Article

Astaxanthin: Sources, biosynthesis, bioactivities, clinical applications, and future perspectives

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Abstract
Astaxanthin, a red-orange keto-carotenoid, has garnered significant scientific and commercial interest due to its potent antioxidant properties and diverse biological activities. Unlike many other antioxidants, astaxanthin's unique molecular structure allows it to span biological membranes, providing comprehensive protection against oxidative stress. This review provides a comprehensive overview of astaxanthin, covering its natural sources, biosynthesis pathways, and chemical characteristics. It details the extensive research on its multifaceted bioactivities, including antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, cardioprotective, and skin-protective effects, supported by in vitro and in vivo studies. The review critically examines human clinical trials investigating its efficacy in areas such as eye health, skin aging, exercise performance, metabolic syndrome, and male fertility. Furthermore, the current state of astaxanthin production (microbial fermentation *vs*. algal cultivation), its applications in aquaculture, nutraceuticals, cosmetics, and food industries, and the global market trends are discussed. Finally, challenges in bioavailability, the need for more robust clinical evidence, and future research directions emphasizing novel delivery systems and exploration of new therapeutic applications are outlined.

Keywords astaxanthin; haematococcus pluvialis; carotenoid; antioxidant; anti-inflammatory; clinical trials; nutraceutical.

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1 Introduction

Carotenoids are a class of over 800 naturally occurring pigments synthesized by plants, algae, and some bacteria and fungi, responsible for the yellow, orange, and red colors in nature (Britton et al., 2004). Among them, astaxanthin (3,3′-dihydroxy-β,β-carotene-4,4′-dione) stands out as one of the most powerful biological antioxidants discovered (Higuera-Ciapara et al., 2006). Its unique structure features hydroxyl (-OH) and keto (=O) moieties on each ionone ring, connected by a polyene chain. This configuration not only contributes to its

vibrant color but, more importantly, endows it with exceptional free radical scavenging capacity. The molecule can quench singlet oxygen, neutralize free radicals like peroxyl and hydroxyl radicals, and inhibit lipid peroxidation more effectively than many other carotenoids and antioxidants such as vitamin E, β-carotene, and lycopene (Nishida et al., 2007; Miki, 1991).

The primary natural source of astaxanthin in the marine food chain is the microalga *Haematococcus pluvialis*, which accumulates high amounts (up to 3-5% dry weight) under stress conditions (Lorenz and Cysewski, 2000). This astaxanthin is then consumed by crustaceans (e.g., krill, shrimp), salmonids, and birds like flamingos, imparting their characteristic pink-red coloration. While synthetic astaxanthin dominates the aquaculture market, natural astaxanthin from *H. pluvialis* and the yeast *Phaffia rhodozyma* (*Xanthophyllomyces dendrorhous*) is increasingly preferred for human nutraceutical and cosmetic applications due to its superior stereoisomeric form (predominantly 3*S*,3′*S*) and consumer demand for natural products (Ambati et al., 2014; Shah et al., 2016).

The past three decades have witnessed an exponential growth in research on astaxanthin, revealing its potential benefits far beyond pigmentation. Extensive preclinical studies have demonstrated its protective effects against oxidative stress and inflammation, which are root causes of many chronic diseases. Consequently, astaxanthin has been investigated for its roles in promoting eye, skin, brain, cardiovascular, and metabolic health, enhancing exercise performance and recovery, and supporting immune function (Yuan et al., 2011). This review synthesizes current knowledge on astaxanthin, from its discovery and biosynthesis to its bioactivities, clinical evidence, industrial production, and future prospects.

2 Discovery and Natural Sources

2.1 Historical Discovery

The history of astaxanthin is intertwined with observations of natural pigmentation. While its presence in marine animals was noted for centuries, its chemical identity was elucidated much later. In 1938, the Nobel laureate Richard Kuhn isolated and described astaxanthin from lobsters, naming it after the Greek words "astakos" (lobster) and "xanthos" (yellow) (Kuhn and Sörensen, 1938). Its complete structure was later confirmed through chemical synthesis (Bernhard et al., 1960). The realization that microalgae were the primary producers came with the work on Haematococcus pluvialis in the mid-20th century (Droop, 1955).

2.2 Primary Natural Producers

2.2.1 Microalgae: *Haematococcus pluvialis*

H. pluvialis is a freshwater green alga and is considered the richest natural source for commercial astaxanthin production. Its life cycle involves a green, motile vegetative stage under favorable conditions and a red, non-motile cyst stage under stress (high light, nutrient deficiency, high salinity). In the cyst stage, it synthesizes and accumulates astaxanthin in cytoplasmic lipid droplets, primarily in esterified forms with fatty acids, as a protective mechanism against oxidative damage (Boussiba, 2000). This high accumulation capacity (1.5–3.0%, sometimes up to 5% dry weight) makes it ideal for industrial cultivation.

2.2.2 Yeast: *Phaffia rhodozyma* (*Xanthophyllomyces dendrorhous*)

This basidiomycetous yeast, discovered on tree exudates in Alaska, produces astaxanthin as its main carotenoid. Its astaxanthin content is lower than *H. pluvialis* (0.05–0.1% dry weight), but it can be grown heterotrophically in fermenters using conventional carbon sources, offering advantages for scalable production (Johnson and An, 1991). The astaxanthin from Phaffia is predominantly in the (3R,3′R) configuration.

2.2.3 Other Sources

Astaxanthin is also found in other organisms like the marine bacterium *Paracoccus carotinifaciens* and some marine algae, but these are less commercially significant. The astaxanthin present in wild salmon, krill, shrimp,

and crab shells is derived from their algal diet.

3 Biosynthesis and Chemistry

3.1 Biosynthetic Pathways

In microorganisms, astaxanthin is synthesized via the isoprenoid pathway. The general steps are: condensation of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) to form geranylgeranyl pyrophosphate (GGPP); condensation of two GGPP molecules to produce phytoene (colorless); and a series of desaturation and isomerization reactions converting phytoene to lycopene (red). Lycopene is then cyclized to form β-carotene. The final steps involve hydroxylation and ketolation at the 3,3′ and 4,4′ positions of the β-ionone rings to produce astaxanthin. Key enzymes include phytoene synthase/desaturase, lycopene cyclase, β-carotene hydroxylase (CrtZ or BCH), and β-carotene ketolase (CrtW or BKT) (Fraser et al., 1997; Misawa, 2011; Fig. 1). In *H. pluvialis*, the genes bkt and crtR-B (hydroxylase) are crucial and are upregulated under stress (Li et al., 2008).

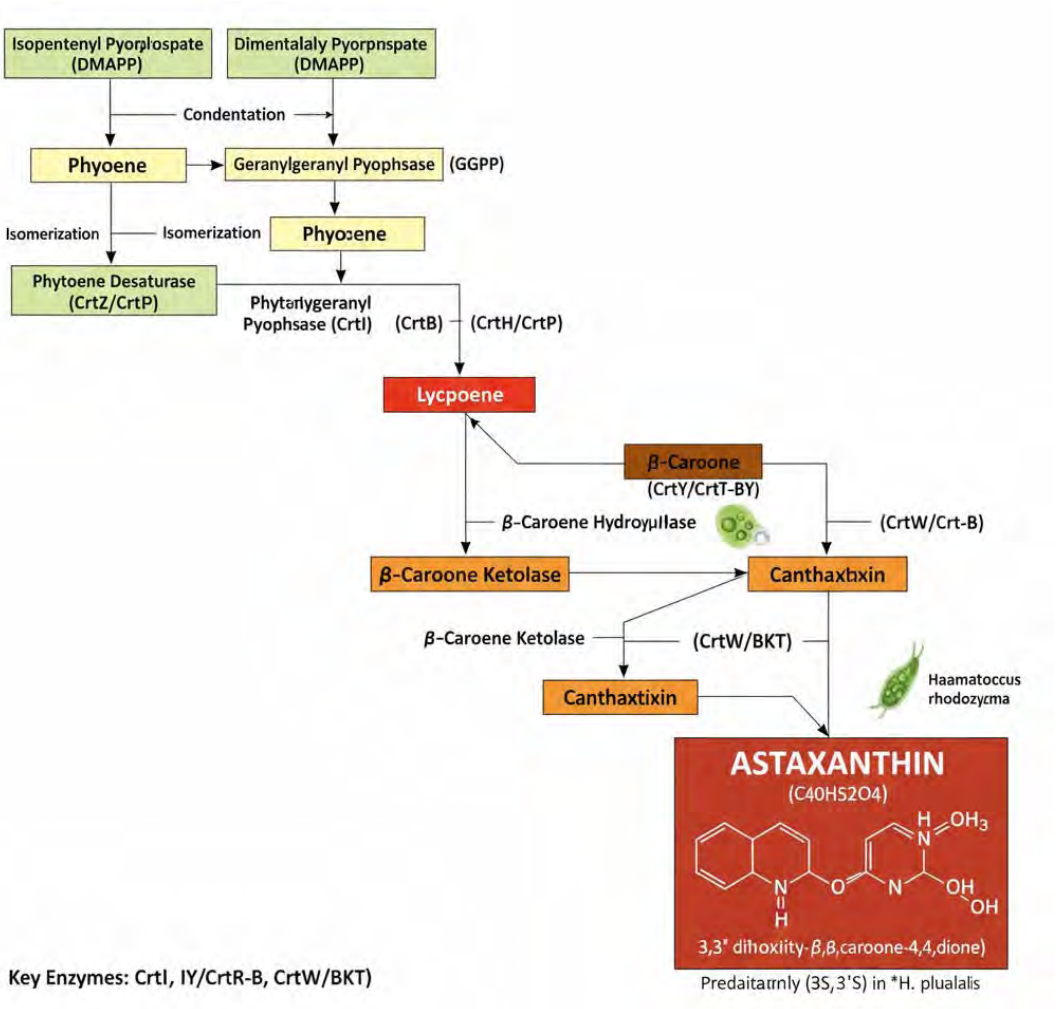

Fig. 1 Astaxanthin biosynthesis pathway.

3.2 Chemical Structure and Stereoisomers

Astaxanthin (C40H52O4) is a xanthophyll carotenoid. Its potent antioxidant activity is attributed to: (1) the conjugated polyene chain, which can delocalize electrons from reactive oxygen species (ROS); (2) the hydroxyl and keto groups on the rings, which can form stable radicals through hydrogen atom transfer and participate in electron transfer (Edge and Truscott, 2010). Astaxanthin exists in three stereoisomeric forms: (3S,3′S), (3R,3′R), and (3R,3′S) (meso). Synthetic astaxanthin is a racemic mixture of the three forms. Natural astaxanthin from *H. pluvialis* is predominantly (3S,3′S), while that from P. rhodozyma is (3R,3′R) (Lorenz and Cysewski, 2000). The (3S,3′S) form is generally considered to have higher biological activity.

4 Bioactivities and Mechanisms of Action

4.1 Antioxidant Activity

Astaxanthin is renowned for its exceptional antioxidant capacity, estimated to be 10 times stronger than zeaxanthin, lutein, canthaxanthin, and β-carotene, and 100-500 times stronger than α-tocopherol in quenching singlet oxygen (Miki, 1991). Its mechanism involves:

Singlet Oxygen Quenching: Efficiently deactivates $^1O_2$ via energy transfer.

Free Radical Scavenging: Neutralizes peroxyl radicals ($ROO^{\bullet}$), superoxide anion ($O_2^{\bullet-}$), hydroxyl radicals (•OH), and peroxynitrite ($ONOO^-$).

Lipid Peroxidation Inhibition: Its polar-nonpolar-polar structure allows it to embed in cell membranes with its rings near the hydrophilic surfaces and the polyene chain within the lipid bilayer, thereby stabilizing membranes and preventing lipid peroxidation chain reactions (Goto et al., 2001; McNulty et al., 2007).

4.2 Anti-inflammatory Effects

Chronic inflammation is a key driver of many diseases. Astaxanthin modulates multiple inflammatory pathways. It downregulates the nuclear factor-kappa B (NF-κB) pathway, a master regulator of inflammation (Huang and Zhang, 2022; Li and Zhang, 2023), leading to reduced production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-6, and prostaglandin E2 (PGE2) (Lee et al., 2003). It also inhibits the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Ohgami et al., 2003). Furthermore, astaxanthin can suppress the activation of the NLRP3 inflammasome (Wang et al., 2022).

4.3 Immunomodulation

Astaxanthin enhances both humoral and cell-mediated immune responses. Studies show it increases the production of immunoglobulins (IgA, IgG, IgM), enhances lymphocyte proliferation, natural killer (NK) cell activity, and cytotoxic T-cell activity (Jyonouchi et al., 1994, 2000). It also modulates macrophage function, increasing phagocytosis and regulating cytokine release.

4.4 Neuroprotective Potential

Due to its ability to cross the blood-brain barrier, astaxanthin shows promise for brain health. It protects neurons from oxidative damage and apoptosis induced by various stressors. It upregulates brain-derived neurotrophic factor (BDNF) and attenuates neuroinflammation (Liu et al., 2009). In models of neurodegenerative diseases like Alzheimer's and Parkinson's, astaxanthin reduces β-amyloid plaque deposition, tau hyperphosphorylation, and dopaminergic neuron loss (Chang et al., 2010; Wang et al., 2010).

4.5 Cardioprotective Effects

Astaxanthin benefits cardiovascular health through multiple mechanisms: improving lipid profiles by increasing HDL and reducing triglycerides (Yoshida et al., 2010); inhibiting LDL oxidation (Iwamoto et al., 2000); reducing blood pressure via enhancing nitric oxide (NO) bioavailability (Monroy-Ruiz et al., 2011); and improving vascular endothelial function and reducing arterial stiffness (Miyawaki et al., 2008).

4.6 Skin Health and Photo-Protection

Astaxanthin protects skin from UV-induced damage by neutralizing ROS generated by UV exposure, reducing inflammation, and preventing matrix metalloproteinase (MMP) activation that degrades collagen and elastin (Yamashita, 1995). It also improves skin moisture, elasticity, and reduces wrinkles (Tominaga et al., 2012).

4.7 Ocular Health

As a carotenoid, astaxanthin accumulates in the eye. It protects retinal photoreceptor cells from light-induced damage and oxidative stress, reduces retinal inflammation, and may improve blood flow in retinal capillaries (Nakajima et al., 2008). It is studied for conditions like age-related macular degeneration (AMD) and eye fatigue.

4.8 Metabolic and Mitochondrial Effects

Astaxanthin improves insulin sensitivity and glucose metabolism in models of diabetes (Uchiyama et al., 2002). It enhances mitochondrial function by reducing mitochondrial ROS and improving oxidative phosphorylation efficiency (Wolf et al., 2010).

From the perspective of network biology, astaxanthin serves as a regulatory and controlling factor in the human biological network (Zhang, 2016, 2018).

5 Human Clinical Trials

5.1 Skin Aging and UV Protection

Several randomized controlled trials (RCTs) support astaxanthin's benefits for skin. A study with 49 healthy women showed that 6 mg/day for 8 weeks significantly improved skin wrinkle parameters, elasticity, moisture content, and reduced age spot size (Tominaga et al., 2017). Another RCT found that a combination of astaxanthin (4 mg/day) with other carotenoids reduced UV-induced skin deterioration and helped maintain skin moisture (Yamashita, 2002).

5.2 Eye Fatigue and Visual Function

Studies on subjects with asthenopia (eye strain) indicate that astaxanthin (4-6 mg/day for 4 weeks) improves accommodative function, reduces symptoms of eye fatigue, and improves critical flicker fusion frequency (Nagaki et al., 2002; Shiratori et al., 2005).

5.3 Exercise Performance and Recovery

Research suggests astaxanthin may enhance endurance and reduce muscle damage. A study on competitive cyclists found that 4 mg/day for 4 weeks increased power output and time to exhaustion (Earnest et al., 2011). Other studies report reduced markers of muscle damage (creatine kinase, lactate dehydrogenase) and inflammation after exercise (Aoi et al., 2008; Djordjevic et al., 2011).

5.4 Cardiovascular and Metabolic Health

Clinical trials show improvements in cardiovascular risk factors. Supplementation (6-12 mg/day) significantly reduced triglycerides and increased HDL-cholesterol while improving LDL particle size in overweight and obese subjects (Yoshida et al., 2010). Another study reported reduced systolic blood pressure and improved arterial elasticity (Miyawaki et al., 2008).

5.5 Male Fertility

Astaxanthin (16 mg/day for 3 months) improved sperm parameters (count, motility, morphology) and pregnancy rates in infertile men, likely by reducing oxidative stress in seminal plasma (Comhaire et al., 2005).

5.6 Safety and Tolerability

Clinical trials consistently report that astaxanthin is well-tolerated with an excellent safety profile at doses up to 40 mg/day for several weeks. No serious adverse effects have been reported. Mild side effects may include stool coloration (reddish) at high doses.

6 Production, Industrial Applications, and Market

6.1 Production Methods

6.1.1 Synthetic Astaxanthin: Chemically synthesized via the Wittig reaction. It accounts for >95% of the market by volume, mainly used in aquaculture feed. It is cost-effective but is a racemic mixture different from natural forms.

6.1.2 Natural Astaxanthin from *H. pluvialis*: Production involves two stages: (1) Green stage: Optimizing growth for biomass under controlled conditions. (2) Red stage: Inducing astaxanthin accumulation under stress in closed photobioreactors (PBRs) or open ponds. PBRs offer better control and higher productivity but at greater cost. Downstream processing includes harvesting, cell disruption (crucial for bioavailability), extraction (supercritical CO_2 or organic solvents), and purification (Olaizola, 2000; Shah et al., 2016).

6.1.3 Fermentation-based Production: Using *Phaffia rhodozyma* in stirred-tank fermenters. Genetic engineering of both *Phaffia* and *H. pluvialis*, as well as heterologous production in faster-growing hosts like *Yarrowia lipolytica* or *E. coli*, are active research areas to improve yield and reduce costs (Chatzifragkou et al., 2022).

6.2 Industrial Applications

6.2.1 Aquaculture: The largest market. Supplementation in feed for salmon, trout, and shrimp to impart the desired pink flesh/shell color and improve survival and immune status (Torrissen et al., 1989).

6.2.2 Nutraceuticals and Dietary Supplements: Sold as softgels, capsules, and tablets for antioxidant support, eye, skin, and joint health. Often combined with other ingredients.

6.2.3 Cosmeceuticals: Incorporated into anti-aging creams, serums, and sunscreens for its protective and skin-rejuvenating properties.

6.2.4 Food and Beverages: Used as a natural colorant (E161j) in foods like salmon sushi, and added to functional beverages.

6.2.5 Animal and Pet Nutrition: For coloration of egg yolks, poultry skin, and to enhance the health and appearance of pets.

6.3 Market Overview

The global astaxanthin market is growing rapidly, driven by rising demand for natural antioxidants in nutraceuticals and cosmetics. The natural astaxanthin segment, though smaller in volume than synthetic, commands a much higher price and is expanding faster. North America and Asia-Pacific are key markets. H. pluvialis-derived astaxanthin is generally recognized as safe (GRAS) by the FDA for use in dietary supplements.

7 Challenges and Future Perspectives

Despite significant progress, several challenges remain:

Bioavailability: Astaxanthin is highly lipophilic and has poor aqueous solubility, leading to low and variable oral bioavailability. Research on novel delivery systems—nanoparticles, emulsions, liposomes, phospholipid complexes (e.g., with phosphatidylcholine)—aims to enhance its absorption and stability (Ranga Rao et al., 2010).

Dose-Response and Long-Term Effects: Optimal dosing for specific health outcomes and long-term safety data beyond a few months are needed.

Mechanistic Clarity: While antioxidant and anti-inflammatory effects are established, precise molecular targets and signaling pathways in humans require further elucidation.

Clinical Evidence: More large-scale, long-term, rigorously designed RCTs are necessary to substantiate health claims and gain wider acceptance in the medical community.

Sustainable and Cost-Effective Production: Innovations in algal cultivation (e.g., hybrid systems, efficient LED lighting, waste valorization) and metabolic engineering are crucial to lower production costs and improve sustainability.

New Applications: Exploring astaxanthin's potential in areas like gut health (microbiome modulation), anti-cancer adjuvant therapy, and mental health (depression, cognitive decline) represents promising future directions.

8 Conclusion

Astaxanthin has evolved from a mere pigment to a high-value bioactive compound with immense potential in health promotion and disease prevention. Its unparalleled antioxidant strength, coupled with multifaceted anti-inflammatory, immunomodulatory, and cellular protective actions, underpins its wide-ranging biological benefits. While strong preclinical evidence abounds, human clinical data, though promising, need to be expanded and strengthened. The industry is moving towards natural sources, primarily Haematococcus pluvialis, driven by consumer preference. Overcoming challenges related to bioavailability, production costs, and definitive clinical proof will be key to unlocking the full potential of this "king of carotenoids." As research continues to unravel its complexities, astaxanthin is poised to play an increasingly significant role in functional foods, nutraceuticals, cosmetics, and possibly pharmaceuticals.

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