe Market and Commercial Application and of Astaxanthin

Currently, almost all commercial astaxanthin is now synthetically manufactured from petrochemical sources, with a yearly turnover of more than $200 million and a retail price of $2000 per kg of pure astaxanthin. In 2014, both natural and synthetic astaxanthin is reported at 280 metric tons worth $447 million in the global market of nutraceuticals, food, cosmetics, and animal feeds. By 2020, it achieves 670 metric tons with $1 billion valuation. The natural source of astaxanthin derived from microalgae *Haematococcus pluvialis* is primarily used in the application of food, beverages, cosmetics, medication, and nutraceuticals for coloring agents and human health. On the other hand, synthetic astaxanthin derived from red yeast *Phaffia rhodozyma* and bacteria *Paracoccus haeundaensis* is mainly used in the livestock, poultry, and aquaculture industry. It is widely used in the aquaculture and salmon business to impart the typical pinkish-red color to farm-raised salmon. Today, synthetic astaxanthin manufacturing still dominates the commercial market, with BASF and Hoffman-La Roche as the leading manufacturers. There are two dominant synthetic commercial astaxanthin productions in the market: DSM Carophyll® Pink 10% CWS (formerly Hoffmann La Roche Carophyll® Pink) and BASF Lucantin® Pink. Hoffmann La Roche has been manufacturing synthetic astaxanthin on a large scale since 1985, effectively filling the international market for the astaxanthin pigment, which is estimated to be worth $150–200 million annually. The rising desire for natural foods, along with the high expense of synthetic pigments, has motivated researchers to look for natural sources of astaxanthin that might be industrialized. The green microalgae *Haematococcus pluvialis* and the red yeast *Phaffia rhodozyma* are the two primary microbial sources that can be entirely produced by synthetic astaxanthin economically. Several small businesses have sprung up to compete with Hoffmann La Roche by providing astaxanthin derived from natural sources (Table 3). Because of their limited manufacturing, these products currently only account for a small portion of the market (McCoy 1999).

Table 3 Commercial application of natural astaxanthin

Brand name	Source	Purpose	Producer	Location
AdoniCare® ARE-C	Metabolic-engineered bacteria	Human nutrition	ENEOS Techno Materials Corporation; JX Nippon ANCI, Inc.	Tokyo. Japan
AstaCos®	*Haematococcus pluvialis*	Food supplements	BDI-Biolife Science GmbH	Austria
AstaFactor	*Haematococcus pluvialis*	Food supplements	Aquasearch, Inc. and the Hawaiian Islands Trading Company LLC	Hawaii, United States
AstaFit®	*Haematococcus pluvialis*	Certified natural cosmetics	BDI-Biolife Science GmbH	Austria
AstaPure®Astaxanthin, AstaPure®Arava	*Haematococcus pluvialis*	Nutraceutical product	Algatechnologies Inc.	Israel
AstaReal®	*Haematococcus pluvialis*	Food supplement, cosmetic, beverage and animal nutrition	AstaReal Group owned by the Japanese pharmaceutical company Fuji Chemical Industries Co., Ltd.	Sweden
BioAstin®	*Haematococcus pluvialis*	Nutraceutical product	Cyanotech Corporation	Hawaii, United States
Ecotone®	*Phaffia Rhodozyma*	Animal nutrition	The Archer-Daniels-Midland Company (ADM)	Chicago, Illinois, United States
NaturAsta	*Haematococcus pluvialis*	Human food and aquatic feed supplements	Jingzhou Natural Astaxanthin	Hubei, China
NOVASTA® Astaxanthin	*Haematococcus pluvialis*	Pet food	AstaReal Group owned by the Japanese pharmaceutical company Fuji Chemical Industries Co., Ltd.	Sweden
Parry Organic Natural Astaxanthin	*Haematococcus pluvialis*	Nutraceutical product	Parry Nutraceuticals	Tamilnadu, India
Panaferd®-AX	Metabolic-engineered bacteria	Fish feed	ENEOS Techno Materials Corporation; JX Nippon ANCI, Inc.	Tokyo. Japan
YunNan Astaxanthin	*Haematococcus pluvialis*	Human Food and aquatic feed supplements	YunNan Alphy Biotech Co., Ltd	Yunnan, China

11 Conclusions and Future Perspectives

The properties and application of astaxanthin have been well-documented based on various current research studies and scientific reports. Astaxanthin is a bioactive molecule with high antioxidant activity to provide many therapeutic effects on human health, including cardiovascular antiaging, anticancer, antihypertension, prevention of cardiovascular and neurodegenerative diseases, treatment of diabetes mellitus and *Helicobacter pylori* infections, improvement of athletic performance, as well as eye and skin protection. Because of its antioxidant effect and anti-inflammatory, some scientists found that it may reduce the harm of new coronary pneumonia caused by coronavirus disease 2019 (COVID-19). In recent studies, astaxanthin can inhibit the activation of the inflammatory reaction by regulating signaling pathways nuclear factor-kappa B, NLRP3, and JAK/STAT. Natural astaxanthin as a therapeutic supplement can alleviate inflammatory cytokine storm and attenuate exacerbation of new coronary pneumonia (Ahmadi and Ayazi-Nasrabadi 2021). In addition, astaxanthin is also broadly used in foods, beverages, cosmetics, nutraceuticals, and animal feeds. Nevertheless, it is seldom known by the public and is undervalued by food producers because of its high cost and restricted availability. Promoter-based Gene Assembly and Simultaneous Overexpression (PGASO) is an innovative technique with a recombinatorial assembly strategy for gene cassettes with different promoters that uses overlapping oligonucleotides. It can be mass-produced in a safe, sustainable, and stable method for various rare and natural high-priced raw materials, such as astaxanthin and other bioactive compounds. This natural synthesis process can replace chemical synthesis to reduce carbon emissions and be environmentally friendly and sustainable. PGASO technology is a genome editing technique that may restructure cellular metabolic pathways and provide microorganisms with new functions. It can produce rare valuable bioactive molecules and specific natural products that cannot be obtained efficiently by chemical synthesis. More comprehensive studies of astaxanthin could be required in the examination of metabolic pathways in vitro and in vivo models for its commercial application. In the future, the application of genome editing techniques for the development of high value-added astaxanthin products, including dietary supplements and animal feed, will not only shorten the research and development process but also reduce their production costs.

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