



Astaxanthin as an anti-aging agent: Extraction, mechanisms, and therapeutic potential

Rumaisya Yasmin Mohd Nazri¹, Lay Kek Teh², Nurul Aqmar Mohamad Nor Hazalin^{2,3}, Lay Jing Seow^{4*} , Eng Keng Seow^{1,3,5,6}

¹Food Science and Technology Program, School of Industrial Technology, Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia.

²Faculty of Pharmacy, Universiti Teknologi MARA, Bandar Puncak Alam, Malaysia.

³Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA, Bandar Puncak Alam, Malaysia.

⁴Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Malaysia.

⁵Food Science Research Group, Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia.

⁶Integrated Nutrition Science and Therapy Research Group (INSPiRE), Faculty of Health Sciences, Universiti Teknologi MARA, Bandar Puncak Alam, Malaysia.

ARTICLE HISTORY

Received on: 28/09/2025

Accepted on: 02/01/2026

Available Online: 05/03/2026

Key words:

Anti-aging, astaxanthin, bioavailability, nutraceutical interventions, pharmaceutical applications.

ABSTRACT

Aging is a complex biological process influenced by molecular, cellular, and environmental factors. In recent years, astaxanthin, a potent carotenoid derived primarily from *Haematococcus pluvialis*, has gained significant attention for its pharmacological properties, including antioxidant, anti-inflammatory, and anti-aging effects. This review explores the biochemical properties, sources, and extraction techniques of astaxanthin, with a focus on advanced methods such as supercritical fluid extraction and microwave-assisted extraction (MAE). Furthermore, the mechanisms underlying aging, including cellular senescence, oxidative stress, mitochondrial dysfunction, and telomere attrition, are discussed to establish a link between astaxanthin's bioactivity and its therapeutic potential in aging-related interventions. Additionally, the bioavailability and pharmacokinetics of astaxanthin are reviewed to highlight its physiological relevance and clinical applications. Current innovations in anti-aging strategies, ranging from lifestyle modifications and nutraceutical interventions to pharmaceutical applications, are also examined. The emerging role of astaxanthin in anti-aging research is emphasized through recent studies on its effects in promoting longevity and skin health. This review aims to provide a comprehensive understanding of astaxanthin's potential as a natural anti-aging agent while identifying future research directions for its pharmaceutical and clinical applications.

1. INTRODUCTION

Aging is a natural but multifaceted biological process that includes a gradual and slow decline in physiological function, which manifests as increasing susceptibility to a variety of diseases and a corresponding reduction in overall quality of life. Many factors influence this multifaceted process, leading researchers to propose several theories that seek to uncover the underlying mechanisms of aging. Among

the most prominent theories are oxidative stress, which posits that the accumulation of free radicals causes cellular damage; mitochondrial dysfunction, which refers to the decline in energy production and increase in production of reactive oxygen species (ROS); and telomere shortening, which highlights telomere participation in cellular aging and senescence [1–3]. Given the rapid increase in the aging global population, there has been a marked surge in interest in effective interventions that may ameliorate the impacts of aging and promote increased longevity. Moreover, as living standards continue to improve in contemporary society and the aging population grows, more individuals are showing interest in aging and anti-aging issues. A significant aspect of aging is the aging of the skin, which tends to be a particular concern for women. In the cosmetic

*Corresponding Author

Lay Jing Seow, Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Malaysia.

E-mail: ljseow@unikl.edu.my

industry, the proportion of anti-aging products in the market has been growing annually [4].

Astaxanthin, a naturally occurring carotenoid predominantly sourced from the green microalgae *Haematococcus pluvialis*, has emerged as a focus of research due to its remarkable properties as a powerful antioxidant, anti-inflammatory, and anti-aging mechanism [5–8]. Scientific studies indicate that astaxanthin has the unique ability to counteract oxidative damage at the cellular level, improve skin elasticity and hydration, and modulate critical biochemical pathways involved in the aging process, including those linked to inflammation and cellular repair [9–12]. In recent years, astaxanthin has been increasingly explored for several applications, including pharmaceutical formulations, functional foods, and cosmeceuticals, owing to its capacity to protect against oxidative stress, reduce inflammatory responses, and enhance overall skin health. However, despite encouraging preclinical outcomes and early-stage findings, the use of astaxanthin faces significant challenges, including its low solubility, issues with stability, and poor bioavailability [13,14]. These limitations emphasize the necessity for ongoing research focused on optimizing delivery systems and developing more effective formulations that can enhance the therapeutic potential of astaxanthin.

Despite many studies examining astaxanthin's biological activity, there remains a notable lack of comprehensive evaluations concerning its pharmacokinetics, advanced extraction methodologies, and therapeutic mechanisms, particularly in the context of aging. This review aims to bridge this existing gap in knowledge by synthesizing current findings related to the molecular mechanisms of astaxanthin, its bioavailability, and the emerging pharmaceutical applications in anti-aging therapies. Furthermore, while the FDA has classified astaxanthin as Generally Recognized as Safe (GRAS) and approved it as a dietary supplement in various countries [15], further clinical evidence is necessary to establish standardized dosing regimens, assess long-term safety, and attain regulatory approval for its broader pharmaceutical applications.

In support of its GRAS designation, multiple preclinical and clinical studies have demonstrated a favorable safety profile for astaxanthin. Human trials have reported good tolerability at doses up to 40 mg/day, with only mild gastrointestinal effects occasionally observed at higher intake levels [16]. Animal studies have also shown no toxic effects even at doses exceeding 1,000 mg/kg/day [16,17]. Additionally, the European Food Safety Authority has proposed an acceptable daily intake of 0.034–0.2 mg/kg body weight for synthetic astaxanthin [18]. These findings indicate that astaxanthin is safe at commonly consumed doses, although further long-term studies are recommended to fully establish its safety at pharmacological levels.

Given its broad safety margin and increasing research interest, this review will comprehensively examine the biochemical properties of astaxanthin, including its natural sources and the latest advancements in extraction technologies used to isolate this potent carotenoid. Furthermore, it will highlight the pharmacokinetic characteristics and therapeutic potential of astaxanthin, with a particular focus on its pharmacological applications in managing aging-related conditions.

2. MATERIALS AND METHODS

2.1. Literature search strategy

A thorough literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar to locate applicable studies on astaxanthin and its anti-aging properties. Keywords such as “astaxanthin,” “oxidative stress,” “aging,” “pharmacokinetics,” and “extraction techniques” were used. Articles published from 2000 to 2025 were included, with a focus on peer-reviewed journals, clinical studies, and recent advances in extraction technologies.

2.2. Inclusion and exclusion criteria

Studies were selected based on specific criteria to ensure relevance and quality. The following inclusion criteria guided our analysis: (I) studies investigating the biochemical properties and pharmacokinetics of astaxanthin; (II) research on astaxanthin's role in aging, oxidative stress, and inflammation; and (III) articles discussing extraction and bioavailability enhancement strategies. References were excluded for (I) studies not related to astaxanthin or its therapeutic applications; (II) non-English publications (unless an English abstract was available); and (III) review articles that did not contribute new experimental findings.

2.3. Data extraction and analysis

The data outlined below were obtained from the chosen studies, including mechanisms of action, extraction techniques, pharmacokinetics, and clinical outcomes. The findings were categorized into major themes such as astaxanthin's antioxidant potential, molecular mechanisms in aging, and pharmaceutical applications.

3. RESULTS AND DISCUSSION

3.1. Astaxanthin: a bioactive carotenoid with pharmaceutical potential

Astaxanthin is a red secondary metabolite with strong antioxidant characteristics that are commonly used in foods, animal feed, cosmetics, nutraceuticals, and pharmaceuticals. Astaxanthin is mainly synthesized using chemicals and is less expensive than natural astaxanthin collected from fish, shrimps, and microorganisms [19]. As a reddish-orange carotenoid that lacks vitamin A and is composed of oxygen, carbon, and hydrogen atoms, astaxanthin belongs to the xanthophyll family. Because of its safety, it is categorized as a “pure antioxidant” [12]. Furthermore, according to Capelli *et al.* (2012), the US Food and Drug Administration classified natural astaxanthin as GRAS. Its use as a nutraceutical has increased as a result, and it is now extensively used [20]. The demand for it is rising globally, and by 2025, it is predicted to reach \$2.57 billion. This study will explore the relevance of astaxanthin, its sources in nature, chemical composition, and the techniques employed for astaxanthin extraction, as well as assessing its possible uses across different industries.

3.1.1. Overview of astaxanthin

Astaxanthin is a pigment from the carotenoid which occurs naturally and belongs to the xanthophyll family. It is

predominantly discovered in oceanic habitats, with microalgae such as *Haematococcus pluvialis* being its most significant source [21]. Astaxanthin is recognized for its vibrant red–orange colour, which it imparts to various marine organisms, including salmon, shrimp, and lobster. Astaxanthin is renowned for its exceptional antioxidant capacity, which significantly exceeds the levels found in other carotenoids such as beta-carotene and lycopene. This potent antioxidant activity enables astaxanthin to effectively combat free radicals, thus lowering oxidative stress and safeguarding against cellular harm. Astaxanthin's robust antioxidant properties and possible health advantages have rendered it highly useful in the nutraceutical, cosmetic, food, and feed sectors [22]. In addition to its antioxidant properties, astaxanthin exhibits a range of other biological activities, including anti-inflammatory, immunomodulatory, and neuroprotective effects [23]. These properties make astaxanthin a compound of great interest for potential therapeutic applications, especially concerning aging and diseases associated with advancing age. Research has shown that astaxanthin is capable of penetrating the blood–brain barrier (BBB), providing protective benefits to the brain and central nervous system. Its ability to integrate into cell membranes allows it to provide protection against lipid peroxidation and maintain cellular integrity [24]. Astaxanthin's bioavailability and metabolism have also been subjects of study, revealing that while it is fat-soluble and best absorbed when consumed with dietary fats, various formulations and delivery methods are being developed to enhance its bioavailability [25]. Overall, astaxanthin's diverse health benefits and its role as a potent bioactive compound underscore its potential in nutritional and therapeutic applications aimed at promoting health and mitigating the effects of aging.

3.1.2. Significance and pharmacological properties of astaxanthin in health

Astaxanthin, a vibrant red pigment that is part of the carotenoid group, has attracted considerable interest in health and nutrition due to its potent antioxidant properties and myriad health benefits. Naturally occurring in microalgae, yeast, salmon, trout, shrimp, crayfish, and the plumage of some birds, astaxanthin stands out for its capacity to counteract free radicals and safeguard cells against oxidative stress. This unique antioxidant capacity is attributed to its molecular structure, which allows it to span cell membranes and provide comprehensive protection. Emerging research has linked astaxanthin to various health benefits, including anti-inflammatory effects, enhanced immune response, improved skin health, and potential protective roles in cardiovascular and neurodegenerative diseases. As a dietary supplement, its safety and efficacy further underscore its significance in promoting overall health and well-being.

3.1.2.1. Antioxidant effects

An antioxidant is a compound that can impede the oxidation process. Free radicals and ROS initiate oxidative damage. These highly reactive compounds are generated by the regular aerobic metabolism of living organisms. When there is an overload of reactive molecules, it can kick off a

chain reaction that leads to the oxidation of proteins, lipids, and deoxyribonucleic acid (DNA). This sequence of events can cause damage to proteins and lipids, as well as harm the DNA, which has been associated with a variety of health issues. Endogenous and exogenous antioxidants, such as carotenoids, have the ability to block this specific sort of oxidative molecules [26]. Long conjugated double bonds called polyene chains, which are found in carotenoids, work as antioxidants by scavenging radicals and quenching singlet oxygen to stop chain reactions. Carotenoids' biological effects could be related to their antioxidant qualities, which are a result of their chemical and physical interactions with cell membranes [26]. As antioxidants, carotenoids can guard against oxidative damage in the bodies of humans, animals, and plants worldwide through this mechanism, which results in a strong antioxidant effect [27].

Astaxanthin possesses one of the highest antioxidant potentials among natural carotenoids, surpassing that of other carotenoids [28]. Astaxanthin is a potent antioxidant carotenoid capable of neutralizing ROS and preventing oxidative damage in biological systems. ROS and free radicals are byproducts of normal aerobic metabolism, but when accumulated in excess, they initiate chain reactions that oxidize proteins, lipids, and DNA—contributing to the pathogenesis of various chronic diseases [26].

Astaxanthin consists of 13 unsaturated conjugated double bonds, which feature unpaired electrons that contribute to its active electronic properties. This carotenoid is capable of donating electrons to neutralize free radicals, transforming them into harmless compounds. Additionally, it effectively quenches singlet oxygen, thereby eliminating free radicals and interrupting their chain reaction [23,29].

Several studies have compared astaxanthin's antioxidant capacity to other carotenoids and vitamins. For example, Naguib [28] reported that astaxanthin exhibits superior antioxidant activity compared to a range of other carotenoids, including lutein, lycopene, α -carotene, and β -carotene. In a study conducted by Ranga Rao *et al.* [30], it was observed that the antioxidant enzymes catalase, superoxide dismutase, peroxidase, and thiobarbituric acid reactive substances showed increased levels in the plasma and liver of rats following the administration of *Haematococcus* biomass extract as a source of astaxanthin. These findings highlight the potential health benefits of astaxanthin due to its remarkable antioxidant properties in biological systems. Astaxanthin has also been shown to be 100 times more effective in neutralizing singlet oxygen than vitamin E and significantly more reactive than β -carotene or α -tocopherol [31]. These findings highlight its exceptional antioxidant potential, often leading to its designation as a “super vitamin E” [27].

In vivo and *in vitro* studies have further supported these properties. Chintong *et al.* [32] conducted an *in vitro* study, utilizing astaxanthin (ASTX) derived from shrimp waste to examine its antioxidant properties [32]. Astaxanthin derived from shrimp waste effectively scavenged 2,2-diphenyl-1-picrylhydrazyl, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radicals, and inhibited β -carotene bleaching *in vitro* [31]. Similarly, Xu *et al.* [33] demonstrated an experiment where they administered a mixture of astaxanthin and flaxseed

oil (FO) to rats on a high-fat diet, which were separated into four groups over a period of 10 weeks (ASTX 1 g/kg mixed with FO, in the following groups: 0% ASTX + FO, 25% ASTX + FO, 50% ASTX + FO, and 75% ASTX + FO). They found that this treatment reduced oxidative stress and lipid peroxidation in the liver that was caused by the high-fat diet [19]. A recent research study stated that dietary astaxanthin can cross the blood-brain barrier and accumulate in the hippocampus and cerebral cortex of rats' brains [20], indicating the potential of astaxanthin to protect neurological function from damage caused by free radicals. In an animal trial, researchers established a weight-drop model of traumatic brain injury *in vivo* using mice and found that astaxanthin significantly mitigated oxidative damage through various signaling pathways [21]. These studies suggest that astaxanthin has neuroprotective potential.

However, the antioxidant potency of astaxanthin may vary depending on the source of extraction (e.g., *Haematococcus* vs. shrimp), isomeric composition (E/Z forms), and formulation (e.g., oil-based or encapsulated). Some studies also differ in the experimental models used (e.g., rats, mice, or cell lines), dosage, or duration, which can influence the reported outcomes. While the collective data support astaxanthin's antioxidant capacity, these methodological differences highlight the importance of interpreting results comparatively and cautiously across studies.

3.1.2.2. Anti-inflammatory effect

Chronic inflammation plays a significant role in developing various diseases, such as cancer, heart disease, and atherosclerosis [13,34]. The production of nitric oxide (NO) during inflammation can cause cell damage when it reacts with superoxide anions to form peroxynitrite [13,35]. Inducible nitric oxide synthase (iNOS) in macrophages generates NO, and it can be activated by different stimuli, including lipopolysaccharides, interferon- γ , and tumor necrosis factor- α (TNF- α) [35]. Nuclear factor- κ B (NF- κ B) is a crucial transcription factor that controls the expression of many inflammatory genes, including TNF- α , interleukin-1 β (IL-1 β), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and iNOS [13,36].

Astaxanthin has demonstrated effective anti-inflammatory properties in various biological systems. A study conducted over 26 weeks on rats demonstrated that natural ASTX reduced liver damage caused by arsenic and mitigated the inflammatory response by modulating the NF- κ B pathway, leading to a decline in pro-inflammatory cytokines such as TNF- α and IL-6 in lipopolysaccharide-stimulated neutrophils, while enhancing their phagocytic and microbicidal functions as well as a decline in the production of superoxide anion and hydrogen peroxide [37,38]. In addition to inhibiting downstream targets like COX-2 and iNOS, ASTX is now known to influence upstream regulatory mechanisms, including activation of nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE), PI3K/Akt, and Sirtuin 1, which collectively help suppress nuclear factor kappa B (NF- κ B) activity and reduce oxidative stress [16,17,39].

ASTX has also shown potential in the treatment of asthma-related inflammation. In a study by Haines *et al.* [40], a combination of *Ginkgo biloba* extract with ASTX (5–200 mg ASTX per kg body weight) and Vitamin C administered

to asthmatic guinea pigs led to a significant reduction in inflammatory cell numbers in bronchoalveolar lavage fluid and an increase in cAMP and cGMP levels in lung tissues, suggesting that astaxanthin may modulate respiratory inflammation and improving lung function.

Regarding organ protection, ASTX has also effectively prevented kidney injury through anti-inflammatory mechanism by suppressing the activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and IL-1 β /IL-18 signaling, likely through reduction of oxidative stress. Excessive amounts of ROS have the potential to trigger the activation of the NLRP3 inflammasome, which in turn can result in the development of acute kidney injury. As a potent antioxidant, ASTX significantly inhibits this activation to prevent kidney damage [27,41]. Additionally, ASTX has shown promise in liver protection against ethanol-mediated inflammation. ASTX interferes with STAT3 signaling, a regulator that in turn reduces the expression of inflammatory and oxidative stress-related genes. This mechanism helps to prevent the recruitment of neutrophils associated with alcoholic hepatitis [42].

ASTX's benefits also extend to skin inflammation. ASTX reduces skin inflammation caused by ultraviolet (UV) rays by decreasing the production of a mediator of inflammation called prostaglandin E2 and nitric oxide through downregulation of iNOS and COX-2. This prevents skin cells from dying when exposed to Ultraviolet B (UVB) radiation by reducing the production of specific inflammation-causing proteins [27,43]. Furthermore, recent research has explored the anti-inflammatory effects of different ASTX geometric isomers. Yang *et al.* [44] showed that while all E/Z isomers reduced TNF- α in a Caco-2 cell model, the 9-Z isomer was most effective in lowering TNF- α , whereas 13-Z more strongly inhibited IL-8 than the all-E form.

Together, these findings suggest that ASTX suppresses inflammation not only by targeting downstream mediators like COX-2 and NF- κ B but also through the regulation of key upstream signaling pathways. This multi-targeted mechanism may account for its broad anti-inflammatory and protective effects across different organs and systems.

3.1.2.3. Anti-aging

Astaxanthin, a powerful antioxidant found in marine organisms such as salmon, krill, and microalgae, has shown significant promise in addressing various aspects of the aging process. This section reviews the current research on astaxanthin's anti-aging benefits, focusing on its mechanisms and efficacy in maintaining youthful skin and cellular health.

Aging in humans is a complex process that brings various health challenges, influenced by genetics, lifestyle, environment, and life events [45]. As the body ages, its ability to repair and defend itself weakens. Premature aging is linked to oxidative stress, as the body's ability to produce energy declines and harmful substances increase, causing damage to cells and tissues. Maintaining a healthy lifestyle and a well-rounded diet can encourage healthy aging and extended well-being [16,46]. There is a growing demand for products that cater to the needs of older individuals, with effective antioxidants being beneficial

for healthy aging. ASX shows promise as a protective agent against aging [39]. It protects the mitochondria's membrane system, enhancing energy production efficiency [46]. Younger individuals tend to be more resilient to harmful substances because they have a well-balanced mitochondrial function, effective antioxidant and DNA repair mechanisms, and active processes for breaking down proteins. Reactive oxygen species, by-products of metabolic processes, can cause detrimental changes in biomolecules [47,48].

Astaxanthin promotes skin health by enhancing elasticity and minimizing the appearance of wrinkles. Its anti-inflammatory and immune-modulating properties, combined with its ability to support DNA repair, further contribute to the overall vitality of the skin [16,49]. In a study, daily supplementation with 6 or 12 mg of astaxanthin prevented the secretion of inflammatory cytokines from keratinocytes and reduced matrix metalloproteinase-1 secretion by dermal fibroblasts, thereby mitigating skin damage and promoting healthy skin in participants [50]. Additionally, astaxanthin reduced trans-epidermal water loss due to UV exposure by decreasing the expression of aquaporin 3 and other proteins, thereby protecting the skin from damage [16,51]. Research by Chung *et al.* [52] also contributed to the fact that astaxanthin significantly inhibited UV-induced cytotoxicity and cell death in epidermal keratinocytes. Clinical studies support the benefits of astaxanthin supplementation on photoaged skin, demonstrating a decrease in UV-induced wrinkle formation while promoting an increase in collagen fibers in the skin [7,52,53].

Aging involves cellular senescence, leading to morphological and physiological changes in tissues and organs. The theory of aging, known as the free radical theory, posits that oxidative stress is a crucial factor in this phenomenon. Astaxanthin's ability to scavenge free radicals helps mitigate oxidative stress, thus slowing down the aging process. Mitochondrial aging, caused by oxidative damage, meanwhile, is another major factor in aging. Astaxanthin has demonstrated the ability to safeguard the permeability of mitochondrial membranes and maintain membrane potential, thereby restoring impaired mitochondrial function [54]. A study conducted on aging dogs found that astaxanthin supplementation led to improvements in mitochondrial content, boosted adenosine triphosphate (ATP) production, and enhanced the activity of respiratory chain complexes, mitigating oxidative damage and mitochondrial dysfunction [55]. Additionally, astaxanthin supplementation has been shown to reverse the age-related decline in mitochondrial respiratory chain complexes I and IV [54].

Astaxanthin plays a protective role for nerve cells by minimizing mitochondrial dysfunction and lowering oxidative stress. This effect suggests astaxanthin may hold therapeutic relevance in neurodegenerative diseases such as Parkinson's, particularly through its ability to reduce mitochondrial dysfunction and oxidative stress in neuronal models [27]. Another study reported in which daily supplementation with 3.6 mg of astaxanthin has been shown to reduce atherosclerosis by blocking the oxidation of low-density lipoproteins [27]. Furthermore, in studies using mouse models, the expression of inflammasomes was regulated by astaxanthin. This regulation inhibited neuroinflammation, reduced the production of

β -amyloid protein, and relieved symptoms of Alzheimer's disease [56]. Astaxanthin can cross the BBB and accumulate in the brain, enhancing brain-derived neurotrophic factor signaling, thus alleviating signs of neurological aging [10,57].

In a study using a type of roundworm called *Caenorhabditis elegans*, astaxanthin was found to activate a protein called DAF-16 in a pathway related to insulin and IGF-1. This activation led to the up-regulation of a gene called age-1 and increased the production of specific protective proteins such as superoxide dismutase, glutathione-S-transferase, and heat shock proteins. As a result, astaxanthin showed anti-aging effects [58]. Different astaxanthin isomers also exhibit varying anti-aging activities, with (3S,3'S) astaxanthin showing the most potent anti-aging activity among the three stereoisomers [59]. According to all those studies mentioned previously, it is proven that astaxanthin has shown significant potential as an anti-aging agent due to its significant antioxidant properties and its effectiveness in protecting against oxidative stress and inflammation, in which this substance offers considerable health benefits. It has demonstrated benefits in maintaining youthful skin, improving mitochondrial function, and protecting against age-related diseases. However, further research is needed to explore the anti-aging effects of different astaxanthin isomers and to confirm these findings in human studies. Nonetheless, astaxanthin's multifaceted mechanisms, ranging from oxidative stress reduction to mitochondrial protection, underscore its potential role in supporting healthy aging and longevity, though further clinical validation remains essential. The multifaceted biological actions of astaxanthin in the aging process consist of oxidative stress reduction, mitochondrial protection and anti-inflammatory effects are illustrated in Figure 1. This visual summary integrates the key molecular pathways and physiological outcomes involved in its proposed anti-aging mechanisms.

Recent studies have also increasingly highlighted the distinct bioactivities of *Z*-isomers (cis-isomers) of astaxanthin, particularly the 9-*Z* and 13-*Z* forms, in aging-related health applications. These isomers demonstrate superior lipid solubility, micellar incorporation, and membrane permeability compared to the all-*E* (trans) form, which contributes to enhanced bioavailability and tissue-specific accumulation. In dermatological models, *Z*-isomer-rich astaxanthin has shown significant potential in improving skin quality. For example, Honda *et al.* [60] reported that topical or dietary administration of 13-*Z*-dominant astaxanthin improved skin hydration, elasticity, and reduced wrinkle formation in UV-B-irradiated hairless mice. These effects were mechanistically linked to reduced oxidative stress markers (e.g., MDA and MMP-1) and enhanced expression of structural proteins such as collagen type I and elastin.

Z-isomers have also demonstrated anti-obesity effects through modulation of metabolic gene expression. In adipocyte models, astaxanthin formulations enriched with *Z*-isomers significantly suppressed lipid accumulation and downregulated lipogenic genes such as SREBP-1c and FAS [61]. These isomers concurrently activated and peroxisome proliferator-activated receptor gamma signaling pathways, promoting fatty acid oxidation and metabolic balance. By reducing both lipid storage and inflammatory signaling, *Z*-isomers may help

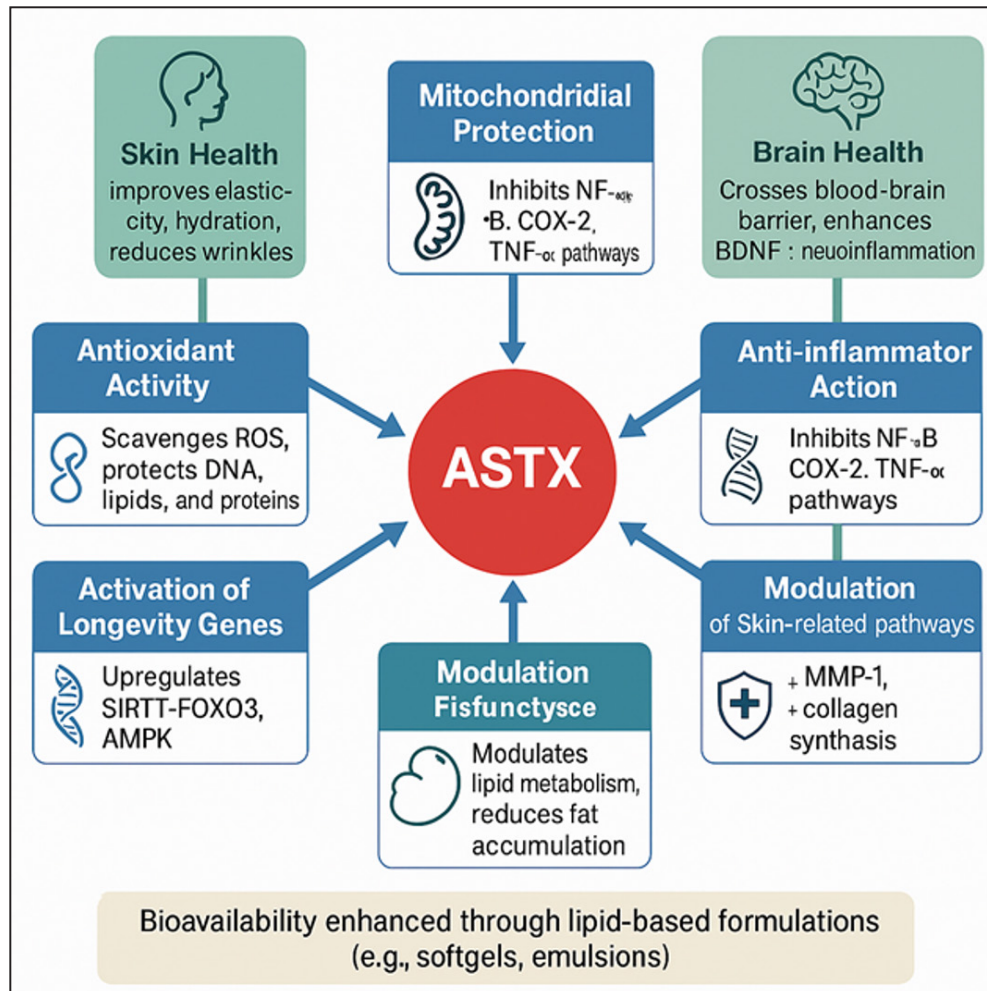


Figure 1. Summary of the primary mechanisms through which astaxanthin contributes to anti-aging benefits. These include antioxidant and anti-inflammatory pathways, mitochondrial protection, gene regulation, and systemic improvements in skin, brain, and metabolic health.

mitigate systemic low-grade inflammation, which is a key hallmark of metabolic aging.

Furthermore, *Z*-isomer-enriched astaxanthin has been shown to influence core aging-related pathways, including Nrf2-ARE, NF- κ B, and SIRT1, which regulate oxidative stress defense, mitochondrial integrity, and inflammation. Pharmacokinetic studies have also revealed that *Z*-isomers reach higher plasma concentrations and exhibit longer half-lives than the all-*E* form, suggesting more sustained biological activity [62–64]. These emerging findings indicate that *Z*-isomer formulations not only offer improved bioavailability but also exert stronger protective effects across multiple aging hallmarks, including oxidative damage, extracellular matrix (ECM) degradation, metabolic dysfunction, and inflammation. By influencing these interconnected pathways, *Z*-isomer-rich astaxanthin formulations represent a next-generation strategy for anti-aging interventions. Their superior pharmacological profile and multi-targeted mechanisms offer strong potential for the development of targeted nutraceuticals or pharmaceuticals aimed at promoting healthy aging. Although current studies suggest strong therapeutic potential, some variation in reported

outcomes, particularly regarding mitochondrial aging and isomeric activity, underscores the need for harmonized research approaches and further validation.

3.2. Biological aspects of aging and their implications

3.2.1. Definition and characteristics of aging

Aging is a biological phenomenon characterized by cellular senescence, when tissues and organs experience progressive degenerative changes in their structure and functions. Overall, this process is accompanied by a range of disorders associated with aging. Numerous theories regarding aging exist, with the free radical theory being one of the most prevalent.

3.2.2. Theories of aging

3.2.2.1. Cellular senescence theory

The cellular senescence aging theory suggests that the accumulation of senescent cells within tissues significantly influences the aging process and the emergence of diseases associated with it. Cellular senescence, characterized by an

irreversible halt in cell division while maintaining metabolic activity, is caused by various factors such as DNA damage, reduction in telomere length, exposure to oxidative stress, and activation of oncogenes. These cells have a special way of aging, known as the senescence-associated secretory phenotype (SASP). They give off a mix of inflammatory messengers, attractants, growth factors, and enzymes that break down proteins known as proteases. The effects of SASP contribute to chronic inflammation and changes in tissue structure and create an environment conducive to tumor development [65].

The presence of senescent cells and their SASP significantly contributes to tissue dysfunction and the progression of various age-related diseases such as osteoarthritis, atherosclerosis, and nervous system disorders. For example, in osteoarthritis, senescent cells in the cartilage release enzymes that degrade the extracellular matrix, leading to joint damage and discomfort [66]. Similarly, in atherosclerosis, senescent cells in the vascular endothelium are associated with an increased risk of heart-related issues due to their role in promoting the formation and vulnerability of arterial plaques [67]. Recent studies have shown that selectively clearing senescent cells, a process known as senolysis, can delay the onset of age-related diseases, improve tissue functionality, and extend lifespan in animal studies. This discovery has led to the development of senolytic medications aimed at targeting and removing senescent cells. Trials have demonstrated that administering senolytics can enhance physical capabilities, reduce inflammation, and improve overall health in elderly mice [68]. These findings underscore the crucial role of cellular senescence in the aging process and suggest that targeting these cells may represent a viable strategy to mitigate age-related tissue deterioration and support the extension of health span.

3.2.2.2. Free radical theory of aging

The Free Radical Theory of Aging, proposed by Denham Harman in the 1950s, hypothesizes that the aging process is a result of the cumulative damage inflicted by free radicals. These free radicals, predominantly ROS, are produced as byproducts of normal cellular metabolism. This theory underscores the impact of oxidative stress on the aging process and highlights the importance of understanding these biological mechanisms. Free radicals are highly reactive molecules that can cause damage to crucial cellular components, such as DNA, proteins, and lipids, through oxidative reactions. The theory suggests that the progressive accumulation of oxidative damage over time results in cellular dysfunction, which is a significant factor in the aging process and the onset of age-related diseases [69].

As organisms age, their capacity to counteract free radicals through antioxidant defense systems decreases, leading to heightened oxidative stress and damage. This oxidative damage is connected to various age-related conditions, such as cancer, cardiovascular diseases, and neurodegenerative disorders like Alzheimer's disease. For example, oxidative damage to DNA can result in mutations and genomic instability, promoting cancer development [70]. Similarly, oxidative damage to proteins and lipids can impair cellular function and contribute to the development of cardiovascular diseases [71].

Although some studies have suggested that antioxidant supplementation could diminish oxidative damage and slow aging, clinical study results must be consistent, with some indicating limited effectiveness in extending lifespan. This may be attributed to the complexities of ROS signaling and the potential for antioxidants to disrupt beneficial ROS-mediated processes. Nevertheless, the impact of oxidative stress on aging remains a crucial area of study, with ongoing research investigating the potential of targeting oxidative damage and enhancing antioxidant defenses to promote healthy aging [72].

3.2.2.3. Mitochondrial theory of aging

The Mitochondrial Theory of Aging, an expansion of the Free Radical Theory, underscores the significance of mitochondrial malfunction in aging. Mitochondria play a critical role in cellular function by facilitating most of the cell's energy production. They generate ATP through the process of oxidative phosphorylation, which is essential for numerous metabolic activities within the cell. However, this process produces ROS as byproducts, which can harm mitochondrial DNA (mtDNA). Unlike nuclear DNA, mtDNA is positioned near the inner mitochondrial membrane, where ROS is produced. It does not have protective histones and efficient repair mechanisms, making it more likely to be harmed by oxidation [73].

Accumulation of mtDNA mutations over time can hinder mitochondrial function, resulting in lower ATP production and a rise in ROS generation, initiating a harmful cycle of mitochondrial dysfunction. This decline in mitochondrial function contributes to decreased cellular energy production, increased cell death, and initiation of inflammatory pathways seen in aging [74]. For example, impaired mitochondrial function can lead to reduced cellular energy availability, influencing the functioning of energy-demanding tissues such as muscle and brain, consequently contributing to age-related declines in muscle strength and cognitive function [75].

Advancing mitochondrial function and lessening mitochondrial ROS production are current areas of research aimed at delaying the aging process and prolonging the period of good health. Mitochondrial-targeted antioxidants, caloric restriction, and exercise can improve mitochondrial health and delay age-related decline. Mitochondrial-targeted antioxidants like MitoQ aim to selectively reduce ROS within mitochondria, protecting mtDNA from oxidative damage and enhancing mitochondrial function [76]. Caloric restriction has been demonstrated to boost mitochondrial biogenesis and function, potentially contributing to its lifespan-extending effects [77]. Regular physical exercise fosters mitochondrial biogenesis and function, improving overall cellular health and fortifying resistance against age-related decline [78].

3.2.2.4. Telomere theory of aging

The ends of linear eukaryotic chromosomes contain telomeres, which are made up of repetitive TTAGGG sequences. Along with other proteins, telomeres form the shelterin complex, which plays a crucial role in preventing degradation or fusion with neighboring chromosomes by identifying double-stranded breaks [79]. The shortening of telomeres indicates a malfunction in this protective mechanism, resulting in cellular senescence

and aging through the activation of the DNA damage response (DDR) [78]. Telomerase maintains telomeres' length by adding the telomeric sequence TTAGGG to the 3' ends [1]. Telomeres play a crucial role in the aging of the skin over time. When telomeres become dysfunctional, they trigger downstream effectors like the cyclin-dependent kinase inhibitors p16 and p21, which stop the cell cycle by activating the DDR pathway. Gradual telomere shortening impedes cell division, contributing to cellular senescence due to intrinsic aging [2].

In contrast, exposure to UVA results in distinct DNA damage within the telomere sequence, causing dysfunction in the telomeres. On the other hand, Sugimoto *et al.* observed that telomere length diminishes without significant differences between sun-exposed and sun-protected areas [80]. The molecular mechanisms involved in telomere shortening, especially in relation to skin aging, are not yet completely understood. When the skin is exposed to UV radiation, it triggers telomere shortening by generating ROS [79]. Birch *et al.* showed that exposure to UVA leads to specific DNA damage in the telomere sequence, causing telomere malfunction [81].

3.2.3. Mechanisms underlying skin aging

3.2.3.1. Molecular mechanism of skin aging

The skin, which is the largest organ of the body, is continuously subjected to environmental factors such as UV rays, smoking, heat, and air pollution. As a result, the skin experiences both extrinsic aging, influenced by external factors, and intrinsic aging, also known as chronological aging. Intrinsic aging, along with programmed aging, arises from persistent chromatic damage caused by various sources. To summarize, intrinsic aging involves gradual changes within the skin at the cellular and molecular levels, including a decrease in collagen production, loss of skin elasticity, and the slowdown of cell turnover. Meanwhile, extrinsic aging accelerates these processes through the external generation of ROS and other damaging agents, leading to increased oxidative stress and inflammation. Oxidative stress, primarily caused by ROS, significantly contributes to cellular damage. To combat this stressor, cells utilize intrinsic defense mechanisms, including enzymes such as superoxide dismutase (SOD), the tripeptide glutathione, and catalase [82]. However, the aging process diminishes the ability to maintain a balanced redox state, leading to the accumulation of ROS and subsequent damage to essential cellular components such as proteins, lipids, and DNA, ultimately causing cellular malfunction [83]. Environmental factors like UV radiation and air pollution also contribute significantly to aging by generating ROS [4].

When cells encounter stress factors, such as DNA damage, they undergo a lasting halt in growth, known as cellular senescence [84]. Recent studies indicate that cellular senescence plays a crucial role in skin aging [85,86]. Senescent cells are characterized by several biomarkers [87]:

Elevated concentrations of cell cycle inhibitor proteins p21WAF1 and p16INK4A.

1. Enhanced activity of the lysosomal enzyme associated with senescence, β -galactosidase.
2. Decreased levels of the nuclear high mobility group box-1.

3. Lamin B1 serves as a structural element of the nuclear lamina.

Additionally, they produce a SASP characterized by the release of inflammatory cytokines, chemokines, matrix proteases, and microRNAs [65]. Temporary signals of cellular senescence during the process of wound healing encourage the development of granulation tissue and support skin regeneration, while also inhibiting uncontrolled cell proliferation that may result in precancerous or cancerous growths. The aging process leads to the buildup of senescent keratinocytes, melanocytes, and fibroblasts, which can contribute to age-related conditions and disturb the natural equilibrium of the skin [86].

Furthermore, the degradation of the ECM results from changes in senescent cells and the excessive production of ROS. Elevated levels of ROS trigger the mitogen-activated protein kinase/activator protein 1 pathway, leading to increased production of matrix metalloproteinases, which ultimately causes collagen degradation [88,89]. Additionally, ROS inhibits collagen synthesis through the TGF- β /Smad signaling pathway [90–92]. Aging cells diminish the expression of tissue inhibitors of metalloproteinases, contributing to the degradation of the ECM by promoting ongoing inflammatory responses and the breakdown of collagen. In particular, senescent fibroblasts secrete a SASP that contains MMP-2, MMP-9, and proinflammatory cytokines like interleukin (IL)-6 and IL-8 [3,86,93]. Furthermore, neutrophil migration following inflammation or UV exposure exacerbates collagen and elastin breakdown by releasing proteolytic enzymes [94,95].

3.3. Extraction and bioavailability of astaxanthin

3.3.1. Chemical composition and structural features of astaxanthin

Astaxanthin, a member of the xanthophylls, is a reddish-orange pigment known for its potent antioxidant activity. As an oxygenated derivative of carotenoids, it stands out for its extraordinary efficacy compared to other antioxidants. Specifically, this compound demonstrates remarkable efficacy, being 65 times more effective than vitamin C, 54 times more potent than β -carotene, 14 times more powerful than vitamin E, and 10 times more effective than other carotenoids, including zeaxanthin, lutein, and canthaxanthin [17]. Astaxanthin has the molecular formula $C_{40}H_{52}O_4$, with a molar mass of 596.84 g/mol [26]. The compound's structure features two terminal rings connected by a polyene chain, and it has two chiral carbons situated at the 3 and 3' positions of the β -ionone ring. At both ends of the molecule, these positions are equipped with hydroxyl groups (-OH). When one of the hydroxyl groups interacts with a fatty acid, a monoester is produced; in contrast, reactions involving both hydroxyl groups lead to the formation of a diester [96]. The diverse esterification patterns contribute to astaxanthin's versatility and its different functionalities in nature.

Astaxanthin exists in various forms, including stereoisomers, geometric isomers, and both free and esterified forms. The most common stereoisomers are (3S, 3'S) and (3R, 3'R), which are the predominant forms found in nature.

Haematococcus pluvialis synthesizes the (3S, 3'S) isomer, while the yeast *Xanthophyllomyces dendrorhous* produces the (3R, 3'R) isomer [97]. Synthetic astaxanthin comprises isomers of (3S, 3'S), (3R, 3'S), and (3R, 3'R).

The main type of astaxanthin found in Antarctic krill, which is called *Euphausia superba*, is the 3R, 3'R form, and it mainly shows up in an esterified form [13]. In contrast, in wild Atlantic salmon, the 3S, 3'S isomer occurs primarily in its free form [26]. Additionally, astaxanthin can adopt different conformations of the polyene chain double bond, such as *cis* or *trans* [17]. *Trans*-isomers are more common because *cis* carotenoids are thermodynamically unstable [96]. This conformational flexibility influences the bioavailability and bioactivity of astaxanthin in different organisms and environments. Astaxanthin is a molecule that is also unstable and readily undergoes oxidation. In nature, it is typically found either bound to proteins, such as in the muscle of salmon or the exoskeleton of lobsters, or combined with one or two fatty acids in an esterified form [13]. These natural complexes enhance the stability of astaxanthin, protecting it from oxidative degradation. The relative percentages of astaxanthin and its esters in krill, copepods, shrimp, and shellfish vary, demonstrating its diverse natural occurrence and ecological roles.

Astaxanthin's structural diversity and robust antioxidant properties make it a valuable compound in both natural ecosystems and commercial applications. Its ability to exist in multiple forms and states, such as free or esterified, *cis* or *trans*-isomers, and conjugated with proteins, enables it to perform various biological functions [97]. These properties contribute to astaxanthin's significant roles in safeguarding cells from oxidative stress, enhancing immune responses, and supporting overall health. Furthermore, the applications of astaxanthin extend beyond its biological roles. In the food industry, it is used as a dietary supplement and a natural colorant, especially in aquaculture to enhance the pigmentation of farmed salmon and shrimp. Its potent antioxidant properties are harnessed in the cosmetic industry for anti-aging products, while its health benefits are increasingly recognized in nutraceuticals.

3.3.2. Microalgae as a sustainable source of astaxanthin

There has been a rise in consumer desire for advanced and inventive cuisine. In addition, customers are currently more mindful of the interconnectedness of water, energy, and food, as well as the correlation between food and health. Within this environment, the food business is actively working towards improving the sustainability of food production and creating food products that possess not only delectable flavors but also nutritional value, functionality, and sustainability [6]. The significance of microalgae in the food business is growing, and there is a rising trend in introducing food products containing microalgae to the market each year [98]. These microorganisms possess numerous benefits in resource and energy utilization compared to other food sources. Additionally, they are abundant in bioactive substances, such as valuable pigments and polyunsaturated fatty acids.

Microalgae have emerged as a highly efficient and scalable source for natural astaxanthin production,

particularly due to their high cellular content and suitability for biotechnological cultivation. Microalgae are eukaryotic, unicellular microorganisms that may grow in a variety of trophic regimes and exhibit remarkable capacities for product accumulation and CO₂ fixation. Numerous applications of microalgae are discussed, including the bioremediation of organic and inorganic contaminants, the bio desalination process, food, animal feed, as well as medicinal and nutraceutical substances [99]. Algal astaxanthin has multiple bioactivities, including astaxanthin, which is why it is in high demand for a variety of health applications, including pharmaceuticals, aquaculture, health foods, cosmetics, and more. Natural astaxanthin remains irreplaceable for human consumption and food additive applications, despite the availability of various low-cost synthetic astaxanthins [100]. Astaxanthin is produced by various microorganisms (such as bacteria, cyanobacteria, yeasts, and algae), as well as plants, fish, prawns, krill, trout, and crabs [19].

Microalgal species generally have a higher concentration of astaxanthin compared to bacteria, yeast, and crustacean species. Natural astaxanthin is abundant in various microalgae species, including *Chlorella zofingiensis*, *H. pluvialis*, *Haematococcus lacustris*, *Neochloris wimmeri*, *Protosiphon botryoides*, *C. zofingiensis*, *Chlorella sorokiniana*, *Scenedesmus acutus*, *Coelastrum sp.* HA1, *Chlorococcum sp.*, and *Euglena sanguine* [25]. Table 1 lists the astaxanthin-producing microbial sources and indicates the astaxanthin concentration in the biomass.

Haematococcus pluvialis is a well-known algae that produces the most astaxanthin out of all of these species, which is why it is frequently used as a source for astaxanthin production in industries [22]. *Haematococcus pluvialis* is a remarkable green microalga that thrives in freshwater environments. This eukaryotic organism consists of a single cell, has a gradual growth rate, and exhibits a complicated life cycle with three unique morphotypes. These morphotypes are the motile green flagellated macrozoid, the stationary palmelloid, and the nonmotile red aplanospore [101]. Natural astaxanthin, which accumulates in greater proportions under stressful situations such as nitrogen deprivation, high temperature, high salinity, bright light, chemical inductions, CO₂ stress, etc., is derived commercially from this microalga [25]. Also, according to Boussiba and Vonshak [102], the highest concentration of astaxanthin is usually found in the red aplanospore morphotype, which occurs in stressful environments that promote astaxanthin accumulation. These stress factors may include excessive light, low salt levels, or nitrogen deficiency. *Haematococcus pluvialis* acquires the capacity to produce astaxanthin and stores it in fat globules when these conditions prevail [103,104].

3.3.3. Extraction techniques for high-purity astaxanthin

3.3.3.1. Conventional techniques for astaxanthin extraction

The compound known as astaxanthin is fat-soluble and found within cells. The typical extraction process for astaxanthin from microorganisms involves two main steps: cell disruption and astaxanthin collection. Mechanical techniques such as grinding, bead milling, ultrasound, and nonmechanical methods such as enzymatic and chemical hydrolysis are commonly used

Table 1. Summary of astaxanthin sources with its respective yield.

Organism	Category	Astaxanthin Yield (% on Dry Weight basis)	Characteristics	References
<i>Haematococcus pluvialis</i>	Microalgae (Chlorophyte)	2.7%–5.0%	Primary commercial source; high-yield strain; widely used in anti-aging formulations and nutraceuticals	[19,30]
<i>Haematococcus pluvialis</i> (K-0084)	Microalgae (Chlorophyte)	2.7%–3.8%	Strain variation affects yield, influencing extraction efficiency	[104]
<i>Haematococcus pluvialis</i> (AQSE002)	Microalgae (Chlorophyte)	3.4%	Lab-isolated strain; potential for biotechnological optimization	[6,25]
<i>Chlamydomonas nivalis</i>	Microalgae (Chlorophyte)	Up to 4.0%	Cold-adapted species; lower yield but potential for stress-induced astaxanthin production	[105]
<i>Neochloris wimmeri</i>	Microalgae (Chlorophyte)	0.6%–1.92%	Potential alternative source; requires further extraction optimization	[106]
<i>Chlorella zofingiensis</i>	Microalgae (Chlorophyte)	0.001%–0.68%	Moderate producer; emerging interest in pharmaceutical applications	[107]
<i>Chromochloris zofingiensis</i>	Microalgae (Chlorophyte)	0.65%	Similar to <i>Chlorella zofingiensis</i> ; potential alternative	[6]
<i>Chlorococcum</i>	Microalgae (Chlorophyte)	0.2%	Low-yield species; less efficient for large-scale pharmaceutical use	[6,26]
<i>Thraustochytrium</i> sp. CHN-3	Labyrinthulomycetes (Protist)	0.2%	Non-microalgal source; requires specialized extraction techniques	[105]
<i>Phormidium fragile</i>	Cyanobacteria	0.0001%	Extremely low yield; not suitable for pharmaceutical extraction	[25]
<i>Phormidium</i> spp.	Cyanobacteria	0.004%	Slightly higher than <i>P. fragile</i>	[106]
<i>Lyngbya confervoides</i>	Cyanobacteria	0.042%	Moderate producer but lacks commercial-scale feasibility	[6,12,26]
<i>Paracoccus haemiensis</i>	Bacteria (Alphaproteobacteria)	0.014%	Pigment-producing bacterium	[108]
<i>Paracoccus carotinifaciens</i> (NITE SD 00017)	Bacteria (Alphaproteobacteria)	Up to 2.2%	High-yield bacterial strain; potential for fermentation-based production	[109]
<i>Sphingomonas astaxanthinifaciens</i>	Bacteria (Alphaproteobacteria)	0.069%	Pigment-producing bacterium	[110]
<i>Agrobacterium aurantiacum</i>	Bacteria (Alphaproteobacteria)	0.01%	Lower yield compared to <i>Paracoccus</i>	[25]
<i>Saccharomyces cerevisiae</i> (Recombinant)	Yeast	1.021%	Genetically engineered for astaxanthin production; applicable for pharmaceutical synthesis	[111]
<i>Xanthophyllomyces dendrorhous</i> (JH)	Yeast	0.5%	Common yeast-based astaxanthin source; lower efficiency than <i>H. pluvialis</i>	[112]
<i>Xanthophyllomyces dendrorhous</i> (VKPM Y2476)	Yeast	0.5%	Commercial strain	[112]
<i>Ulva lactuca</i>	Macroalgae (Ulvophyceae)	0.01%	Low-yield green macroalga; limited pharmaceutical application	[19,26]
<i>Enteromorpha intestinalis</i>	Macroalgae (Ulvophyceae)	0.02%	Moderate yield green alga	[19,26]

for cell disruption [113]. Following cell disruption, astaxanthin can be effectively extracted using solvent extraction methods.

The most frequently used solvents for astaxanthin extraction currently are ethanol, acetone, sulfuric acid, hexane, isopropyl alcohol, acetone dichloromethane, and ethyl acetate. Among these, acetone is considered the most suitable due to its more remarkable similarity to astaxanthin because of its higher carbonyl group content [114,115]. The fact in breaking the tough and thick cell walls of algae and yeasts is complex, posing a significant challenge for astaxanthin extraction. Therefore, microbial astaxanthin extraction focuses primarily on treatments

that can break the cell wall, thus releasing the astaxanthin [116]. The traditional method for astaxanthin extraction involves a combination of solvent extraction and physical crushing. For instance, a method by Sarada *et al.* [117] utilized hydrochloric acid to break cells of *H. pluvialis* and extracted astaxanthin with acetone, resulting in a 96%–99% recovery rate.

Meanwhile, hydrochloric acid treatment facilitated 86%–94% extractability of astaxanthin [117]. Mechanical cell disruption followed by acetone extraction was used by Mendes-Pinto *et al.* [118] resulting in an astaxanthin recovery rate of only 85%. Although the recovery rate of astaxanthin using acid

treatment followed by organic solvent extraction was higher, this method may not be suitable for the food industry. As a result, it is necessary to develop greener extraction technologies to replace the chemical processes. Considering the lipophilic characteristics of astaxanthin, utilizing oil-based solvents for extraction presents a more practical and effective methodology. Dong *et al.* [119] developed a similar solvent extraction method using soybean oil but achieved a recovery rate of only 0.9%. Sunflower and coconut oils also can pull out natural astaxanthin pretty well, with recovery rates of 26.3 µg/g for sunflower oil and 24.7 µg/g for coconut oil [120]. The recovery of astaxanthin is influenced by the ratio of two oil phases and temperature [121]. Along with typical oil-based solvents, three innovative hydrophobic deep eutectic solvents made from oleic acid and terpenes (thymol, DL-menthol, and geraniol) were utilized to extract astaxanthin from *H. pluvialis*, achieving a recovery rate of 60% for astaxanthin [122].

Physical methods have been explored as an alternative to chemical approaches for breaking cell walls. Grinding is a simple physical method used for this purpose. A pretreatment technique that includes continuous grinding, succeeded by extraction with ethanol and hexane, achieved recoveries of 21 mg/g and 35 mg/g of astaxanthin, respectively [123]. Similarly, astaxanthin extraction was achieved using bead milling with lower recoveries (18 mg/g) [124]. Ultrasound is commonly used for breaking down cells because of its ability to create acoustic cavitation in liquids, facilitating improved penetration and diffusion of solvents into the cell membrane. [125]. For example, ultrasonic radiation at 200 W using ethyl acetate solution extraction obtained 27.58 mg/g of astaxanthin

recovery, and ultrasonic radiation achieved 17.34 mg/g of astaxanthin recovery using a mixed solvent extraction method with an equal ratio of ethanol and ethyl acetate [121].

3.3.3.2. Advanced extraction strategies for pharmaceutical-grade astaxanthin

Astaxanthin is naturally produced by various microorganisms, including microalgae, bacteria, yeast, and some macroalgae. However, among these sources, *H. pluvialis* is recognized as the most viable and commercially significant due to its exceptionally high astaxanthin content (up to 5.0% of dry cell weight) [19,30]. This microalga is widely utilized in pharmaceutical and nutraceutical formulations, particularly for its potent anti-aging and antioxidant properties. While alternative sources such as *C. zofingiensis*, *Paracoccus carotinifaciens*, and genetically engineered yeast strains have been explored, their lower yields and extraction challenges limit large-scale production. Efficient extraction techniques, such as Supercritical Fluid Extraction (SFE) and Microwave-Assisted Extraction (MAE), are crucial for optimizing astaxanthin recovery from *H. pluvialis*, ensuring high purity and bioactivity for pharmaceutical applications. Table 2 provides a summary of astaxanthin sources, their obtained yields, and their relevance to pharmaceutical extraction and anti-aging research.

Among various extraction methods (Table 2), SFE and MAE are among the most widely studied and effective techniques for pharmaceutical applications due to their high efficiency, eco-friendliness, and ability to preserve astaxanthin's bioactivity. SFE, with a reported yield of 58.50 µg/g, is particularly advantageous in producing solvent-free

Table 2. Extraction methods of astaxanthin from *Haematococcus pluvialis* for pharmaceutical applications.

Extraction method	Solvent/ Co-solvent	Temperature (°C)	Pressure (MPa/ Bar)	Time (minutes)	Yield	Relevance	References
Supercritical Carbon Dioxide (SC-CO ₂)	CO ₂ + Ethanol	40–80	15–25 MPa (150–250 bar)	120	58.50 ± 2.62 µg/g	High-purity extraction; solvent-free, ideal for pharmaceuticals and nutraceuticals	[126]
Microwave-Assisted Extraction (MAE)	Acetone, Methanol, Ethanol, Dichloromethane	5 (solvent boiling point)	–	–	57.42%	Fast, preserves antioxidant activity; suitable for formulations requiring high bioactivity	[114,127,128]
Hydrochloric Acid-Acetone Extraction (HCl-ACE)	Acetone + 3M HCl pretreatment	100 W (microwave)	–	60	19.8 mg/g	Enhances antioxidant properties, useful for topical and anti-aging formulations	[129]
Ultrasound-Assisted Extraction (UAE)	Ethanol, Acetone	40-60	–	30–60	17.34 ± 0.85 mg/g	Eco-friendly, improves extract purity, applicable for liquid supplements and skin-care products	[114,125,130,131]
Liquid Biphasic Flotation (LBF)	Ethanol + Salt	25	–	–	–	Enhances solubility, making it suitable for drug formulations	[132]
Pressurized Liquid Extraction (PLE)	Hexane, Ethanol	50–200	10.34 MPa	20	0.8%–37.1 %	Efficient for pharmaceutical-grade extracts with improved solubility	[123,130]

extracts suitable for drug formulations, whereas MAE enhances extraction rates while minimizing thermal degradation, making it ideal for cosmeceutical applications. Compared to conventional techniques, these methods provide superior selectivity and bioavailability, making them the preferred choice for pharmaceutical-grade astaxanthin production.

3.3.3.2.1. Supercritical fluid extraction: a high-purity approach

There is limited research on the extraction of astaxanthin using SFE. Most studies have predominantly focused on extracting this carotenoid from microalgae (*Haematococcus pluvialis*) using conventional methods with limited exploration of the effects of temperature, pressure, and extraction flow rate on extraction yields. Moreover, the extensive use of organic solvents by various global industries poses a significant threat to the environment. SFE is an environmentally friendly substitute for the use of organic solvents in extraction processes. The tightening of environmental regulations on the use of widely used industrial solvents, many of which pose risks to human health, has spurred the development of SFE technologies. Supercritical fluids offer advantages such as simplicity and minimal degradation of delicate compounds [126]. In comparison to traditional extraction methods, SFE is faster due to higher mass transfer rates in supercritical fluids as opposed to liquid solvents. However, a drawback of SC-CO₂ is its limited ability to extract slightly polar analytes from solid matrices due to its low solvating power and weak interaction with the matrices [133]. To enhance the efficiency of CO₂ extraction for astaxanthin, the use of polar co-solvents was necessary to increase the solubility of the analytes and reduce their interaction with the matrix.

Supercritical fluid extraction is a unique state of matter that behaves like a gas, allowing it to flow through solids and like a liquid, enabling it to dissolve substances [134]. SFE is more efficient in recovering astaxanthin than traditional solvent extraction methods [135]. For instance, Wang *et al.* utilized SFE with sunflower oil to extract astaxanthin from *Haematococcus pluvialis*, achieving a recovery rate of 87.42%, comparable to ethanol [136]. Due to its high diffusion coefficient and low viscosity, supercritical carbon dioxide (scCO₂) is the most widely used supercritical fluid [137]. Moreover, supercritical carbon dioxide extraction is considered an environmentally friendly process [138]. However, given the fact that astaxanthin has low solubility in scCO₂, co-solvents such as ethanol are necessary to enhance its solubility. By further optimizing operating pressure and temperature, it is possible to achieve an astaxanthin extraction rate similar to traditional acetone extraction [139]. For example, when utilizing 20% ethanol as a co-solvent at low pressure (8 MPa) and 55°C for 15 minutes, the recovery rate of astaxanthin reached 98.3% [140]. Despite the environmental benefits and efficiency of SFE in astaxanthin extraction, its widespread application is limited by high capital and operating costs.

3.3.3.2.2. Microwave-assisted extraction: efficiency and bioactivity retention

A new technique for microwave-assisted extraction, building on traditional solvent extraction methods, has been

proposed. By utilizing acetone as the solvent, a 74% recovery of astaxanthin was achieved under conditions of 720 W power and 2450 MHz microwave frequency [114]. Microwaves are a form of electromagnetic energy that transfers heat and mass from the inside of a substance to the surrounding medium, which is the opposite of what occurs in traditional extraction methods [141]. Microwave heating leads to a rapid increase in temperature by distributing energy throughout the food. The localized heating from the radiation results from ionic conduction and dipole rotation [127]. This process creates pressure within the cells, promoting the release of bioactive components from the cells into the surrounding medium [128]. This process disrupts plant cell walls and releases intracellular compounds, thereby enhancing mass transfer and increasing the extraction yield of carotenoids [131]. MAE offers several advantages, including reduced extraction time and energy consumption, higher yields of carotenoids due to effective cell wall disruption, and reduced solvent use, making it more environmentally friendly. Additionally, the ability to control microwave power and extraction time allows for selective extraction of desired compounds [130].

Carotenoids, including beta-carotene, astaxanthin, lycopene, and lutein, are natural colorants that offer important health advantages, such as being antioxidants and potentially aiding in the prevention of chronic illnesses. MAE has been effectively used to isolate carotenoids from different plant sources, such as fruits, vegetables, and microalgae, making it especially suitable for obtaining these beneficial compounds. Recent progress in MAE has concentrated on refining extraction conditions to maximize both the quantity and purity of carotenoids. Research has investigated the impact of microwave power, extraction duration, type of solvent, and solvent-to-material ratio on the efficiency of carotenoid extraction [131]. Developments such as the use of environmentally friendly solvents, the combination of MAE with other extraction methods, and the integration of MAE with analytical techniques have also improved the process's efficiency and sustainability [130].

For example, researchers have explored using environmentally friendly solvents such as ethanol and water to improve the extraction process's sustainability and safety for consumers and the environment [142]. The combination of MAE with other methods like ultrasound-assisted extraction or SFE has demonstrated synergistic effects, resulting in higher extraction efficiencies and improved preservation of carotenoids [131]. Advanced optimization methods such as response surface methodology have been used to methodically examine and enhance extraction parameters, ensuring the maximal recovery of carotenoids [130]. MAE represents a significant advancement in carotenoid extraction, providing numerous advantages over traditional methods. Its ability to rapidly and effectively extract high yields of carotenoids with reduced solvent usage makes MAE an appealing choice for industrial and research purposes. To summarize, continuous advancements and refinements in MAE will likely further improve its effectiveness, solidifying its position as a critical technique in natural product extraction.

Importantly, these advanced extraction techniques not only improve yield and efficiency but also help preserve

the chemical stability and bioactivity of astaxanthin. These green methods are increasingly favored for pharmaceutical development, as they support formulation into clinically viable delivery systems, such as lipid-based capsules and nanoemulsions, which enhance bioavailability and therapeutic effectiveness.

3.4. Bioavailability and pharmacokinetics of astaxanthin in pharmaceuticals

3.4.1. Bioavailability of astaxanthin

3.4.1.1. Digestion and absorption of astaxanthin

Astaxanthin, a fat-soluble carotenoid, exhibits enhanced absorption when consumed with dietary oils. This increased absorption is crucial for its proper functioning in living organisms, as it significantly influences immune function, as demonstrated in various *in vitro* and *in vivo* assays [143,144]. Research has indicated that when astaxanthin is used together with fish oil, it encourages reductions in lipid and cholesterol levels in the plasma and improves the phagocytic activity of activated neutrophils compared to using astaxanthin or fish oil separately [145]. Notably, astaxanthin is reported to be more effective than fish oil in improving immune response and reducing the risk of vascular and infectious diseases. The combination of astaxanthin and fish oil has been observed to reduce the proliferation activity of T- and B-lymphocytes. Additionally, this combination results in decreased levels of O₂, H₂O₂, and NO production, while promoting increased activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Moreover, it induces calcium release within the cytosol [146].

The bioavailability of astaxanthin is often reduced due to its weak stability and water solubility, stemming from structural challenges. Astaxanthin undergoes metabolic transformation before excretion, with its metabolites detected in various rat tissues [146]. Single-dose administration of 100 mg astaxanthin has confirmed its bioavailability in human plasma [63]. Lipid-based formulations, where high amounts of carotenes are solubilized into the oil phase of the food matrix, have been shown to enhance astaxanthin bioavailability in humans [147]. Recent studies report astaxanthin accumulation in rat plasma and liver after feeding with *Haematococcus* biomass as a source of astaxanthin [26,30]. The absorption process involves emulsification and mixing with phospholipids, cholesterol, bile salts, free fatty acids, and lysophospholipids to form mixed micelles. These micelles are absorbed by the epithelial cells of the small intestine and converted into chylomicrons, which are then discharged into the lymphatic system to enhance blood flow and distribute astaxanthin across various tissues [143,144].

3.4.1.2. Absorption and Activity of Astaxanthin Isomers (E/Z and Stereoisomers)

The bioavailability and biological activity of astaxanthin are strongly influenced by its chemical form, whether free or esterified, and its structural isomerism, including both stereoisomers and E/Z (trans/cis) isomers. Free astaxanthin, typically found in wild salmon and synthetic sources, is

absorbed more rapidly in the human gastrointestinal tract due to its unbound structure. However, this form is more chemically unstable, being prone to oxidative degradation during digestion and storage. In contrast, esterified astaxanthin, especially the mono- and di-ester forms found in *H. phuvialis*, shows greater chemical stability but requires enzymatic hydrolysis before absorption, which may delay and reduce uptake, making it more suitable for long-term supplementation and formulation [16,148]. Beyond esterification, the geometric configuration of astaxanthin also influences its absorption efficiency.

Several studies, including those by Queen *et al.* [9] and Björklund *et al.* [16], have shown that Z-isomers (cis) of astaxanthin, such as 9-Z and 13-Z, exhibit improved solubility in lipids, better micellar incorporation, and enhanced transmembrane transport efficiency compared to the all-E (trans) form. This increased solubility improves bioavailability, especially when delivered through lipid-based formulations. Additionally, Z-isomers have been linked to enhanced biological activities, including improved skin elasticity and anti-adipogenic effects [9,16]. These characteristics position Z-isomers as a valuable target for enhancing astaxanthin's pharmacokinetic profile in both dietary supplements and pharmaceutical formulations.

Regardless of the form ingested, isomerization between all-E (trans) and Z (cis) forms of astaxanthin can occur during digestion and cellular uptake, influenced by pH, enzymatic conditions, and the lipid environment of the gastrointestinal tract [63,116]. This dynamic interconversion not only affects the extent of absorption but may also alter the biological activity of the compound. Clinical and experimental studies support this phenomenon, in which Coral-Hinostroza *et al.* [64] observed elevated levels of Z-isomers in plasma following ingestion of all-E astaxanthin with a purity of 95.2%, suggesting significant *in vivo* isomerization during digestion and absorption. Furthermore, recent studies have shown that Z-isomers, specifically 9-Z and 13-Z, exhibit enhanced solubility in lipid environments, improved micellar incorporation, and superior transmembrane transport efficiency compared to the all-E form. These findings highlight the critical importance of understanding and optimizing astaxanthin's isomeric composition to improve its pharmacokinetic profile and design more effective dietary and pharmaceutical formulations.

Interestingly, selective uptake and transformation of astaxanthin stereoisomers occur in human plasma. Following the consumption of a stereoisomeric mixture comprising (3R,3'R), (3R,3'S; meso), and (3S,3'S) forms in a 31:49:20 ratio, Coral-Hinostroza *et al.* [64] reported that the (3R,3'R) isomer selectively accumulated in plasma, accounting for approximately 54% of the total astaxanthin content. This finding suggests a stereoselective transport or metabolic preference for the (3R,3'R) configuration. Further supporting this, another study by Thakur [148] has also shown that following oral administration of mixed stereoisomers, the (3R,3'R) form preferentially accumulates in circulation, indicating that stereoisomeric differences significantly influence absorption, tissue distribution, and potentially biological activity.

Beyond mammals, recent studies have reported selective accumulation of astaxanthin isomers in other species

such as fish, crustaceans, and birds. For instance, different proportions of *Z*- and all-*E*-isomers have been detected in salmonids, shrimp, and poultry tissues, reflecting species-specific absorption and metabolic processing [149,150]. In crustaceans like shrimp and krill, *Z*-isomers have been shown to dominate muscle tissues despite diets containing mostly all-*E* forms [150]. These findings support the hypothesis that selective isomer absorption is not exclusive to mammals but a broader biological phenomenon that may influence pigment deposition, immune function, and oxidative stress resistance across species.

In response to these findings, formulation strategies such as nanoemulsions, solid lipid nanoparticles, and liposomal carriers have been explored to enhance absorption, especially for esterified or less bioavailable isomers. These delivery systems improve astaxanthin's solubility, protect against oxidative degradation, and promote controlled release [151].

3.4.2. Pharmacokinetics of astaxanthin

Astaxanthin, a naturally occurring carotenoid, has attracted considerable research because of its powerful antioxidant effects and potential health advantages. Comprehending the pharmacokinetics of astaxanthin, which encompasses its absorption, distribution, metabolism, and excretion, is essential for maximizing its therapeutic efficacy. Astaxanthin is a hydrophobic molecule, indicating its ability to dissolve in fats and oils. The absorption of this characteristic is greatly affected, and it is improved when ingested along with dietary lipids. When consumed, astaxanthin is combined with bile salts, phospholipids, cholesterol, free fatty acids, and lysophospholipids to form mixed micelles. Micelles aid in the transportation of astaxanthin through the watery environment of the intestinal lumen to the enterocytes, which are the cells responsible for absorption in the small intestine [143,144]. Astaxanthin is assimilated into enterocytes and then integrated into chylomicrons, which are lipoprotein particles that are released into the lymphatic system and later enter the bloodstream. Interestingly, carotenoid absorption can be increased by a high-cholesterol diet and decreased by a low-fat diet [27].

After entering the bloodstream, astaxanthin is evenly dispersed to different tissues in the body. Due to its lipophilic properties, it can easily pass through cell membranes and build up in tissues that have a high lipid content, such as the liver, adipose tissue, skin, and the central nervous system [17]. A noteworthy finding [152] is that astaxanthin can pass through the BBB, indicating possible neuroprotective benefits. Furthermore, astaxanthin is extensively metabolized in the liver through oxidation and conjugation pathways, forming several metabolites. The metabolites in question consist of hydroxylated and demethylated derivatives, which are capable of being identified in both plasma and urine. Astaxanthin's metabolic routes are mediated by cytochrome P450 enzymes, specifically *CYP3A4*, which have a substantial impact on its biotransformation [153]. Upon intake, astaxanthin can undergo isomerization, leading to the creation of several isomers that are then absorbed and identified in the plasma [63,64].

Astaxanthin and its metabolites are primarily eliminated by the biliary-fecal pathway, with a minor amount being excreted in the urine. The reported elimination half-life of astaxanthin ranges from 16 to 24 hours, depending on the dosage and formulation employed [63]. The considerably extended half-life of astaxanthin enables consistent levels of the compound in the bloodstream after repeated doses. The study conducted by Coral-Hinostroza *et al.* [64] found that when all-*cis* astaxanthin was consumed, there was a notable presence of *trans*-isomers in the plasma. This suggests that there was a considerable conversion of isomers throughout the process of digestion and absorption. In addition, multiple pharmacokinetic studies have emphasized formulation's significance in improving astaxanthin's bioavailability. Studies have demonstrated that lipid-based formulations, which utilize oils or phospholipids, greatly enhance the absorption and bioavailability of astaxanthin in comparison to formulations that do not contain lipids [64]. Moreover, the absorption of astaxanthin in the body is influenced by various factors, including particular isomers that are present. The *Z*-isomer of astaxanthin has demonstrated superior transmembrane transport efficiency and bioavailability in comparison to other isomers, which are frequently transformed amongst each other during cellular uptake [44]. The absorption and conversion of specific optical isomers, such as (3*R*,3'*R*), (3*R*,3'*S*; *meso*), and (3*S*,3'*S*) astaxanthin, also affects how it is distributed and made available in the human body [64].

Astaxanthin's pharmacokinetics is marked by quick absorption when ingested with dietary fats, widespread distribution to different tissues, significant hepatic metabolism, and primary excretion by the biliary-fecal pathway. Understanding the pharmacokinetic properties of astaxanthin is essential for optimizing its therapeutic potential. By focusing on these characteristics, researchers can develop effective formulations that enhance the absorption and overall efficacy of this compound in the body. Astaxanthin possesses distinct characteristics, such as its capacity to traverse the blood-brain barrier and its varying absorption rates depending on the isomeric forms. These features highlight its potential as a potent antioxidant that offers a wide range of health advantages.

3.5. Innovations in anti-aging research: the role of astaxanthin

3.5.1. Overview of current research on anti-aging strategies

Recent progress in anti-aging research has been driven by collaboration across different disciplines, leveraging advancements in biology, medicine, and technology. Researchers are currently focused on understanding the underlying factors—mechanisms of aging and creating interventions to decelerate or reverse these processes. The primary areas of study have delved into genetic, cellular, and molecular aspects, including telomere shortening, oxidative stress, and cellular senescence. Key areas of interest involve the exploration of sirtuins, signaling pathways, and the impact of caloric restriction on longevity. Additionally, investigations have been conducted on the potential of stem cell therapies, regenerative medicine, and advanced biomedical technologies such as CRISPR to address age-related decline. Another important realm of exploration involves the identification

of aging biomarkers, which are essential for early detection of age-related illnesses and evaluating interventions' effectiveness. The study of epigenetics has contributed additional insights into the influence of environmental factors and lifestyle choices on aging. These intersecting research areas have set the stage for novel anti-aging treatments to prolong life span and improve health span, which refers to the duration of time spent in good health.

3.5.2. Anti-aging interventions: traditional to modern approaches

The pursuit of ways to address aging involves a diverse array of interventions. These can range from simple lifestyle adjustments to more advanced pharmaceutical and nutraceutical solutions. The overarching goal of these approaches is to prolong lifespan and elevate health span, thereby ensuring a higher quality of life during later years.

3.5.2.1. Lifestyle-based anti-aging strategies

Lifestyle changes are crucial when fighting against aging as they create a solid basis for health and long life. Participating in consistent physical activity, maintaining a well-rounded diet, and ensuring sufficient sleep are essential elements of a healthy lifestyle. Studies indicate that regular exercise improves cardiovascular health and cognitive function and reduces the likelihood of chronic conditions like diabetes and hypertension [154].

Physical activity supports healthy aging through various mechanisms, including improved mitochondrial function, decreased oxidative stress, and enhanced autophagy [155]. Aerobic activities like walking, running, and cycling significantly benefit cardiovascular health. At the same time, resistance training helps maintain muscle mass and strength, crucial for sustaining mobility and independence in old age [156].

Nutritional approaches also play a crucial part in anti-aging. Diets abundant in antioxidants, polyphenols, and omega-3 fatty acids assist in decreasing oxidative stress and inflammation, both critical factors in the aging process [157]. The Mediterranean diet, renowned for its emphasis on fruits, vegetables, whole grains, nuts, and olive oil, has been thoroughly researched, proven effective, and linked to reduced risks of chronic diseases and improved cognitive function [158]. Additionally, intermittent fasting and calorie restriction have demonstrated the potential to extend lifespan and enhance metabolic health in animal research. However, further study is necessary to confirm these benefits in humans [159].

Effectively managing stress is another crucial aspect of a healthy lifestyle. Practices such as mindfulness and meditation are connected to lower cortisol levels and better maintenance of telomeres, which are protective caps on chromosomes that shorten with age [160]. Chronic stress can accelerate aging by causing systemic inflammation and cellular damage. Activities such as yoga, *tai chi*, and meditation can relieve stress, promoting mental and physical well-being [161]. By integrating regular exercise, a nutritious diet, and effective stress management techniques, individuals can significantly improve their health and longevity, establishing lifestyle changes as a fundamental component of anti-aging strategies.

3.5.2.2. Pharmacological approaches to aging management

Pharmacological strategies in the pursuit of anti-aging predominantly hinge on identifying and deploying drugs and compounds that intricately target the biological underpinnings of aging. Among the frontier areas of investigation stands the development of senolytics. These pioneering drugs operate on a meticulously selective principle to purge senescent cells, which, over time, progressively accumulate, ushering in tissue dysfunction and systemic inflammation. This pursuit has been significantly bolstered by seminal research such as that of Kirkland and Tchkonia [162] demonstrated measurable efficacy of senolytics like dasatinib and quercetin in ameliorating physical decline and extending the health span in animal models, as meticulously documented by [33].

Parallel to the exploration of senolytics, the potential encapsulated in NAD⁺ precursors, inclusive of nicotinamide riboside and nicotinamide mononucleotide, has been rigorously evaluated for their capacity to amplify mitochondrial functionality and pioneer the repair of DNA damages. The decline of NAD⁺ levels, synonymous with advancing age, predicates a cascade of cellular energy deficits alongside heightened susceptibility to stress-induced damages. The pioneering work by Saxton and Sabatini [163], alongside subsequent investigations by Yoshino *et al.* [62], shed light on the noteworthy implications of NAD⁺ precursor supplementation. Such interventions have been heralded for their broad benefits, spanning enhancements in metabolic processes, cognitive faculties, and the overarching vitality in preclinical models.

Beyond its well-documented antioxidant and anti-inflammatory roles, astaxanthin has recently been shown to influence core cellular aging mechanisms, including those targeted by NAD⁺ boosters and senolytics. Astaxanthin activates SIRT1, a NAD⁺ dependent deacetylase involved in mitochondrial biogenesis, DNA repair, and suppression of age-related inflammation. Through this action, astaxanthin may help maintain NAD⁺ levels and improve cellular energy metabolism [151]. Astaxanthin also modulates the FOXO3 transcription factor, which governs stress resistance and longevity-related genes [148,151]. Additionally, astaxanthin's ability to reduce pro-inflammatory cytokines such as IL-6 and TNF- α , commonly secreted by senescent cells, suggests potential senolytic-like effects by mitigating the SASP. These actions suggest astaxanthin as a nutraceutical candidate not only for antioxidant protection but also for modern anti-aging strategies targeting cellular senescence and mitochondrial health. Future studies are encouraged to validate these mechanistic effects in human aging models.

An equally intriguing dimension of anti-aging pharmacology is encapsulated in using Rapamycin, an inhibitor of the mTOR signaling pathway. The discrete modulation of metabolic and stress-response pathways via mTOR inhibition has been associated with tangible extensions in lifespan and health span across various model organisms. As a central regulator of cellular growth and metabolism, the critical role of mTOR positions its inhibition as a pivotal strategy for fostering autophagy, curtailing inflammation, and refining metabolic functionality. This has been substantiated by research endeavors,

including those comprehensive reviews by Saxton and Sabatini [164], charting the course for potential clinical applications in humans aimed at anti-aging outcomes.

Venturing beyond pharmacological interventions, the domain of regenerative medicine, with a spotlight on stem cell therapies, unveils profound frontiers for anti-aging interventions. Stem cell therapies are envisioned as a transformative avenue for replacing deteriorated or senescent cells, catalyzing tissue repair and rejuvenation. Though embryonic in their developmental stage, preliminary findings, as discussed by Trounson and McDonald [165], reflect optimistic prognoses for addressing a spectrum of conditions, including osteoarthritis, cardiovascular anomalies, and neurodegenerative disorders, showcasing the multifaceted potential of regenerative medicine in the quest against aging.

3.5.2.3. Nutraceutical strategies for aging prevention

Nutraceuticals, specialized compounds derived from food sources, are at the forefront of innovative anti-aging strategies. Due to their natural origins, these products offer substantial health benefits that intersect the realms of nutrition and pharmaceutical efficacy.

Resveratrol emerges as a standout in the ongoing pursuit of longevity and health preservation. Primarily found in grapes, berries, and red wine, resveratrol has gained scientific acclaim for its ability to activate sirtuins, a family of proteins pivotal in cellular health and regulation. This activation, mirroring the life-extending benefits observed in caloric restriction, catapults resveratrol to the forefront of anti-aging research. A seminal study by Baur *et al.* [166] elucidates how resveratrol's interaction with sirtuins may enhance metabolic health, diminish inflammation, and strengthen the body's ability to cope with stress, all vital in promoting longevity.

Curcumin, the vibrant, bioactive compound in turmeric, is celebrated for its anti-inflammatory and antioxidant prowess. This compound has been shown to defend against age-associated diseases and cognitive decline, highlighting its importance in longevity studies. Research documented by Cole *et al.* [167] supports curcumin's capacity to fend off oxidative damage and reduce inflammation. Furthermore, the modulation of aging-related molecular pathways such as NF- κ B, mTOR, and AMPK holds significant therapeutic potential in anti-aging interventions. NF- κ B is involved in immune response and inflammation, with chronic activation linked to age-related diseases; its inhibition could reduce inflammation and disease incidence. mTOR regulates cell growth and survival, with hyperactivation associated with aging and decreased lifespan; inhibiting mTOR, as seen with rapamycin, may extend lifespan and health span. AMPK maintains cellular energy balance, enhancing autophagy and mitochondrial function; increased AMPK activity is linked to extended lifespan and improved health. Thus, targeting these pathways could effectively slow aging and improve overall health [168].

The antioxidant astaxanthin, derived from certain microalgae species, represents another cornerstone in the fight against aging. Its unparalleled antioxidative properties protect the skin from the detrimental effects of photoaging and promote overall skin health and vibrancy. Higuera-Ciapara *et al.* [96]

alongside Ambati *et al.* [26], emphasize astaxanthin's unique ability to embed into cellular membranes, shielding them from oxidative stress and inflammation. Clinical studies, including those by Yamashita [12], corroborate astaxanthin's efficacy in enhancing skin elasticity, reducing wrinkles, and improving skin aesthetics, marking it as an invaluable tool in the cosmeceutical field.

3.5.3. Role of astaxanthin in anti-aging therapeutics

3.5.3.1. Studies on astaxanthin supplementation and longevity

Astaxanthin, a potent carotenoid, has been extensively studied for its potential benefits on longevity and overall health. Research across various model organisms has demonstrated its capacity to extend lifespan and improve markers associated with aging. Studies using the nematode *Caenorhabditis elegans* have provided valuable insights into the anti-aging properties of astaxanthin. Yazaki *et al.* [169] conducted an experiment where *C. elegans* were supplemented with astaxanthin, significantly extending their lifespan. Additionally, these nematodes exhibited enhanced resistance to oxidative stress, which is a critical factor in the aging process. The study highlighted the potential mechanisms through which astaxanthin exerts its effects, including the upregulation of stress response genes and the reduction of ROS levels [169].

Human clinical trials have further substantiated the benefits of astaxanthin supplementation. Tominaga *et al.* [170] conducted a study on the effects of astaxanthin on skin health. Participants who received astaxanthin supplements showed improved skin elasticity and reduced wrinkles. These findings highlight astaxanthin's potential as a nutraceutical for promoting youthful skin and mitigating the visible signs of aging. The antioxidant effects of astaxanthin are vital for safeguarding skin cells against oxidative damage, helping to preserve both the health and appearance of the skin [170].

Moreover, astaxanthin has been shown to enhance immune function in aging populations. The immune system naturally weakens with age, increasing susceptibility to infections and diseases. Astaxanthin supplementation has been associated with improved immune response, suggesting that it can help maintain a robust immune system in elderly individuals. This enhancement of immune function is vital for longevity and overall health, as a robust immune system is essential for combating age-related diseases. Astaxanthin derived from microalgae is commonly commercialized as a nutritional supplement in capsule form. Products such as Natural Astaxanthin 5 mg Softgels (Solgar, NJ, USA) and Astapure[®] Astaxanthin Complex (Igenus Healthcare Nutrition, Cambridge, UK), as well as those listed in Table 3 below, are widely available. These supplements have gained popularity due to their documented health benefits, including anti-aging effects and improved immune function [6, 105].

Although Table 3 primarily features astaxanthin in softgel and capsule forms, it is important to recognize that bioavailability can still vary widely depending on formulation characteristics. As a lipophilic compound, astaxanthin requires incorporation into lipid-based carriers to enhance absorption [129]; however, differences in excipient types, oil composition,

Table 3. Overview of commercial food products enriched with natural astaxanthin.

Product	Company	Dosage form	Efficacy	Astaxanthin dose	Country	References
Better Foods Astaxanthin	Better Foods GmbH	Capsule	Product commercialized as an antioxidant support and a support for a healthy skin (based on product claims).	4 mg per capsule	Germany	[6]
PurZanthin Ultra	Nature's Products, Inc.	Softgel	Antioxidant support for cell in the body including eyes, skin and heart (based on product claims).	12 mg per soft gel	Canada	[171]
Astaxanthin Gold™	Nutrigold Inc.	Softgel	Supports eye, joint, skin, and immune health (based on product claims)	4 mg per soft gel	USA	[172]
Natural Astaxanthin	Nutravita Ltd.	Softgel	Natural astaxanthin product; efficacy details not specified	0.9 mg per soft gel	UK	[6]
EyeScience Natural Astaxanthin	EyeScience Labs, Inc.	Capsule	Clinically shown to support eye health and visual focus.	12 mg per capsule	Ohio	[173]
Best Astaxanthin	BioAstin	Softgel	Marketed for cell membrane and blood flow support (based on product claims).	6 mg per soft gel	-	[174]
Sila Astaxanthin	Sila	Capsule	Natural astaxanthin product; efficacy details not specified	12 mg per capsule	Taiwan	[6]
Dr. Mercola Astaxanthin	Dr. Mercola Premium Supplements	Capsule	Supports healthy aging and muscle recovery (based on product claims).	4 mg per capsule	NA	[175]
Vivanaturals Astaxanthin from microalgae	Viva Naturals Inc.	Softgel	Promote the development of firm and healthy skin; support immune health (based on product claims).	4 mg per soft gel	Canada	[6]
Ox Nature Natural Hawaiian	Ox Nature	Softgel	Natural astaxanthin product; efficacy details not specified	4 mg per soft gel	Portugal	[176]
Solgar Natural Astaxanthin	Solgar Global Manufacture	Capsule	Supports healthy skin (based on product claims).	5 mg per soft gel	NA	[177]
Time Health Astaxanthin	Time Health Ltd.	Capsule	Natural astaxanthin product; efficacy details not specified	7 mg per capsule	UK	[6]

and capsule stability can influence uptake efficiency. Even within softgel formulations, factors such as particle dispersion, encapsulation technique, and co-delivered lipids affect gastrointestinal absorption and systemic availability. Furthermore, emerging technologies like nanoemulsions and liposomes have been explored to further improve astaxanthin's bioavailability compared to conventional capsules. These considerations underscore the need to critically evaluate formulation strategies beyond product type alone.

Astaxanthin's applications also extend beyond supplements and food products. It is increasingly utilized in the cosmetics industry for its antioxidant properties. Products such as Bloom Orchid Face Cream and Green Vitamin Concentrate Serum (Freshly Cosmetics, Barcelona, Spain) leverage the benefits of astaxanthin to enhance skin health. A study conducted by Cheng *et al.* [178] compared a mask containing astaxanthin to one formulated with vitamin E. The astaxanthin mask demonstrated superior antioxidant capacity and had a half-life of 70 weeks. This stability and efficacy make astaxanthin an attractive ingredient for cosmetic formulations to reduce oxidative damage and promote skin health. Despite the growing global market for astaxanthin-based products, Malaysia has a notable need for such products. This presents a significant opportunity for the Malaysian biotechnology and

nutraceutical sectors to explore and develop astaxanthin-based products. Given Malaysia's rich biodiversity and potential for microalgae cultivation, local production and commercialization of astaxanthin could position the country as a critical player in the global market. The development of astaxanthin-based supplements, functional foods, and cosmetics could meet the rising consumer demand for natural antioxidants and anti-aging products, providing economic benefits and contributing to public health.

3.5.3.2. Molecular mechanisms of astaxanthin in aging prevention

The impressive anti-aging benefits of astaxanthin arise from its extraordinary capacity to influence critical biological pathways related to oxidative stress, inflammation, and overall cellular health. Astaxanthin is a potent antioxidant that effectively neutralizes harmful free radicals, protecting cells from oxidative damage. This is particularly important in aging, as the accumulation of oxidative damage is a defining feature of the aging process [28]. Astaxanthin helps maintain cellular integrity and function by reducing oxidative stress, ultimately slowing down aging.

Astaxanthin's anti-inflammatory properties also play a crucial role in its effectiveness as an anti-aging agent. By hindering key inflammatory pathways like the NF- κ B

signaling pathway, astaxanthin reduces the production of pro-inflammatory cytokines implicated in numerous age-related conditions [151]. For example, research has demonstrated that astaxanthin can reduce the levels of key inflammatory markers, including TNF- α , IL-1 β , and IL-6. These substances are crucial players in the processes of chronic inflammation and aging. [11]. Moreover, evidence shows that at the mitochondrial level, astaxanthin boosts mitochondrial function, which in turn enhances energy metabolism and lowers the generation of ROS [179]. Enhanced mitochondrial function is crucial for maintaining optimal cellular energy levels and minimizing oxidative damage, essential for healthy aging. Additionally, astaxanthin's ability to protect mitochondrial membranes from oxidative damage further supports its role in maintaining cellular function and longevity [180].

Furthermore, astaxanthin has been demonstrated to impact gene expression associated with longevity and stress resistance. Studies indicate that astaxanthin can increase the expression of antioxidant enzymes and stress response proteins, contributing to improved cellular resilience and longevity [21]. For example, there have been reports indicating that astaxanthin increases the expression of SOD and catalase. Both are essential for detoxifying reactive oxygen species and safeguarding cells from oxidative damage [181]. These findings suggest that astaxanthin employs a diverse strategy to combat aging. Astaxanthin emerges as a multifaceted anti-aging agent by reducing oxidative stress, modulating inflammatory responses, and enhancing cellular health. The evidence supporting its potential in promoting longevity and protecting against age-related conditions positions it as a valuable component in developing anti-aging therapies. However, despite these mechanistic insights, human studies remain limited and inconsistent. While several trials confirm improvements in skin elasticity and markers of oxidative stress with doses ranging from 4–12 mg/day [16,39], other clinical data are inconclusive due to small sample sizes, short intervention periods, and varying astaxanthin purity. Furthermore, some trials report no statistically significant benefits in endurance performance or lipid metabolism, raising questions about dose-response thresholds and inter-individual variability.

Despite the strength of preclinical and mechanistic findings, the translation to clinical efficacy remains controversial. One of the most debated challenges is astaxanthin's poor and variable bioavailability [27,148] due to its lipophilic nature, poor water solubility, and chemical instability. These factors thus directly affect the pharmacokinetics and therapeutic outcomes. Moreover, comparative studies suggest that the type of formulation (e.g., oil-based capsules, nanoemulsions, and liposomes) significantly influences its absorption [129]. For example, lipid-based delivery systems have been shown to improve plasma bioavailability by up to two-fold compared to powder or crystalline forms [182]. However, the lack of formulation standardization across studies and products has contributed to inconsistent clinical results. Some trials using softgel astaxanthin observed statistically significant improvements in oxidative stress markers and skin parameters, while others with similar dosing but different formulations found negligible effects [9,13,105,129,141,182].

Another point of contention involves stereoisomeric composition and dosage. Most commercial astaxanthin is derived from *H. pluvialis* and contains a mixture of (3S,3'S), (3R,3'S), and (3R,3'R) stereoisomers. However, emerging evidence suggests that certain isomers (e.g., 3S,3'S or Z-isomers) may exert stronger biological activity or higher affinity for lipid membranes [59,148]. Despite this, few clinical trials specify the isomeric composition used, making it difficult to replicate or compare findings.

Additionally, human trial outcomes vary widely, not only due to differences in formulation and dose but also due to population variability (age, sex, diet, and baseline oxidative status), short intervention periods, and inadequate control for confounding factors. For example, while some studies report improved cognitive performance and skin hydration in elderly adults [9,152,183], others observe only modest or nonsignificant changes in inflammatory biomarkers or cardiovascular outcomes.

These inconsistencies highlight the critical need for well-designed, large-scale, placebo-controlled studies with standardized astaxanthin formulations and well-defined inclusion criteria. Without such data, the pharmacological credibility of astaxanthin in human aging interventions remains mechanistically supported but clinically under-validated.

4. CONCLUSION

Astaxanthin has emerged as a potent bioactive compound with significant potential in anti-aging and pharmaceutical applications. Its strong antioxidant, anti-inflammatory, and skin-protective properties have been supported by both preclinical and clinical studies, indicating its potential to combat age-related cellular damage and enhancing skin health. However, its effectiveness is largely dependent on efficient extraction techniques and improved bioavailability strategies. Moreover, advanced extraction methods such as SFE and MAE have demonstrated superior efficiency in preserving astaxanthin's bioactivity, making them ideal for pharmaceutical formulations. Furthermore, challenges related to astaxanthin's poor water solubility and low bioavailability necessitate innovative delivery approaches, including nanoencapsulation, liposomal formulations, and lipid-based delivery systems.

Future research should focus on clinical validation and regulatory approval to facilitate astaxanthin's integration into pharmaceutical and cosmeceutical products. Specifically, well-designed randomized clinical trials should evaluate the safety, optimal dosing, delivery systems, and comparative efficacy of different astaxanthin isomers across aging-related endpoints such as skin elasticity, cognitive function, and metabolic health. Additionally, exploring combination therapies with other anti-aging agents may enhance its therapeutic potential. With continued advancements in extraction technologies and formulation strategies, astaxanthin exhibits multiple anti-aging mechanisms for the development of effective anti-aging interventions in both topical and systemic applications.

5. ACKNOWLEDGMENTS

The authors gratefully acknowledge the support provided by Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), Shah Alam, Faculty of Pharmacy, Universiti

Teknologi MARA (UiTM), Puncak Alam and Faculty of Pharmacy and Health Sciences Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP). We also extend our appreciation to the Integrative Pharmacogenomics Institute (iPROMISE), the Food Science Research Group, and the Integrated Nutrition Science and Therapy Research Group (INSPiRE) for their assistance.

6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

7. FINANCIAL SUPPORT

There is no funding to report.

8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All the data are available to the authors and shall be provided upon request.

11. PUBLISHER'S NOTE

All claims expressed in this article are solely those of the authors and do not necessarily represent those of the publisher, the editors and the reviewers. This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

12. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

REFERENCES

- Buckingham EM, Klingelutz AJ. The role of telomeres in the ageing of human skin. *Exp Dermatol.* 2011;20(4):297–302. doi: <https://doi.org/10.1111/j.1600-0625.2010.01242.x>
- Victorelli S, Passos JF. Telomeres and cell senescence - size matters not. *EBioMedicine.* 2017;21:14–20. doi: <https://doi.org/10.1016/j.ebiom.2017.03.027>
- Wang AS, Dreesen O. Biomarkers of cellular senescence and skin aging. *Front Genet.* 2018;9:389916. doi: <https://doi.org/10.3389/fgene.2018.00247>
- He X, Wan F, Su W, Xie W. Research progress on skin aging and active ingredients [Internet]. *Molecules Internet.* 2023;28(14):1–28. Available from: <https://pubmed.ncbi.nlm.nih.gov/37513428/>
- Oslan SNH, Tan JS, Oslan SN, Matanjun P, Mokhtar RAM, Shapawi R, *et al.* *Haematococcus pluvialis* as a potential source of astaxanthin with diverse applications in industrial sectors: current research and future directions. *Molecules.* 2021;26(21).
- Villarro S, Ciardi M, Morillas-España A, Sánchez-Zurano A, Acien-Fernández G, Lafarga T. Microalgae derived astaxanthin: research and consumer trends and industrial use as food. *Foods.* 2021;10(10).
- Li X, Matsumoto T, Takuwa M, Saeed Ebrahim Shaiku Ali M, Hirabashi T, Kondo H, *et al.* Protective effects of astaxanthin supplementation against ultraviolet-induced photoaging in hairless mice. *Biomedicines.* 2020;8(2):1–14. doi: <https://doi.org/10.3390/biomedicines8020018>
- Davinelli S, Nielsen ME, Scapagnini G. Astaxanthin in skin health, repair, and disease: a comprehensive review. *Nutrients.* 2018;10(4):522. doi: <https://doi.org/10.3390/nu10040522>
- Queen CJJ, Sparks SA, Marchant DC, Mcnaughton LR. The effects of astaxanthin on cognitive function and neurodegeneration in humans: a critical review. *Nutrients.* 2024;16(6):16. doi: <https://doi.org/10.3390/nu16060826>
- Fakhri S, Yosifova Aneva I, Farzaei MH, Sobarzo-Sánchez E. The neuroprotective effects of astaxanthin: therapeutic targets and clinical perspective. *Molecules.* 2019;24(14):2640. doi: <https://doi.org/10.3390/molecules24142640>
- Wang S, Qi X. The putative role of astaxanthin in neuroinflammation modulation: mechanisms and therapeutic potential. *Front Pharmacol.* 2022;13:916653. doi: <https://doi.org/10.3389/fphar.2022.916653>
- Yamashita E. Astaxanthin as a medical food. *Funct Foods Heal Dis.* 2013;3(7):254–68.
- Li B, Lee JY, Luo Y. Health benefits of astaxanthin and its encapsulation for improving bioavailability: a review. *J Agric Food Res.* 2023;14:100685.
- Zhao T, Yan X, Sun L, Yang T, Hu X, He Z, *et al.* Research progress on extraction, biological activities and delivery systems of natural astaxanthin. *Trends Food Sci & Technol.* 2019;91:354–61.
- Brendler T, Williamson EM. Astaxanthin: how much is too much? A safety review. *Phyther Res.* 2019;33(12):3090–111.
- Björklund G, Gasmi A, Lenchyk L, Shanida M, Zafar S, Mujawdiya PK, *et al.* The Role of Astaxanthin as a Nutraceutical in Health and Age-Related Conditions [Internet]. *Molecules Internet.* 2022;27(21):7167. Available from: <https://www.mdpi.com/1420-3049/27/21/7167>
- Medoro A, Intriери M, Passarella D, Willcox DC, Davinelli S, Scapagnini G. Astaxanthin as a metabolic regulator of glucose and lipid homeostasis. *J Funct Foods.* 2024;112:105937.
- Turck D, Castenmiller J, De Henauw S, Hirsch-Ernst KI, Kearney J, Maciuk A, *et al.* Safety of astaxanthin for its use as a novel food in food supplements [Internet]. *EFSA J.* 2020;18(2):5993. doi: <https://doi.org/10.2903/j.efsa.2020.5993>
- Debnath T, Bandyopadhyay TK, Vanitha K, Bobby MN, Nath Tiwari O, Bhunia B, *et al.* Astaxanthin from microalgae: a review on structure, biosynthesis, production strategies and application. *Food Res Int.* 2024;176:113841.
- Capelli B, Cysewski GR. The world's best kept health secret: natural astaxanthin. *J Chem Inf Model.* 2012;53:4.
- Ding W, Peng J, Zhao Y, Zhao P, Xu JW, Li T, *et al.* A strategy for boosting astaxanthin accumulation in green microalga *Haematococcus pluvialis* by using combined diethyl aminoethyl hexanoate and high light. *J Appl Phycol.* 2019;31(1):171–81.
- Sun T. An alternative route for astaxanthin biosynthesis in green algae. *Plant Physiol.* 2020;183(3):812–3. doi: <https://doi.org/10.1104/pp.20.00643>
- Aneesh PA, Ajeeshkumar KK, Lekshmi RGK, Anandan R, Ravishankar CN, Mathew S. Bioactivities of astaxanthin from natural sources, augmenting its biomedical potential: a review. *Trends Food Sci Technol.* 2022;125:81–90. doi: <https://doi.org/10.1016/j.tifs.2022.05.004>
- Rizzardi N, Pezzolesi L, Samori C, Senese F, Zalambani C, Pitacco W, *et al.* Natural astaxanthin is a green antioxidant able to

- counteract lipid peroxidation and ferroptotic cell death. *Int J Mol Sci.* 2022;23(23):1–16. doi: <https://doi.org/10.3390/ijms232315137>
25. Dutta S, Kumar SPJ, Banerjee R. A comprehensive review on astaxanthin sources, structure, biochemistry and applications in the cosmetic industry. *Algal Res.* 2023;74:103168. doi: <https://doi.org/10.1016/j.algal.2023.103168>
 26. Ambati R, Phang SM, Ravi S, Aswathanarayana R. Astaxanthin: sources, extraction, stability, biological activities and its commercial applications—a review [Internet]. *Mar Drugs Internet.* 2014;12(1):128–52. Available from: <https://www.mdpi.com/1660-3397/12/1/128>
 27. Liu X, Xie J, Zhou L, Zhang J, Chen Z, Xiao J, *et al.* Recent advances in health benefits and bioavailability of dietary astaxanthin and its isomers. *Food Chem.* 2023;404:134605. doi: <https://doi.org/10.1016/j.foodchem.2022.134605>
 28. Naguib YMA. Antioxidant activities of astaxanthin and related carotenoids. *J Agric Food Chem.* 2000;48(4):1150–4. doi: <https://doi.org/10.1021/jf991106k>
 29. Bharti A, Hooda V, Jain U, Chauhan N. Astaxanthin: a nature's versatile compound utilized for diverse applications and its therapeutic effects [Internet]. *3 Biotech Internet.* 2025;15(4):88. Available from: <https://link.springer.com/article/10.1007/s13205-025-04241-5>
 30. Ranga Rao A, Raghunath Reddy RL, Baskaran V, Sarada R, Ravishankar GA. Characterization of microalgal carotenoids by mass spectrometry and their bioavailability and antioxidant properties elucidated in rat model. *J Agric Food Chem.* 2010;58(15):8553–69. doi: <https://doi.org/10.1021/jf101187k>
 31. Fakhri S, Abbaszadeh F, Dargahi L, Jorjani M. Astaxanthin: a mechanistic review on its biological activities and health benefits. *Pharmacol Res.* 2018;136:1–20. doi: <https://doi.org/10.1007/s13205-025-04241-5>
 32. Chintong S, Phatvej W, Rerk-Am U, Waiprib Y, Klaypradit W. *In vitro* antioxidant, antityrosinase, and cytotoxic activities of astaxanthin from shrimp waste. *Antioxidants.* 2019;8(5):128. doi: <https://doi.org/10.3390/antiox8050128>
 33. Xu J, Rong S, Gao H, Chen C, Yang W, Deng Q, *et al.* A combination of flaxseed oil and astaxanthin improves hepatic lipid accumulation and reduces oxidative stress in high fat-diet fed rats. *Nutrients.* 2017;9(3):271. doi: <https://doi.org/10.3390/nu9030271>
 34. Speranza L, Pesce M, Patruno A, Franceschelli S, Lutiis MAD, Grilli A, *et al.* Astaxanthin treatment reduced oxidative induced pro-inflammatory cytokines secretion in U937: sHP-1 as a novel biological target. *Mar Drugs.* 2012;10(4):890–9. doi: <https://doi.org/10.3390/md10040890>
 35. Jannel S, Caro Y, Bermudes M, Petit T. Novel insights into the biotechnological production of *Haematococcus pluvialis*-derived astaxanthin: advances and key challenges to allow its industrial use as novel food ingredient. *J Mar Sci Eng.* 2020;8(10):789. doi: <https://doi.org/10.3390/jmse8100789>
 36. Kishimoto Y, Tani M, Uto-Kondo H, Iizuka M, Saita E, Sone H, *et al.* Astaxanthin suppresses scavenger receptor expression and matrix metalloproteinase activity in macrophages. *Eur J Nutr.* 2010;49(2):119–26. doi: <https://doi.org/10.1007/s00394-009-0056-4>
 37. Zhang Z, Guo C, Jiang H, Han B, Wang X, Li S, *et al.* Inflammation response after the cessation of chronic arsenic exposure and post-treatment of natural astaxanthin in liver: potential role of cytokine-mediated cell–cell interactions. *Food Funct.* 2020;11(10):9252–62. doi: <https://doi.org/10.1039/D0FO01223H>
 38. Macedo RC, Bolin AP, Marin DP, Otton R. Astaxanthin addition improves human neutrophils function: *in vitro* study. *Eur J Nutr.* 2010;49(8):447–57. doi: <https://doi.org/10.1007/s00394-010-0103-1>
 39. Sorrenti V, Davinelli S, Scapagnini G, Willcox BJ, Allsopp RC, Willcox DC. Astaxanthin as a putative geroprotector: molecular basis and focus on brain aging. *Mar Drugs.* 2020;18(7):351. doi: <https://doi.org/10.3390/md18070351>
 40. Haines DD, Varga B, Bak I, Juhasz B, Mahmoud FF, Kalantari H, *et al.* Summative interaction between astaxanthin, Ginkgo biloba extract (EGb761) and vitamin C in Suppression of respiratory inflammation: a comparison with ibuprofen. *Phyther Res [Internet].* 2011;25(1):128–36. doi: <https://doi.org/10.1002/ptr.3160>
 41. Song L, Yao S, Zheng D, Xuan Y, Li W. Astaxanthin attenuates contrast-induced acute kidney injury in rats via ROS/NLRP3 inflammasome. *Int Urol Nephrol.* 2022;54(6):1355–64. doi: <https://doi.org/10.1007/s11255-021-03015-1>
 42. Han JH, Lee YS, Im JH, Ham YW, Lee HP, Han SB, *et al.* Astaxanthin ameliorates lipopolysaccharide-induced neuroinflammation, oxidative stress and memory dysfunction through inactivation of the signal transducer and activator of transcription 3 pathway. *Mar Drugs.* 2019;17(2):123. doi: <https://doi.org/10.3390/md17020123>
 43. Yoshihisa Y, Rehman MU, Shimizu T. Astaxanthin, a xanthophyll carotenoid, inhibits ultraviolet-induced apoptosis in keratinocytes. *Exp Dermatol.* 2014;23(3):178–83. doi: <https://doi.org/10.1111/exd.12347>
 44. Yang C, Zhang H, Liu R, Zhu H, Zhang L, Tsao R. Bioaccessibility, cellular uptake, and transport of astaxanthin isomers and their antioxidative effects in human intestinal epithelial Caco-2 cells. *J Agric Food Chem.* 2017;65(47):10223–32. doi: <https://doi.org/10.1021/acs.jafc.7b04254>
 45. Gasmí A, Chirumbolo S, Peana M, Mujawdiya PK, Dadar M, Menzel A, *et al.* Biomarkers of senescence during aging as possible warnings to use preventive measures. *Curr Med Chem.* 2020;28(8):1471–88. doi: <https://doi.org/10.2174/0929867327999200917150652>
 46. Björklund G, Shanaida M, Lysiuk R, Butnariu M, Peana M, Sarac I, *et al.* Natural compounds and products from an anti-aging perspective. *Molecules.* 2022;27(20):7084. doi: <https://doi.org/10.3390/molecules27207084>
 47. Björklund G, Dadar M, Martins N, Chirumbolo S, Goh BH, Smetanina K, *et al.* Brief challenges on medicinal plants: an eye-opening look at ageing-related disorders. *Basic Clin Pharmacol Toxicol.* 2018;122(6):539–58. doi: <https://doi.org/10.1111/bcpt.12972>
 48. Chirumbolo S, Björklund G, Lysiuk R, Vella A, Lenchyk L, Upry T. Targeting cancer with phytochemicals via their fine tuning of the cell survival signaling pathways. *Int J Mol Sci.* 2018;19(11):3568. doi: <https://doi.org/10.3390/ijms19113568>
 49. Singh KN, Patil S, Barkate H. Protective effects of astaxanthin on skin: recent scientific evidence, possible mechanisms, and potential indications. *J Cosmet Dermatol.* 2020;19(1):22–7. doi: <https://doi.org/10.1111/jocd.13019>
 50. Tominaga K, Hongo N, Fujishita M, Takahashi Y, Adachi Y. Protective effects of astaxanthin on skin deterioration. *J Clin Biochem Nutr.* 2017;61(1):33–9. doi: <https://doi.org/10.3164/jcbr.17-35>
 51. Komatsu T, Sasaki S, Manabe Y, Hirata T, Sugawara T. Preventive effect of dietary astaxanthin on UVA-induced skin photoaging in hairless mice. *PLoS One.* 2017;12(2):e0171178. doi: <https://doi.org/10.1371/journal.pone.0171178>
 52. Chung BY, Park SH, Yun SY, Yu DS, Lee YB. Astaxanthin protects ultraviolet B-induced oxidative stress and apoptosis in human keratinocytes via intrinsic apoptotic pathway. *Ann Dermatol.* 2022;34(2):125. doi: <https://doi.org/10.5021/ad.2022.34.2.125>
 53. Ng QX, De Deyn MLZQ, Loke W, Foo NX, Chan HW, Yeo WS. Effects of astaxanthin supplementation on skin health: a systematic review of clinical studies. *J Diet Suppl.* 2021;18(2):169–82. doi: <https://doi.org/10.1080/19390211.2020.1739187>
 54. Liu H, Zhang X, Xiao J, Song M, Cao Y, Xiao H, *et al.* Astaxanthin attenuates D-galactose-induced brain aging in rats by ameliorating oxidative stress, mitochondrial dysfunction, and regulating metabolic markers. *Food Funct.* 2020;11(5):4103–13. doi: <https://doi.org/10.1039/D0FO00633E>
 55. Park JS, Mathison BD, Hayek MG, Zhang J, Reinhart GA, Chew BP. Astaxanthin modulates age-associated mitochondrial dysfunction in healthy dogs. *J Anim Sci.* 2013;91(1):268–75. doi: <https://doi.org/10.2527/jas.2012-5341>
 56. Che H, Li Q, Zhang T, Wang D, Yang L, Xu J, *et al.* Effects of astaxanthin and docosahexaenoic-acid-acylated astaxanthin on Alzheimer's disease in APP/PS1 double-transgenic mice. *J Agric*

- Food Chem. 2018;66(19):4948–57. doi: <https://doi.org/10.1021/acs.jafc.8b00988>
57. Wu W, Wang X, Xiang Q, Meng X, Peng Y, Du N, *et al.* Astaxanthin alleviates brain aging in rats by attenuating oxidative stress and increasing BDNF levels. *Food Funct.* 2013;5(1):158–66. doi: <https://doi.org/10.1039/C3FO60400D>
58. Liu X, Liu H, Chen Z, Xiao J, Cao Y. DAF-16 acts as the “hub” of astaxanthin’s anti-aging mechanism to improve aging-related physiological functions in *Caenorhabditis elegans*. *Food Funct.* 2021;12(19):9098–1110. doi: <https://doi.org/10.1039/D1FO01069G>
59. Liu X, Luo Q, Cao Y, Goulette T, Liu X, Xiao H. Mechanism of different stereoisomeric astaxanthin in resistance to oxidative stress in *Caenorhabditis elegans*. *J Food Sci.* 2016;81(9):H2280–7. doi: <https://doi.org/10.1111/1750-3841.13417>
60. Honda M, Nakayama Y, Nishikawa S, Tsuda T. Z-Isomers of lycopene exhibit greater liver accumulation than the all-E-isomer in mice. *Biosci Biotechnol Biochem.* 2020;84(2):428–31. doi: <https://doi.org/10.1111/1750-3841.13417>
61. Xie J, Cai R, Hou X, Zhao K, Xiao J, Cao Y, *et al.* Z-Astaxanthin exhibits superior anti-obesity effects in *Caenorhabditis elegans*: insights from geometric isomers and signaling pathways [Internet]. *J Sci Food Agric.* 2025;105(9):4795–807. Available from: <https://pubmed.ncbi.nlm.nih.gov/40059044/>
62. Yoshino J, Baur JA, Imai SI. NAD⁺ intermediates: the biology and therapeutic potential of NMN and NR. *Cell Metab.* 2018;27(3):513–28. doi: <https://doi.org/10.1016/j.cmet.2017.11.002>
63. Østerlie M, Bjerkeng B, Liaaen-Jensen S. Plasma appearance and distribution of astaxanthin E/Z and R/S isomers in plasma lipoproteins of men after single dose administration of astaxanthin. *J Nutr Biochem.* 2000;11(10):482–90. doi: [https://doi.org/10.1016/S0955-2863\(00\)00104-2](https://doi.org/10.1016/S0955-2863(00)00104-2)
64. Coral-Hinostroza GN, Ytrestøyl T, Ruyter B, Bjerkeng B. Plasma appearance of unesterified astaxanthin geometrical E/Z and optical R/S isomers in men given single doses of a mixture of optical 3 and 3’R/S isomers of astaxanthin fatty acyl diesters. *Comp Biochem Physiol Part C Toxicol Pharmacol.* 2004;139(1–3):99–110. doi: <https://doi.org/10.1016/j.cca.2004.09.011>
65. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol.* 2010;5:99–118. doi: <https://doi.org/10.1146/annurev-pathol-121808-102144>
66. Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, *et al.* Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. *Nat Med.* 2017;23(6):775–81. doi: <https://doi.org/10.1038/nm.4324>
67. Childs BG, Baker DJ, Kirkland JL, Campisi J, Van Deursen JM. Senescence and apoptosis: dueling or complementary cell fates?. *EMBO Rep.* 2014;15(11):1139–53. doi: <https://doi.org/10.15252/embr.201439245>
68. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, *et al.* Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. *Nature.* 2016;530(7589):184–9. doi: <https://doi.org/10.1038/nature16932>
69. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol.* 1956;11(3):298–300. doi: <https://doi.org/10.1093/geronj/11.3.298>
70. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J.* 2003;17(10):1195–214. doi: <https://doi.org/10.1096/fj.02-0752rev>
71. Madamanchi NR, Runge MS. Mitochondrial dysfunction in atherosclerosis. *Circ Res.* 2007;100(4):460–73. doi: <https://doi.org/10.1161/01.RES.0000258450.44413.96>
72. Kirkwood TBL. Understanding the odd science of aging. *Cell.* 2005;120(4):437–47. doi: <https://doi.org/10.1016/j.cell.2005.01.027>
73. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu Rev Genet.* 2005;39:359–407. doi: <https://doi.org/10.1146/annurev.genet.39.110304.095751>
74. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194. doi: <https://doi.org/10.1016/j.cell.2013.05.039>
75. Sun N, Youle RJ, Finkel T. The mitochondrial basis of aging. *Mol Cell.* 2016;61(5):654–66. doi: <https://doi.org/10.1016/j.molcel.2016.01.028>
76. Smith RAJ, Murphy MP. Animal and human studies with the mitochondria-targeted antioxidant MitoQ. *Ann N Y Acad Sci.* 2010;1201:96–103. doi: <https://doi.org/10.1111/j.1749-6632.2010.05627.x>
77. Civitarese AE, Carling S, Heilbronn LK, Hulver MH, Ukropcova B, Deutsch WA, *et al.* Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS Med.* 2007;4(3):485–94. doi: <https://doi.org/10.1371/journal.pmed.0040076>
78. Jia D, Tian Z, Wang R. Exercise mitigates age-related metabolic diseases by improving mitochondrial dysfunction. *Ageing Res Rev.* 2023;91102087. doi: <https://doi.org/10.1016/j.arr.2023.102087>
79. Lee H, Hong Y, Kim M. Structural and functional changes and possible molecular mechanisms in aged skin. *Int J Mol Sci.* 2021;22(22):12489. doi: <https://doi.org/10.3390/ijms222212489>
80. Sugimoto M, Yamashita R, Ueda M. Telomere length of the skin in association with chronological aging and photoaging. *J Dermatol Sci.* 2006;43(1):43–7. doi: <https://doi.org/10.1016/j.jdermsci.2006.02.004>
81. Birch J, Barnes PJ, Passos JF. Mitochondria, telomeres and cell senescence: implications for lung ageing and disease [Internet]. *Pharmacol Ther Internet.* 2018;183:34–49. Available from: <https://pubmed.ncbi.nlm.nih.gov/28987319/>
82. Steenvoorden DPT, Beijersbergen Van Henegouwen GMJ. The use of endogenous antioxidants to improve photoprotection. *J Photochem Photobiol B Biol.* 1997;41(1-2):1–10. doi: [https://doi.org/10.1016/S1011-1344\(97\)00081-X](https://doi.org/10.1016/S1011-1344(97)00081-X)
83. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev.* 2020;59:101036. doi: <https://doi.org/10.1016/j.arr.2020.101036>
84. Hayflick L. The limited *in vitro* lifetime of human diploid cell strains. *Exp Cell Res.* 1965;37(3):614–36. doi: [https://doi.org/10.1016/0014-4827\(65\)90211-9](https://doi.org/10.1016/0014-4827(65)90211-9)
85. Fitsiou E, Pulido T, Campisi J, Alimirah F, Demaria M. Cellular senescence and the senescence-associated secretory phenotype as drivers of skin photoaging [Internet]. *J Invest Dermatol.* 2021;141(4S):1119–26. Available from: <https://pubmed.ncbi.nlm.nih.gov/33349436/>
86. Wlaschek M, Maity P, Makrantonaki E, Scharffetter-Kochanek K. Connective tissue and fibroblast senescence in skin aging. *J Invest Dermatol.* 2021;141(4):985–92. doi: <https://doi.org/10.1016/j.jid.2020.09.031>
87. Ho CY, Dreesen O. Faces of cellular senescence in skin aging. *Mech Ageing Develop.* 2021;198:111525. doi: <https://doi.org/10.1016/j.mad.2021.111525>
88. Chung JH, Kang S, Varani J, Lin J, Fisher GJ, Voorhees JJ. Decreased extracellular-signal-regulated kinase and increased stress-activated MAP kinase activities in aged human skin *in vivo*. *J Invest Dermatol.* 2000;115(2):177–82. doi: <https://doi.org/10.1046/j.1523-1747.2000.00009.x>
89. Shin SH, Lee YH, Rho NK, Park KY. Skin aging from mechanisms to interventions: focusing on dermal aging. *Front Physiol.* 2023;14:1195272. doi: <https://doi.org/10.3389/fphys.2023.1195272>
90. Quan T, He T, Kang S, Voorhees JJ, Fisher GJ. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor- β type II receptor/smad signaling. *Am J Pathol.* 2004;165(3):741. doi: [https://doi.org/10.1016/S0002-9440\(10\)63337-8](https://doi.org/10.1016/S0002-9440(10)63337-8)

91. Quan T, Xiang Y, Liu Y, Qin Z, Yang Y, Bou-Gharios G, *et al.* Dermal fibroblast CCN1 expression in mice recapitulates human skin dermal aging. *J Invest Dermatol.* 2021;141(4S):1007–6. doi: <https://doi.org/10.1016/j.jid.2020.07.019>
92. He T, Quan T, Shao Y, Voorhees JJ, Fisher GJ. Oxidative exposure impairs TGF- β pathway via reduction of type II receptor and SMAD3 in human skin fibroblasts. *Age (Omaha).* 2014;36(3):1079–94. doi: <https://doi.org/10.1007/s11357-014-9623-6>
93. Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, Van Doorn R, Desmet CJ, *et al.* Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell.* 2008;133(6):1019–31. doi: <https://doi.org/10.1016/j.cell.2008.03.039>
94. Li Y, Xia W, Liu Y, Remmer HA, Voorhees J, Fisher GJ. Solar ultraviolet irradiation induces decorin degradation in human skin likely via neutrophil elastase. *PLoS One.* 2013;8(8):e72563. doi: <https://doi.org/10.1371/journal.pone.0072563>
95. Sharma MR, Mitrani R, Werth VP. Effect of TNF α blockade on UVB-induced inflammatory cell migration and collagen loss in mice. *J Photochem Photobiol B Biol.* 2020;213:112072. doi: <https://doi.org/10.1016/j.jphotobiol.2020.112072>
96. Higuera-Ciapara I, Félix-Valenzuela L, Goycoolea FM. Astaxanthin: a review of its chemistry and applications. *Crit Rev Food Sci Nutr.* 2006;46(2):185–96. doi: <https://doi.org/10.1080/10408690590957188>
97. Hussein G, Sankawa U, Goto H, Matsumoto K, Watanabe H. Astaxanthin, a carotenoid with potential in human health and nutrition. *J Nat Prod.* 2006;69(3):443–9. doi: <https://doi.org/10.1021/np050354+>
98. Lafarga T. Effect of microalgal biomass incorporation into foods: nutritional and sensorial attributes of the end products. *Algal Res.* 2019;41:101566. doi: <https://doi.org/10.1016/j.algal.2019.101566>
99. Molino A, Iovine A, Casella P, Mehriya S, Chianese S, Cerbone A, *et al.* Microalgae characterization for consolidated and new application in human food, animal feed and nutraceuticals. *Int J Environ Res Public Heal.* 2018;15(11):2436. doi: <https://doi.org/10.3390/ijerph15112436>
100. Patel AK, Tambat VS, Chen CW, Chauhan AS, Kumar P, Vadrle AP, *et al.* Recent advancements in astaxanthin production from microalgae: a review. *Bioresour Technol.* 2022;364:128030. doi: <https://doi.org/10.1016/j.biortech.2022.128030>
101. Wayama M, Ota S, Matsuura H, Nango N, Hirata A, Kawano S. Three-dimensional ultrastructural study of oil and astaxanthin accumulation during encystment in the green alga *Haematococcus pluvialis*. *PLoS One.* 2013;8(1):e53618. doi: <https://doi.org/10.1371/journal.pone.0053618>
102. Boussiba S, Vonshak A. Astaxanthin accumulation in the green alga *Haematococcus pluvialis*. *Plant Cell Physiol [Internet].* 1991;32(7):1077–82. doi: <https://doi.org/10.1093/oxfordjournals.pcp.a078171>
103. Damiani MC, Popovich CA, Constenla D, Leonardi PI. Lipid analysis in *Haematococcus pluvialis* to assess its potential use as a biodiesel feedstock. *Bioresour Technol.* 2010;101(11):3801–7. doi: <https://doi.org/10.1093/oxfordjournals.pcp.a078171>
104. Aflalo C, Meshulam Y, Zarka A, Boussiba S. On the relative efficiency of two- vs. one-stage production of astaxanthin by the green alga *Haematococcus pluvialis* [Internet]. *Biotechnol Bioeng Internet.* 2007;98(1):300–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/17318905/>
105. Nishida Y, Berg PC, Shakersain B, Hecht K, Takikawa A, Tao R, *et al.* Astaxanthin: past, present, and future [Internet]. *Mar Drugs Internet.* 2023;21(10):514. Available from: <https://www.mdpi.com/1660-3397/21/10/514/htm>
106. Orosa M, Torres E, Fidalgo P, Abalde J. Production and analysis of secondary carotenoids in green algae [Internet]. *J Appl Phycol.* 2000;12(3–5):553–6. doi: <https://doi.org/10.1023/A:1008173807143>
107. Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. *Mol Nutr Food Res.* 2011;55(1):150–65. doi: <https://doi.org/10.1002/mnfr.201000414>
108. Ide T, Hoya M, Tanaka T, Harayama S. Enhanced production of astaxanthin in *Paracoccus* sp. strain N-81106 by using random mutagenesis and genetic engineering [Internet]. *Biochem Eng J.* 2012;65:37–43. Available from: <https://ui.adsabs.harvard.edu/abs/2012BioEJ.65.37I/abstract>
109. Hayashi M, Ishibashi T, Kuwahara D, Hirasawa K. Commercial production of astaxanthin with *Paracoccus carotinifaciens*. *Adv Exp Med Biol [Internet].* 2021;1261:11–20. Available from: https://link.springer.com/chapter/10.1007/978-981-15-7360-6_2
110. Kim SH, Kim JH, Lee BY, Lee PC. The astaxanthin dideoxyglycoside biosynthesis pathway in *Sphingomonas* sp. PB304 [Internet]. *Appl Microbiol Biotechnol.* 2014;98(24):9993–10003. Available from: <https://pubmed.ncbi.nlm.nih.gov/25193422/>
111. Nutakor C, Kanwugu ON, Kovaleva EG, Glukhareva TV. Enhancing astaxanthin yield in *Phaffia rhodozyma*: current trends and potential of phytohormones [Internet]. *Appl Microbiol Biotechnol.* 2022;106(9–10):3531–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/35579685/>
112. Yamamoto K, Hara KY, Morita T, Nishimura A, Sasaki D, Ishii J, *et al.* Enhancement of astaxanthin production in *Xanthophyllomyces dendrorhous* by efficient method for the complete deletion of genes [Internet]. *Microb Cell Fact.* 2016;15(1):1–8. doi: <https://doi.org/10.1186/s12934-016-0556-x>
113. Rammuni MN, Ariyadasa TU, Nimarshana PHV, Attalage RA. Comparative assessment on the extraction of carotenoids from microalgal sources: astaxanthin from *H. pluvialis* and β -carotene from *D. salina*. *Food Chem.* 2019;277:128–34. doi: <https://doi.org/10.1016/j.foodchem.2018.10.066>
114. Ruen-ngam D, Shotipruk A, Pavasant P. Comparison of extraction methods for recovery of astaxanthin from *Haematococcus pluvialis*. *Sep Sci Technol.* 2011;46(1):64–70. doi: <https://doi.org/10.1080/01496395.2010.493546>
115. Zhu HZ, Jiang S, Wu JJ, Zhou XR, Liu PY, Huang FH, *et al.* Production of high levels of 3S,3'S-Astaxanthin in *Yarrowia lipolytica* via iterative metabolic engineering. *J Agric Food Chem.* 2022;70(8):2673–83. doi: <https://doi.org/10.1021/acs.jafc.1c08072>
116. Khoo KS, Lee SY, Ooi CW, Fu X, Miao X, Ling TC, *et al.* Recent advances in biorefinery of astaxanthin from *Haematococcus pluvialis*. *Bioresour Technol.* 2019;288:121606. doi: <https://doi.org/10.1016/j.biortech.2019.121606>
117. Sarada R, Vidhyavathi R, Usha D, Ravishankar GA. An efficient method for extraction of astaxanthin from green alga *Haematococcus pluvialis*. *J Agric Food Chem.* 2006;54(20):7585–8. doi: <https://doi.org/10.1021/jf060737t>
118. Mendes-Pinto MM, Raposo MFJ, Bowen J, Young AJ, Morais R. Evaluation of different cell disruption processes on encysted cells of *Haematococcus pluvialis*: effects on astaxanthin recovery and implications for bio-availability. *J Appl Phycol.* 2001;13(1):19–24. doi: <https://doi.org/10.1023/A:1008183429747>
119. Dong S, Huang Y, Zhang R, Wang S, Liu Y. Four different methods comparison for extraction of astaxanthin from green alga *Haematococcus pluvialis*. *Sci World J.* 2014;2014:1–7. doi: <https://doi.org/10.1155/2014/694305>
120. Sachindra NM, Mahendrakar NS. Process optimization for extraction of carotenoids from shrimp waste with vegetable oils. *Bioresour Technol.* 2005;96(10):1195–200. doi: <https://doi.org/10.1016/j.biortech.2004.09.018>
121. Zhou D, Fei Z, Liu G, Jiang Y, Jiang W, Lin CSK, *et al.* The bioproduction of astaxanthin: a comprehensive review on the microbial synthesis and downstream extraction. *Biotechnol Adv.* 2024;74:108392. doi: <https://doi.org/10.1016/j.biotechadv.2024.108392>

122. Pitacco W, Samori C, Pezzolesi L, Gori V, Grillo A, Tiecco M, *et al.* Extraction of astaxanthin from *Haematococcus pluvialis* with hydrophobic deep eutectic solvents based on oleic acid. *Food Chem.* 2022;379:132156. doi: <https://doi.org/10.1016/j.foodchem.2022.132156>.
123. Jaime L, Rodríguez-Meizoso I, Cifuentes A, Santoyo S, Suarez S, Ibáñez E, *et al.* Pressurized liquids as an alternative process to antioxidant carotenoids' extraction from *Haematococcus pluvialis* microalgae. *LWT - Food Sci Technol.* 2010;43(1):105–12. doi: <https://doi.org/10.1016/j.lwt.2009.06.023>
124. Nobre B, Marcelo F, Passos R, Beirão L, Palavra A, Gouveia L, *et al.* Supercritical carbon dioxide extraction of astaxanthin and other carotenoids from the microalga *Haematococcus pluvialis*. *Eur Food Res Technol.* 2006;223(6):787–90.
125. Ghafoor K, Choi YH, Jeon JY, Jo IH. Optimization of ultrasound-assisted extraction of phenolic compounds, antioxidants, and anthocyanins from grape (*Vitis vinifera*) seeds. *J Agric Food Chem.* 2009;57(11):4988–94. doi: <https://doi.org/10.1021/jf9001439>
126. Radzali SA, Masturah M, Baharin BS, Rashidi O, Rahman RA. Optimisation of supercritical fluid extraction of astaxanthin from *Panaeus monodon* waste using ethanol-modified carbon dioxide. *J Eng Sci Technol.* 2016;11(5):722–36. doi: <https://doaj.org/article/f2404c7f8cf34f4798c08e01870ddd76>
127. Bouras M, Chadni M, Barba FJ, Grimi N, Bals O, Vorobiev E. Optimization of microwave-assisted extraction of polyphenols from *Quercus* bark. *Ind Crops Prod.* 2015;77:590–601. doi: <https://doi.org/10.1016/j.indcrop.2015.09.018>
128. Mandal V, Mandal SC. Design and performance evaluation of a microwave based low carbon yielding extraction technique for naturally occurring bioactive triterpenoid: oleanolic acid. *Biochem Eng J.* 2010;50(1–2):63–70. doi: <https://doi.org/10.1016/j.bej.2010.03.005>
129. Vakarelova M, Zanoni F, Donà G, Fierri I, Chignola R, Gorrieri S, *et al.* Microencapsulation of astaxanthin by ionic gelation: effect of different gelling polymers on the carotenoid load, stability and bioaccessibility. *Int J Food Sci Technol.* 2023;58(5):2489–97. doi: <https://doi.org/10.1111/1541-4337.12253>
130. Ameer K, Shahbaz HM, Kwon JH. Green extraction methods for polyphenols from plant matrices and their byproducts: a review. *Compr Rev Food Sci Food Saf.* 2017;16(2):295–315. doi: <https://doi.org/10.1016/j.bej.2010.03.005>
131. Rodríguez-Rojo S, Visentin A, Maestri D, Cocero MJ. Assisted extraction of rosemary antioxidants with green solvents. *J Food Eng.* 2012;109(1):98–103. doi: <https://doi.org/10.1016/j.jfoodeng.2011.09.029>
132. Dewati PR, Rochmadi, Rohman A, Yuliestyan A, Budiman A. Equilibrium modeling of astaxanthin extraction from *Haematococcus pluvialis*. *Indones J Chem.* 2021;21(3):554–63. doi: <https://doi.org/10.22146/ijc.56965>
133. Pawliszyn J. Kinetic model of supercritical fluid extraction. *J Chromatogr Sci.* 1993;31(1):31–7. doi: <https://doi.org/10.1093/chromsci/31.1.31>
134. Williams JR, Clifford AA, Al-Saidi SHR. Supercritical fluids and their applications in biotechnology and related areas. *Mol Biotechnol.* 2002;22(3):263–86. doi: <https://doi.org/10.1385/MB:22:3:263>
135. Herrero M, Cifuentes A, Ibanes E. Sub- and supercritical fluid extraction of functional ingredients from different natural sources: plants, food-by-products, algae and microalgae: a review. *Food Chem.* 2006;98(1):136–48. doi: <https://doi.org/10.1016/j.foodchem.2005.05.058>
136. Wang L, Yang B, Yan B, Yao X. Supercritical fluid extraction of astaxanthin from *Haematococcus pluvialis* and its antioxidant potential in sunflower oil. *Innov Food Sci Emerg Technol* [Internet]. 2012;13:120–7. doi: <https://doi.org/10.1016/j.ifset.2011.09.004>
137. Saini RK, Keum YS. Carotenoid extraction methods: a review of recent developments. *Food Chem.* 2018;240:90–103. doi: <https://doi.org/10.1016/j.foodchem.2017.07.099>
138. Ahn Y, Bae SJ, Kim M, Cho SK, Baik S, Lee JI, *et al.* Review of supercritical CO₂ power cycle technology and current status of research and development. *Nucl Eng Technol.* 2015;47(6):647–1. doi: <https://doi.org/10.1016/j.net.2015.06.009>
139. Reyes FA, Mendiola JA, Ibañez E, Del Valle JM. Astaxanthin extraction from *Haematococcus pluvialis* using CO₂-expanded ethanol. *J Supercrit Fluids.* 2014;92:75–83. doi: <https://doi.org/10.1016/j.supflu.2014.05.013>
140. Cheng X, Qi Z, Burdyny T, Kong T, Sinton D. Low pressure supercritical CO₂ extraction of astaxanthin from *Haematococcus pluvialis* demonstrated on a microfluidic chip. *Bioresour Technol.* 2018;250:481–5. doi: <https://doi.org/10.1016/j.biortech.2017.11.070>
141. Bakshi RA, Sodhi NS, Wani IA, Khan ZS, Dhillon B, Gani A. Bioactive constituents of saffron plant: extraction, encapsulation and their food and pharmaceutical applications. *Appl Food Res.* 2022;2(1):100076. doi: <https://doi.org/10.1016/j.afres.2022.100076>
142. Nawaz H, Shad MA, Rehman N, Andaleeb H, Ullah N. Effect of solvent polarity on extraction yield and antioxidant properties of phytochemicals from bean (*Phaseolus vulgaris*) seeds. *Braz J Pharm Sci.* 2020;56:17129. doi: <https://doi.org/10.1590/s2175-97902019000417129>
143. Reoul E. Mechanisms of carotenoid intestinal absorption: where do we stand? [Internet]. *Nutrients.* 2019;11(4):838. Available from: <https://pubmed.ncbi.nlm.nih.gov/31013870/>
144. Visioli F, Artaria C. Astaxanthin in cardiovascular health and disease: mechanisms of action, therapeutic merits, and knowledge gaps [Internet]. *Food Funct Internet.* 2017;8(1):39–63. Available from: <https://pubmed.ncbi.nlm.nih.gov/27924978/>
145. Barros MP, Marin DP, Bolin AP, De Cássia Santos Macedo R, Campoio TR, Fineto C, *et al.* Combined astaxanthin and fish oil supplementation improves glutathione-based redox balance in rat plasma and neutrophils. *Chem Biol Interact.* 2012;197(1):58–67. doi: <https://doi.org/10.1016/j.cbi.2012.03.005>
146. Otton R, Marin DP, Bolin AP, De Cássia Santos Macedo R, Campoio TR, Fineto C, *et al.* Combined fish oil and astaxanthin supplementation modulates rat lymphocyte function. *Eur J Nutr.* 2012;51(6):707–18. doi: <https://doi.org/10.1007/s00394-011-0250-z>
147. Wang J, Liu S, Wang H, Xiao S, Li C, Li Y, *et al.* *Xanthophyllomyces dendrorhous*-derived astaxanthin regulates lipid metabolism and gut microbiota in obese mice induced by a high-fat diet. *Mar Drugs.* 2019;17(6):337. doi: <https://doi.org/10.3390/md17060337>
148. Thakur N. Natural origins, bioavailability, and therapeutic potential of astaxanthin: a systematic review across diverse health applications. *Afr J Biomed Res.* 2024;27(3):5929–39. doi: <https://doi.org/10.53555/AJBR.v27i3S.3453>
149. Honda M, Kamizono S, Illijas MI, Nakamura T. Effect of feeding astaxanthin with different E/Z-isomer ratios on astaxanthin accumulation in Pacific white shrimp *Litopenaeus vannamei* [Internet]. *Eur J Lipid Sci Technol Internet.* 2023;125(12):2300173. doi: <https://doi.org/10.1002/ejlt.202300173>
150. Yu W, Liu J. Astaxanthin isomers: selective distribution and isomerization in aquatic animals [Internet]. *Aquaculture.* 2020;520:734915. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0044848619324421?via%3Dihub>
151. Medoro A, Davinelli S, Milella L, Willcox B, Allsopp R, Scapagnini G, *et al.* Dietary astaxanthin: a promising antioxidant and anti-inflammatory agent for brain aging and adult neurogenesis. *Mar Drugs.* 2023;21(12):1–17. doi: <https://doi.org/10.3390/md21120643>
152. Katagiri M, Satoh A, Tsuji S, Shirasawa T. Effects of astaxanthin-rich *Haematococcus pluvialis* extract on cognitive function: a randomised, double-blind, placebo-controlled study. *J Clin Biochem Nutr.* 2012;51(2):102–7. doi: <https://doi.org/10.3164/jcbn.D-11-00017>
153. Mercke Odeberg J, Lignell A, Pettersson A, Höglund P. Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations. *Eur J Pharm*

- Sci. 2003;19(4):299–304. doi: [https://doi.org/10.1016/S0928-0987\(03\)00135-0](https://doi.org/10.1016/S0928-0987(03)00135-0)
154. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol.* 2012;2(2):1143–211. doi: <https://doi.org/10.1002/j.2040-4603.2012.tb00425.x>
 155. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, *et al.* Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature.* 2012;481(7382):511–5. doi: <https://doi.org/10.1038/nature10758>
 156. Valenzuela PL, Ortiz-Alonso J, Bustamante-Ara N, Vidán MT, Rodríguez-Romo G, Mayordomo-Cava J, *et al.* Individual responsiveness to physical exercise intervention in acutely hospitalized older adults. *J Clin Med.* 2020;9(3):797. doi: <https://doi.org/10.3390/jcm9030797>
 157. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JPE. Polyphenols and human health: prevention of disease and mechanisms of action. *Nutrients.* 2010;2(11):1106. doi: <https://doi.org/10.3390/nu2111106>
 158. Trichopoulou A, Bamia C, Lagiou P, Trichopoulos D. Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. *Am J Clin Nutr.* 2010;92(3):620–5. doi: <https://doi.org/10.3945/ajcn.2010.29619>
 159. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metab.* 2014;19(2):181–92. doi: <https://doi.org/10.1016/j.cmet.2013.12.008>
 160. Epel E, Daubenmier J, Moskowitz JT, Folkman S, Blackburn E. Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. *Ann N Y Acad Sci.* 2009;1172:34. doi: <https://doi.org/10.1111/j.1749-6632.2009.04414.x>
 161. Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann N Y Acad Sci.* 2016;1373(1):13–24. doi: <https://doi.org/10.1111/nyas.12998>
 162. Kirkland JL, Tchkonja T. Cellular senescence: a translational perspective [Internet]. *EBioMedicine Internet.* 2017;21:21–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/28416161/>
 163. Imai SI, Guarente L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol.* 2014;24(8):464. doi: <https://doi.org/10.1016/j.tcb.2014.04.002>
 164. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease [Internet]. *Cell Internet.* 2017;168(6):960–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/28283069/>
 165. Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges [Internet]. *Cell Stem Cell.* 2015;17(1):11–22. Available from: <https://pubmed.ncbi.nlm.nih.gov/26140604/>
 166. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, *et al.* Resveratrol improves health and survival of mice on a high-calorie diet [Internet]. *Nature.* 2006;444(7117):337–42. Available from: <https://pubmed.ncbi.nlm.nih.gov/17086191/>
 167. Cole GM, Teter B, Frautschy SA. Neuroprotective effects of curcumin. *Adv Exp Med Biol.* 2007;595:197–212. Available from: <https://pubmed.ncbi.nlm.nih.gov/17569212/>
 168. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, *et al.* Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol.* 2017;174(11):1325–48. doi: <https://doi.org/10.1111/bph.13621>
 169. Yazaki K, Yoshikoshi C, Oshiro S, Yanase S. Supplemental cellular protection by a carotenoid extends lifespan via Ins/IGF-1 signaling in *Caenorhabditis elegans*. *Oxid Med Cell Longev.* 2011;2011:1–9. doi: <https://doi.org/10.1155/2011/596240>
 170. Tominaga K, Hongo N, Karato M, Yamashita E. Cosmetic benefits of astaxanthin on humans subjects. *Acta Biochim Pol.* 2012;59(1):43–7. doi: https://doi.org/10.18388/abp.2012_2168
 171. Astaxanthin | Eye Health | AOR Inc. Canada [Internet]. [cited 2025 Mar 4]. Available from: https://aor.ca/fr/ingredients/astaxanthin-haematococcus-pluvialis/?srsltid=AfmBOoqwTDYHPScPtdt_SAK_FMIrEWzGopbpGBVW5LFN4RbAUzZmxyr
 172. Nutrigold Astaxanthin Gold - Azure Standard [Internet]. [cited 2025 Mar 4]. Available from: <https://www.azurestandard.com/shop/product/nutritional-supplements/natural-supplements/astaxanthin/softgels/astaxanthin-gold/30546>
 173. EyeScience Astaxanthin 12 mg | Basic Brands Inc. [Internet]. [cited 2025 Mar 4]. Available from: https://basicbrandsinc.com/products/eyescience-astaxanthin-12-mg?srsltid=AfmBOoo164hpfEDoY2_m d C r a t u m R B A D X F 7 c 3 1 Q r D C x y Y c J 3 2 - m5K0q2X&variant=47463208059179
 174. BioAstin – Nutrex Hawaii [Internet]. [cited 2025 Mar 4]. Available from: <https://www.nutrex-hawaii.com/pages/bioastin?srsltid=AfmBOOpEgi6ypOAxrhpGfhVTUUY5vzunGhMYO9k9nHOawxOT4ME3j-v>
 175. Dr. Mercola, Astaxanthin, 12 mg, 30 Capsules [Internet]. [cited 2025 Mar 4]. Available from: https://ml.iherb.com/pr/dr-mercola-astaxanthin-12-mg-30-capsules/84639?srsltid=AfmBOoQsQW8UsDyO7Qrk-S7_H_nfwxUykgWrtxq2O-X5SPI2L15PtB5
 176. Natural Hawaiian Astaxanthin 4mg + VITAMIN E • NAXA Verified • 60 CAPS – OX Nature [Internet]. [cited 2025 Mar 4]. Available from: <https://www.oxnature.com/products/astaxantina-natural-havaiana-4mg-vitamina-e-naxa-verified-60-capsulas-vegan-softgel>
 177. Natural Astaxanthin 5 mg Softgels | Beauty | Solgar [Internet]. [cited 2025 Mar 4]. Available from: <https://www.solgar.com/products/natural-astaxanthin-5-mg-softgels/>
 178. Cheng XY, Xiong YJ, Yang MM, Zhu MJ. Preparation of astaxanthin mask from *Phaffia rhodozyma* and its evaluation. *Process Biochem.* 2019;79:195–202. doi: <https://doi.org/10.1016/j.procbio.2018.12.027>
 179. Krestinin R, Baburina Y, Odinkova I, Kruglov A, Sotnikova L, Krestinina O. The effect of astaxanthin on mitochondrial dynamics in rat heart mitochondria under ISO-induced injury. *Antioxidants.* 2023;12(6):1247. doi: <https://doi.org/10.3390/antiox12061247>
 180. Wolf AM, Asoh S, Hiranuma H, Ohsawa I, Iio K, Satou A, *et al.* Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress. *J Nutr Biochem.* 2010;21(5):381–9. doi: <https://doi.org/10.1016/j.jnutbio.2009.01.011>
 181. Yeh PT, Huang HW, Yang CM, Yang WS, Yang CH. Astaxanthin inhibits expression of retinal oxidative stress and inflammatory mediators in Streptozotocin-Induced diabetic rats. *PLoS One.* 2016;11(1):146438. doi: <https://doi.org/10.1371/journal.pone.0146438>
 182. Ranjbar S, Emamjomeh A, Sharifi F, Zarepour A, Aghaabbasi K, Dehshahri A, *et al.* Lipid-based delivery systems for flavonoids and flavonolignans: liposomes, nanoemulsions, and solid lipid nanoparticles [Internet]. *Pharmaceutics Internet.* 2023;15(7):1944. Available from: <https://www.mdpi.com/1999-4923/15/7/1944/htm>
 183. Chucair AJ, Rotstein NP, Sangiovanni JP, During A, Chew EY, Politi LE. Lutein and zeaxanthin protect photoreceptors from apoptosis induced by oxidative stress: relation with docosahexaenoic acid. *Invest Ophthalmol Vis Sci.* 2007;48(11):5168–77. doi: <https://doi.org/10.1167/iovs.07-0037>

How to cite this article:

Nazri RYM, Teh LK, Hazalin NAMN, Seow LJ, Seow EK. Astaxanthin as an anti-aging agent: Extraction, mechanisms, and therapeutic potential. *J Appl Pharm Sci.* 2026;16(04):028-051. DOI: 10.7324/JAPS.2026.234783