

Astaxanthin in metabolic control: From regulatory mechanisms to therapeutic prospects

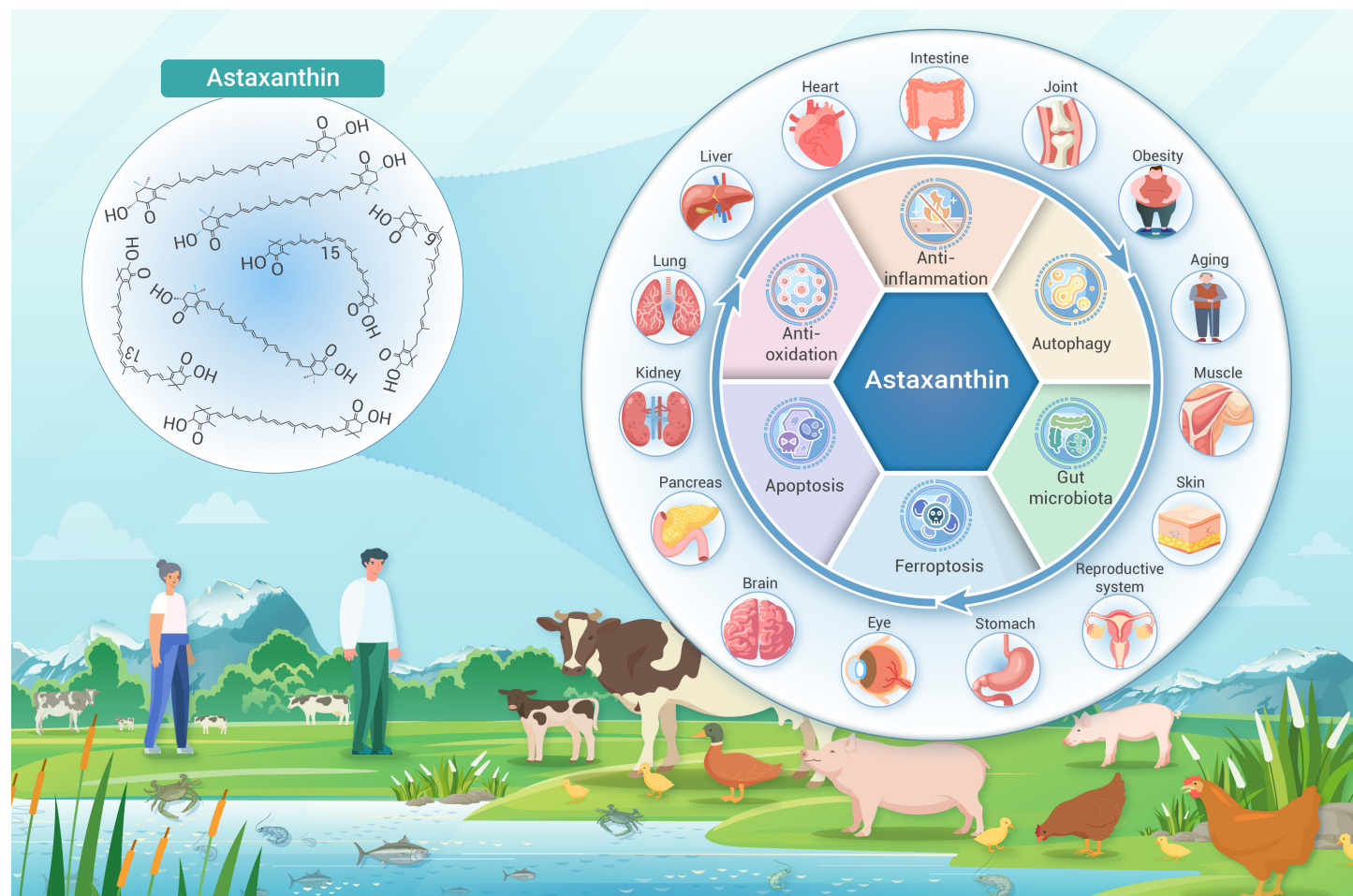
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Describe structures giving astaxanthin (AST) super-antioxidant activity and their functional differences.
- Highlight how AST regulates oxidative stress, inflammation, autophagy, apoptosis, ferroptosis, and microbes.
- Prospect AST use during key stages of healthy development in humans and animals.

Astaxanthin in metabolic control: From regulatory mechanisms to therapeutic prospects

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Astaxanthin, a naturally occurring exogenous antioxidant, possesses a unique molecular structure defined by conjugated double bonds and polar end groups, giving it unparalleled antioxidant capacity - exceeding β -carotene and α -tocopherol by orders of magnitude. Notably, astaxanthin surpasses traditional antioxidants not only in radical scavenging potency, but also in multiple metabolic modulating effects. Accumulating evidence confirms that dietary astaxanthin accumulates in intestinal tissues and the systemic circulation, where it orchestrates cellular signaling pathways to restore homeostasis under pathophysiological stress. Despite the well-established broad-spectrum bioactivities of astaxanthin, the multi-target regulatory mechanisms underlying its metabolic modulation remain incompletely elucidated. This review systematically unravels the structure-activity relationships that govern astaxanthin's biological potency, focusing on the mechanisms by which astaxanthin regulates oxidative stress, inflammation, autophagy, apoptosis, ferroptosis and gut microbiota-host interactions via metabolically activated molecular signaling during critical windows of health development in humans and animals. A deeper understanding of astaxanthin's mechanisms may pave the way for improved astaxanthin-based interventions in the future, ultimately advancing health management and prevention strategies.

INTRODUCTION

Humans and most animals cannot synthesize astaxanthin and thus must obtain it from food. Two main types of commercially available astaxanthin have been approved for human and animal use: (1) the synthetic form derived from petroleum via chemical synthesis,^{1,2} and (2) the natural variant biosynthesized by microalgae, fungi (yeasts), bacteria, or accumulated in seafood, such as salmon, trout, krill, shrimp and lobster.³ The results of recent animal experiments and clinical trials have led to an increased awareness of the advantages of astaxanthin in maintaining normal physiological processes and preventing and treating various diseases, including gastrointestinal, cardiovascular, and neurodegenerative diseases, as well as metabolic disorders associated with obesity and aging.^{4,5} Previous research has demonstrated that astaxanthin functions as a cellular antioxidant regulator, exhibiting distant structures and sources that determine its specific applications and capacity to scavenge free radicals.⁶ Recent studies have also indicated that astaxanthin metabolism is broadly associated with functional modifications, including anti-apoptotic and anti-inflammatory effects, autophagy, and microbiota modulation. A recent study confirmed that astaxanthin could guard against oxidative stress by regulating mammalian target of rapamycin (mTOR) activation and inhibiting inflammatory cytokine secretion in an effusive otitis media model.⁷

Although current reviews on the properties of astaxanthin are quite comprehensive, certain limitations remain. In particular, these reviews tend to ignore the effects of different astaxanthin isomers on target organ selectivity, and most focus on a single function or mechanism of action, ignoring the

intricate relationships between multiple functions and mechanisms. For example, astaxanthin enhances autophagy while inhibiting oxidative stress and apoptosis in a spinal cord injury model,⁸ whereas it can induce reactive oxygen species (ROS)-dependent apoptosis and block protective autophagy in a liver injury model.⁹ The differential modulation of oxidative stress, apoptosis and autophagy highlights the need to further explore the interactions between the multiple functions and mechanisms of action of astaxanthin. Therefore, we briefly describe the structural features that determine the bioactivity of astaxanthin and the physiological functions of its different isomers. Our review then focuses on the mechanisms by which astaxanthin regulates oxidative stress, inflammation, autophagy, apoptosis, ferroptosis, and gut microbial-host interactions through metabolic activation of molecular signaling during critical windows of health development in humans and animals.

ASTAXANTHIN STRUCTURAL CHARACTERISTICS

Molecular architecture and functional group disposition

Astaxanthin is chemically designated 3,3'-dihydroxy- β , β '-carotene-4,4'-dione, has the molecular formula $C_{40}H_{52}O_4$, and presents a molecular weight of 596.84 g/mol.² Structurally, the astaxanthin molecule consists of a nonpolar core with multiple conjugated unsaturated double bonds flanked by a polar six-membered ring structure decorated with hydroxyl (OH) and keto (C=O) groups.¹⁰ The unsaturated double bonds present in astaxanthin enable it to donate electrons, thus facilitating its interaction with free radicals and its power to neutralize ROS.² Furthermore, the structure of the conjugated double bonds makes astaxanthin hydrophobic and gives it a distinct orange-red color.¹⁰ The existence of a greater amount of conjugated unsaturated double bonds confers astaxanthin with antioxidant power approximately 40 and 100 times higher than that of β -carotene and α -tocopherol, respectively.³ In addition, astaxanthin presents three different optical isomers, including a pair of enantiomers (3S, 3'S and 3R, 3'R) and a mesoscopic form (3R, 3'S) (Figure 1).¹¹ Furthermore, astaxanthin can be classified into two geometrical isomer configurations, namely, trans (E-) and cis (Z-) geometrical isomers, owing to the presence of cis- or trans-coupled double bonds in its molecular structure (Figure 1).¹²

Astaxanthin isomer-specific bioactivity profiles and tissue tropism

Astaxanthin typically exists as isomer mixtures,¹³ with bioactivity divergences primarily manifesting in antioxidant potency, bioavailability, and tissue-specific accumulations (Figure 2). Cis (Z-) astaxanthin has a higher single linear oxygen (1O_2) quenching capacity than all-trans (E-) astaxanthin, whereas optical isomers (3S, 3'S vs 3R, 3'R) display comparable singlet oxygen (1O_2) quenching capacity.¹² Astaxanthin is susceptible to oxidation and is commonly found in the form of more stable and bioavailable astaxanthin esters. Increasing the carbon chain length and decreasing the degree of unsaturation of fatty acids increases the stability of astaxanthin in the astaxanthin ester, but decreases its bioavailability.¹⁴ Studies have shown that cis

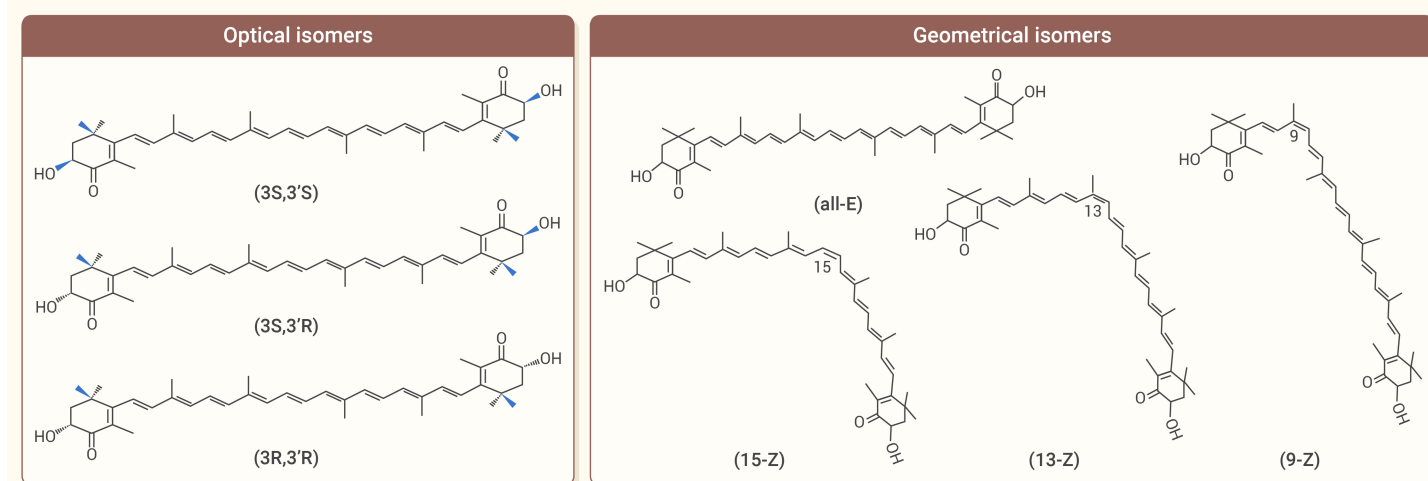


Figure 1. Structure of astaxanthin Astaxanthin shows optical isomers from varied hydroxyl (-OH) attachments to chiral carbons at C3 and C3' of its hexacyclic rings: (3S, 3'S), (3R, 3'R) enantiomers, and meso (3R, 3'S). The molecular structure of astaxanthin contains both cis and trans double bonds, giving rise to cis and trans isomers. Common forms include the all-trans (all-T) and 9-cis (9-Z), 13-cis (13-Z), 15-cis (15-Z) isomers with cis bonds at C9, C13, C15.

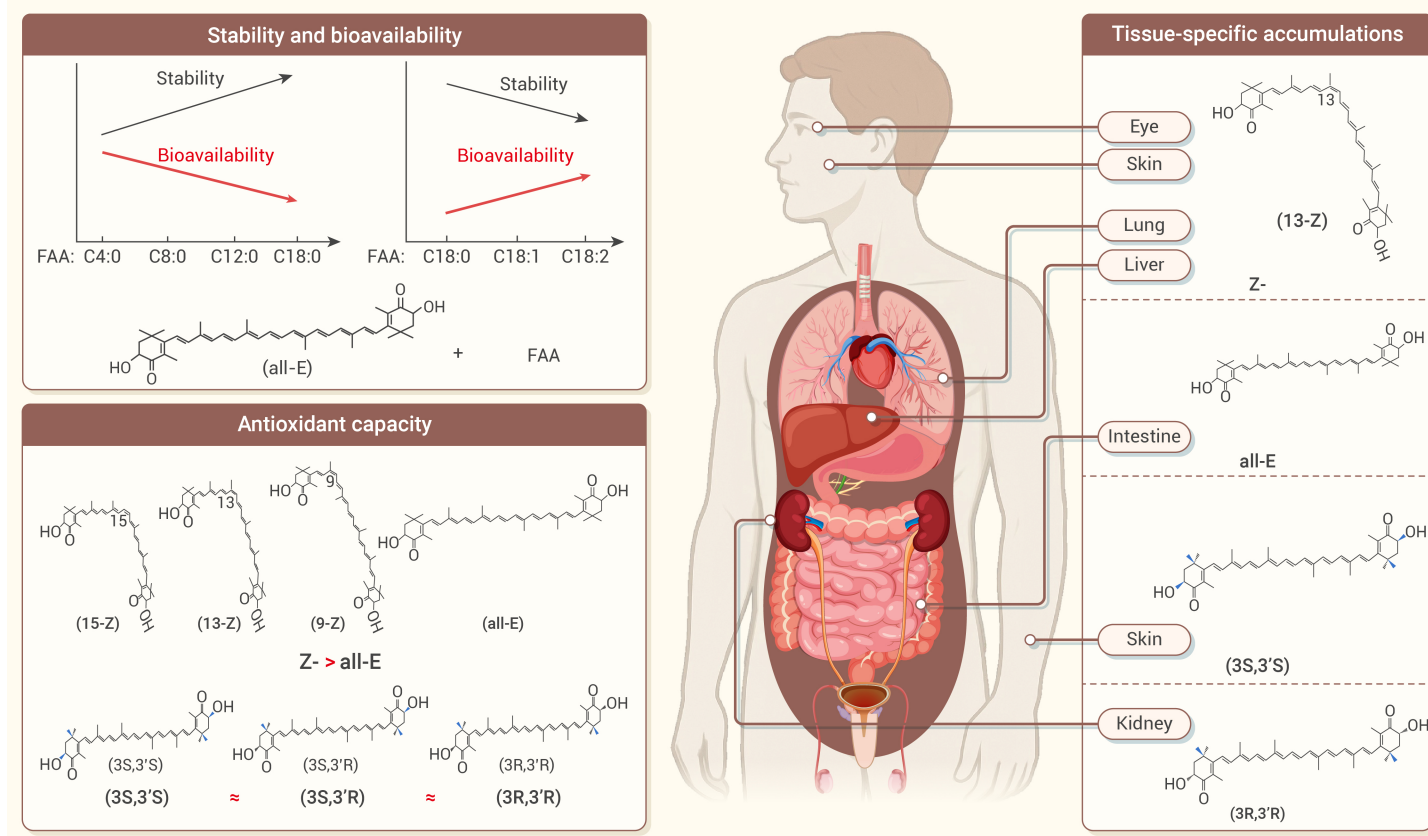


Figure 2. Astaxanthin isomer-specific bioactivity profiles and tissue tropism Stability of astaxanthin esters increases with fatty acid chain length, but bioavailability decreases; stability decreases and bioavailability increases with increased unsaturation of the fatty acid chain. Cis-astaxanthin (Z-) exhibits superior singlet oxygen quenching capacity compared to all-trans (E-) isomers, while show equivalent antioxidant capacity. Cis-isomers (e.g., 13Z-) display enhanced bioavailability and tissue-specific accumulation (skin, lung, prostate, eye), whereas all-E isomers dominate intestinal enrichment; the optical isomers 3S,3'S and 3R,3'R predominate in the skin and kidney, respectively.

(Z-) astaxanthin isomers have significant advantages in bioavailability and tissue (skin, lung, prostate, eye, etc.) accumulation efficiency over the all-trans (all-E) isomers, with the tissue-targeted accumulation characteristics of the 13Z- isomer being particularly prominent.¹⁵ Furthermore, astaxanthin isomers in *Oncorhynchus mykiss* exhibited a dual tissue-selective distribution of geometric and optical isomers: the all-E-isomer was predominantly enriched in the intestine, the 13Z-isomer was significantly elevated in the liver, while the skin and posterior kidney showed a 2:1 and 3:1 ratio preference for the (3S, 3'S) and (3R, 3'R) isomers, respectively, with this distribution pattern maintaining independent correlation to dietary isomer composition.¹⁶

Multi-omics evidence reveals a fourfold bioavailability advantage of natural astaxanthin (e.g., *H. pluvialis*) over synthetic counterparts, with distinct metabolic activation pathways – synthetic forms enhance antioxidant capacity via arachidonic acid pathway activation through carotenoid feedback inhibition, whereas natural isomers boost mitochondrial oxidative phosphorylation to remodel energy metabolism.¹⁷ The mechanisms underlying the distinct bioactivities of astaxanthin isomers remain unclear. However, current evidence suggests that differences in intestinal absorption and transmembrane transport may be important factors.¹⁸ Studies using cell lines and mouse models have shown that Z-isomers of astaxanthin (particularly the 9Z

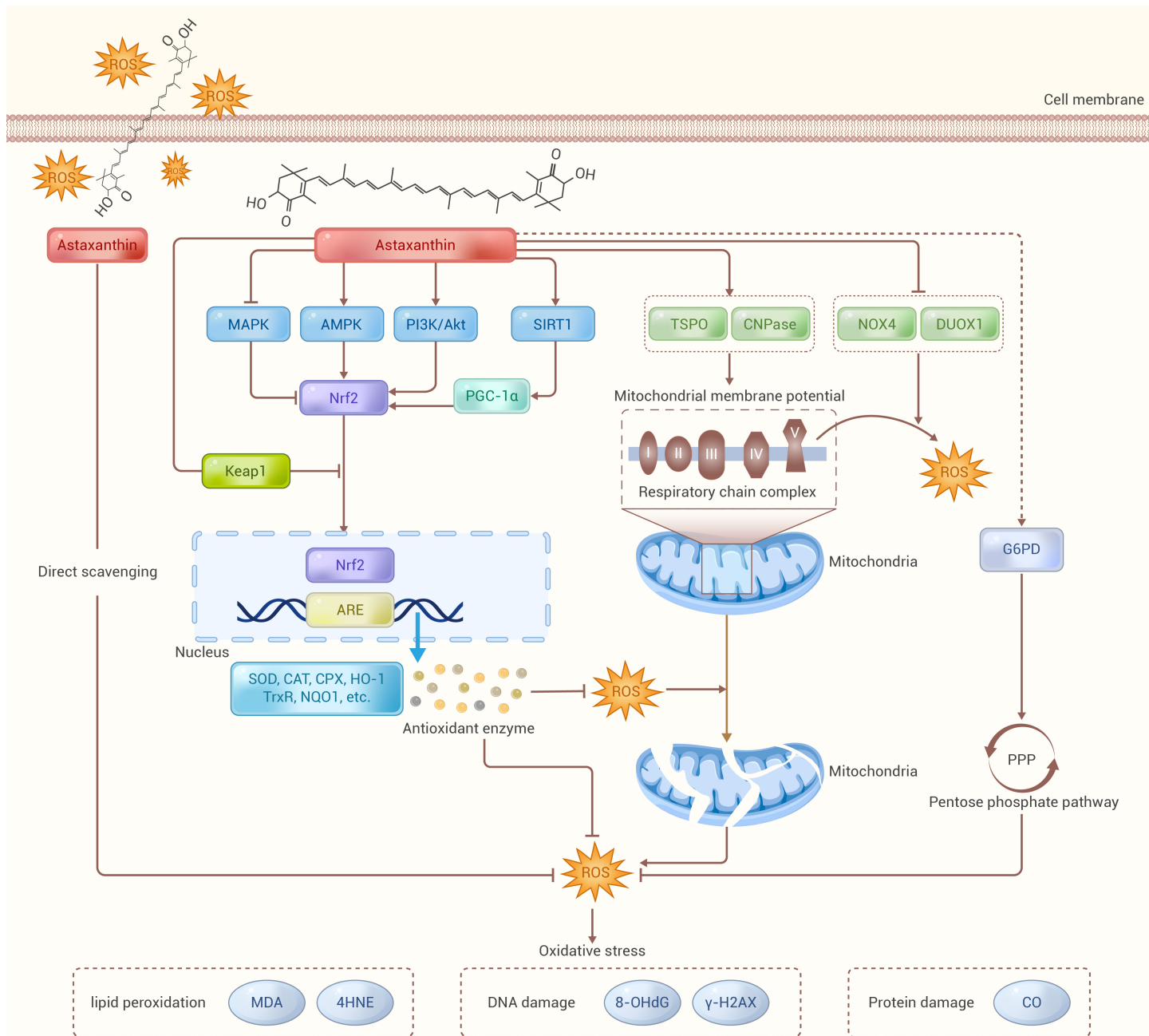


Figure 3. Regulatory mechanisms of astaxanthin on oxidative stress Astaxanthin directly scavenges free radicals, promotes Nrf2-ARE binding to enhance the expression of antioxidant enzymes such as SOD, CAT, and GPX, and activates signaling pathways like MAPK, AMPK, PI3K/Akt, and SIRT1/PGC-1α. Additionally, it stabilizes mitochondrial membranes, protects respiratory chain complexes, inhibits NADPH Oxidase 4 (NOX4) and Dual Oxidase 1 (DUOX1) activity to reduce ROS production, and may enhance antioxidant capacity by regulating the pentose phosphate pathway (PPP). Translocator Protein (TSPO),

isomer) exhibit higher binding affinity to intestinal Cluster of Differentiation 36 compared to the all-E isomer, which results in improved intestinal absorption and transport of the Z-isomers.¹⁹

REGULATORY MECHANISM UNDERLYING METABOLIC CONTROL BY ASTAXANTHIN

Astaxanthin serves as a potent exogenous antioxidant that safeguards the health of both humans and animals upon ingestion. Current interest in using natural and synthetic astaxanthin is focused on its antioxidant properties. Existing studies have also shown that astaxanthin plays an effective role in oxidative stress, inflammation, apoptosis, autophagy, ferroptosis, and gut microbiota by activating signal transducer factors or communicating gut microbial signals across the gut-liver axis.

Alleviated oxidative stress

Several studies have reported that astaxanthin exerts antioxidative effects

by reducing the build-up of excessive ROS and preventing lipid peroxidation, DNA damage, and protein peroxidation caused by various stresses (Figure 3). The antioxidant properties of astaxanthin exhibit a time- and dose-dependent pattern under specific conditions, such as inhibition of oxidative stress associated with ischemia/reperfusion-induced brain damage in rats.²⁰ Astaxanthin reduces the overproduction of cellular ROS to control oxidative stress via three pathways. First, the lipid solubility of astaxanthin gives it the ability to cross the cellular membrane and neutralize free radicals both within and outside the cellular membrane via double-bond electron transfer.²¹ Second, incorporating astaxanthin improves the functionality of endogenous antioxidant enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT).²² For example, Park *et al.*²³ reported that astaxanthin supplementation upregulated SOD1/2 expression and attenuated the levels of DNA damage marker 8-hydroxydeoxyguanosine and lipid peroxidation marker 4-hydroxynonenal in gerbils treated with transient forebrain ischemia for 15 min. Fu *et al.*²⁴ reported that astaxanthin alleviates oxidative

stress by modulating GPX, SOD, and CAT enzymatic activities and decreasing the concentration of malondialdehyde (MDA) in hydrogen peroxide-induced placental trophoblast cells. Third, astaxanthin safeguards mitochondrial function and integrity, regulating the production and consumption of ROS and ATP.²⁵ Stress-induced imbalance in ROS leads to reduced activity of the mitochondrial respiratory chain complex, resulting in excessive ROS production in the mitochondrial electron transport chain.²⁶ Concurrently, disruption of the mitochondrial membrane structure by ROS enhances its permeability, resulting in the release of ROS produced by mitochondria into the cytoplasm.²⁷ Research has shown that astaxanthin increase the activity of the mitochondrial respiratory chain complex and ATPase during oxidative stress and protect membrane permeability by maintaining normal levels of 2', 3'-cyclic nucleotide 3'-phosphodiesterase and mitochondrial transporter proteins.²⁸ Additionally, Astaxanthin also reduces ROS production in the mitochondrial respiratory chain by inhibiting the expression of NADPH oxidase 4 and NADPH oxidase Dual Oxidase 1.²⁹

Furthermore, previous research has established that astaxanthin activates the nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway, a key player in reducing ROS levels and alleviating oxidative stress. In the cytoplasm, Kelch-like ECH-associated protein-1 (Keap1) can bind to Nrf2 via E3 ubiquitin ligase, leading to the inactivation and degradation of Nrf2.³ Astaxanthin has also been demonstrated to elevate Nrf2 levels by competitively binding to Keap1, resulting in the inactivation of Keap1 and translocation of Nrf2 from the cytoplasm to the nucleus, thereby promoting antioxidant enzymes expression.^{3,30} Activation of the Nrf2-ARE pathway is also involved in the ability of astaxanthin to exert mitochondrial protective effects, including the inhibition of mitochondria-associated processes such as lipid peroxidation and calcium accumulation.³¹ Further studies have revealed that astaxanthin can activate Nrf2 by regulating several upstream factors. Astaxanthin may regulate Nrf2 signaling by inhibiting mitogen-activated protein kinase (MAPK) pathway-related key target phosphorylation of P38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK).³² Moreover, astaxanthin has been reported to modulate Nrf2 and Heme Oxygenase 1 (HO-1) expression and prevent the decline of mitochondrial membrane potential and the reduction of complex I and V activities through the activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway upstream of Nrf2 signaling in H₂O₂-induced SH-SY5Y cells.³³ Li *et al.*³⁴ reported that dietary intake of astaxanthin alleviates oxidative stress in mice fed high-fat diet by increasing the expression of Nrf2 and its upstream activator, adenosine monophosphate-activated protein kinase (AMPK). Similarly, dietary astaxanthin enhances Nrf2-mediated antioxidant enzymes expression by modulating the NAD-dependent deacetylase sirtuin-1 (SIRT1) pathway, which exerts a protective effect in high-fat diet-fed mice.³⁵ In Alzheimer's disease mice, astaxanthin therapy alleviates oxidative stress in the hippocampus, which is associated with astaxanthin-induced activation of the SIRT1/peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) signaling pathway.³⁶ Apart from enhancing antioxidant enzymes (such as thioredoxin) activity, astaxanthin may be involved in alleviating copper ion-induced oxidative stress in rat models and erythrocyte models by modulating the pentose phosphate pathway using glucose-6-phosphate dehydrogenase (G6PD) as a possible target.³⁷ Astaxanthin regulates redox homeostasis via interconnected pathways such as Nrf2/ARE, MAPK, PI3K/Akt, AMPK, and SIRT1/PGC-1α, which require deeper investigation in future studies. The time- and dose-dependent effects of astaxanthin observed across different models highlight the importance of considering specific physiological and pathological contexts when evaluating its antioxidant efficacy. To date, antioxidant research on astaxanthin has focused primarily on cellular and animal models, with little systematic clinical validation in humans. Furthermore, integrating multi-omics approaches that consider both epigenetics and the gut microbiome is expected to elucidate astaxanthin's comprehensive role in metabolic homeostasis and provide a theoretical foundation for precision nutritional interventions.

Modulated apoptosis

The regulation of apoptosis by astaxanthin is bi-directional, both inhibiting and promoting apoptosis, and its specific effects depend on the cell type, pathological state and dose of astaxanthin. In normal or damaged cells,

astaxanthin exerts anti-apoptotic effects by reducing oxidative stress, maintaining mitochondrial homeostasis, and activating protective signaling pathways such as Nrf2, PI3K/Akt, and MAPK. On the contrary, in cancer cells or fibroblasts, astaxanthin can promote apoptosis through mechanisms such as activating the p53 pathway, increasing ROS levels, or inducing mitochondrial dysfunction. In addition, astaxanthin can trigger apoptotic responses through non-ROS-dependent mechanisms, such as inhibition of pro-survival signaling pathways such as PI3K/Akt, Nuclear Factor Kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3).

Inhibition of apoptosis. Cell damage, such as DNA damage and mitochondrial oxidative damage, is an important signal for initiating mitochondrial-mediated apoptosis in abnormal physiological and pathological states. A hallmark of mitochondria-mediated apoptosis is a decrease in the anti-apoptotic signal B-cell Lymphoma 2 (Bcl-2), accompanied by an increase in the pro-apoptotic signal Bcl-2-associated X Protein (Bax), leading to the release of cytochrome C (Cyt C) from the mitochondria into the cytoplasm, which subsequently activates the caspase cascade.³⁸ Previous research suggests that astaxanthin effectively inhibits apoptosis through various mechanisms (Figure 4).

First, astaxanthin activates the Nrf2 pathway to reduce ROS levels, thereby mitigating oxidative damage that disrupts the balance between apoptotic factors such as Bcl-2 and Bax. For example, in aflatoxin B1-induced IPEC-J2 cells, astaxanthin treatment increased Nrf2 and antioxidant enzymes (HO-1 and NAD(P)H Quinone Dehydrogenase 1) expression, while downregulated apoptotic genes (Cyt C, Bax/Bcl2 ratio, caspase-9, and caspase-3) expression to inhibit cell apoptosis.³⁹ In addition, Zhang *et al.*⁴⁰ showed that astaxanthin modulates the SIRT1/Nrf2/ Peroxiredoxin 2 (Prx2)/ASK1/p38 pathway and inhibits apoptosis mediated by DNA damage induced by traumatic brain injury. Other studies have shown that the inhibition of DNA damage-mediated apoptosis by astaxanthin is related to its regulation of the ubiquitination of DNA repair proteins (Ku70/80).⁴¹ Astaxanthin inhibits cellular damage-induced ROS accumulation and P53 activation-mediated apoptosis. Further research has revealed that astaxanthin mediates the upregulation of the P53 upstream inhibitor gene MDM4 by downregulating miR-494-3p, thereby suppressing pyroxicam-induced myocardial cell apoptosis.⁴² In an anoxia-reoxygenation model of rat cardiomyocytes, rno-miR-125b-5p was identified as a MicroRNA regulated by astaxanthin to inhibit apoptosis.⁴³

Second, as central regulators of apoptosis, mitochondria are protected by astaxanthin in terms of structure and function, which is one of the key mechanisms by which it inhibits apoptosis. Studies have confirmed that astaxanthin increases the activity of mitochondrial respiratory chain complexes, stabilizes mitochondrial membrane potential, and maintains mitochondrial membrane integrity. Furthermore, astaxanthin promotes the expression of mitochondrial-encoded genes, increases mitochondrial copy number,⁴⁴ and inhibits excessive mitochondrial fission,⁴⁵ thus maintaining mitochondrial function and effectively inhibiting apoptosis. Sun *et al.*⁴⁶ reported that astaxanthin ameliorates muscle cell apoptosis in tail-suspended mice by increasing mitochondrial respiratory chain activity, inhibiting Cyt C release, and activating caspase 3.

Moreover, activation of the PI3K/Akt pathway is a key mechanism by which astaxanthin inhibits mitochondrial apoptosis. Studies have suggested that astaxanthin modulates the expression and phosphorylation of Akt and its downstream substrates Glycogen Synthase Kinase-3 Beta (GSK-3β) and Bad, thereby inhibiting apoptosis mediated by Cyt C, caspase family proteins and Bcl-2 family proteins.⁴⁷ To illustrate, Fu *et al.*⁴⁸ reported that astaxanthin activates the PI3K/Akt/GSK-3β pathway in a model of rat spinal cord ischemia-reperfusion, thereby ameliorating injury and inhibiting apoptosis. Notably, astaxanthin-mediated phosphorylation of Akt and GSK3β promotes the release of Nrf2 from Keap1, subsequently enabling its nuclear translocation.^{49,50}

In addition, astaxanthin inhibits apoptosis by regulating the MAPK pathway. It reduces the phosphorylation of c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 in the MAPK pathway, thereby preventing hepatocyte apoptosis induced by ischemia/reperfusion and paracetamol in mice.⁵¹ Moreover, astaxanthin inhibits ER stress-mediated apoptosis by reducing glutamate-induced intracellular calcium levels and inhibiting calpain activity, possibly through its regulation of the MAPK path-

Astaxanthin inhibits apoptosis

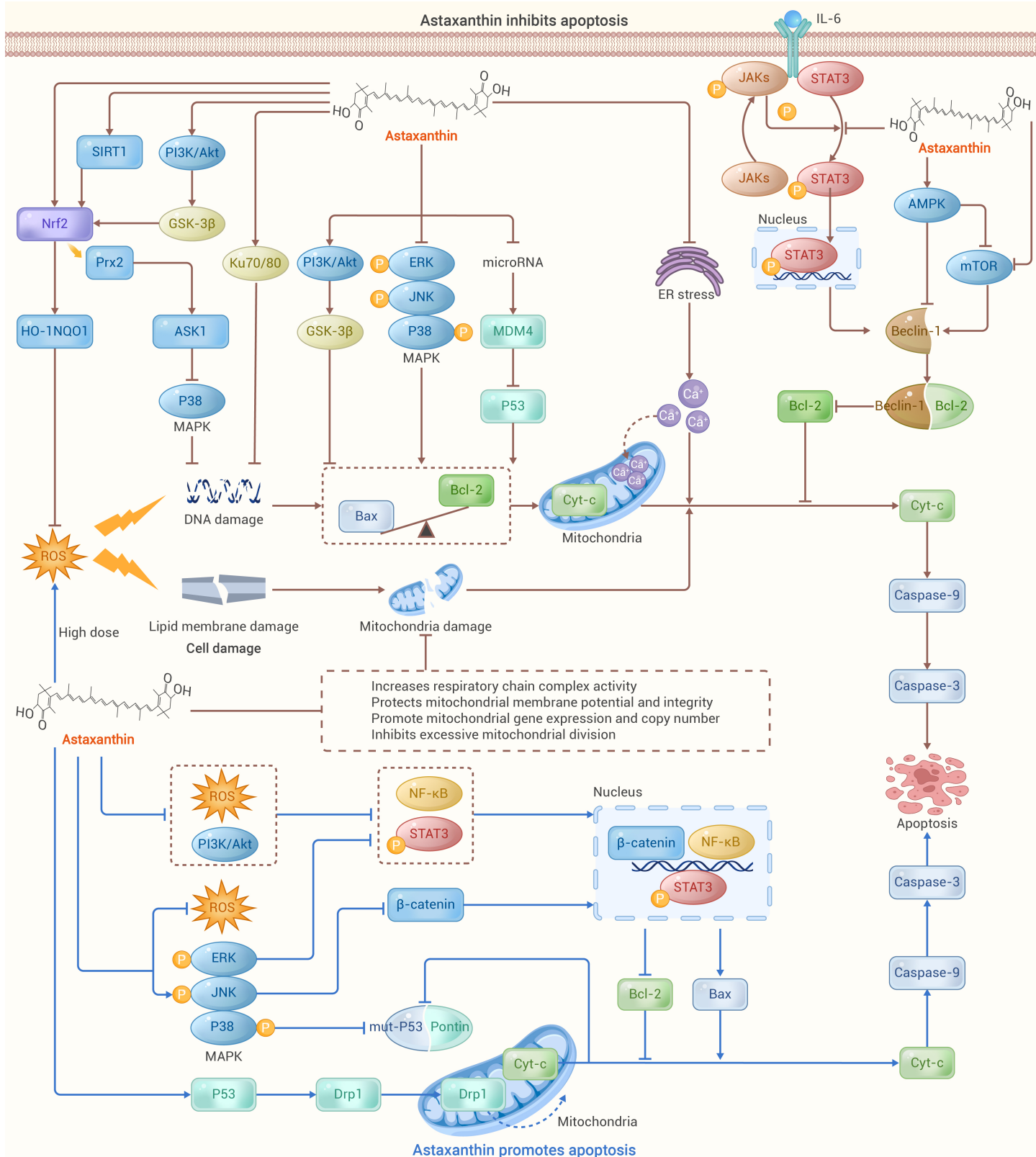


Figure 4. Regulatory mechanisms of astaxanthin on apoptosis Astaxanthin primarily inhibits the initiation and progression of apoptosis (black lines) by reducing cellular damage and protecting mitochondrial structure and function. Its regulation of key signaling pathways, including Nrf2, PI3K/Akt, MAPK, P53, AMPK/mTOR, and JAK/STAT3, as well as endoplasmic reticulum stress and microRNAs, contributes to this process. Conversely, astaxanthin can promote apoptosis (red lines) in tumor or specific pathological cells by increasing ROS levels, activating the P53 pathway, inhibiting PI3K/Akt and NF-κB, and enhancing mitochondria-mediated apoptotic signaling.

way.⁵² In addition, astaxanthin mediates apoptosis by regulating the Janus kinase (JAK)/STAT3 and AMPK/mTOR signaling pathways, which control the interaction between the pro-autophagy factors Beclin-1 and Bcl-2. In a mouse model of ceruloplasmin-induced acute pancreatitis, Astaxanthin

exerts an anti-apoptotic effect by impeding the phosphorylation of JAK and its downstream effector STAT3, thereby hindering the association between Bcl-2 and Beclin-1.⁵³

These findings suggest that astaxanthin inhibits apoptosis via multiple

signaling pathways; however, more in-depth mechanistic studies are warranted. Future research should further elucidate organelle-specific apoptotic processes and the crosstalk between autophagy and apoptosis. Additionally, the potential involvement of epigenetic regulation in astaxanthin-mediated apoptosis remains an important yet underexplored area.

Induction of apoptosis. Of note, astaxanthin can not only inhibit apoptosis but also promote apoptosis in some special cases or tumor cells, particularly in cancer cells. Astaxanthin induces apoptosis by regulating several signaling pathways (Figure 4). First, it activates the p53 pathway, which stimulates the expression of apoptosis-related genes, thereby promoting apoptosis. Like in breast cancer cells, astaxanthin treatment increased p53 activity, leading to increased apoptosis.⁵⁴ Moreover, Zhang *et al.*⁵⁵ demonstrated that astaxanthin promotes apoptosis in fibroblasts from fibrotic rat lungs by increasing p53-mediated dynamin-related protein-1 (Drp1) expression and facilitating its translocation to mitochondria.

Second, high doses of astaxanthin may promote apoptosis in cancer cells by increasing ROS levels. For example, in glioblastoma cell lines (e.g., U251-MG, T98G, U87-MG GBM, and CRT-MG), high concentrations of astaxanthin significantly increase ROS levels, ultimately triggering apoptosis.⁵⁶ However, recently published research suggests that astaxanthin does not always rely on ROS overload to induce apoptosis. The apoptotic potential exhibited by astaxanthin in oral squamous cell carcinoma is independent of ROS overload. Instead, it acts by inhibiting PI3K/Akt kinase activity, blocking the activation of NF- κ B and STAT-3, thereby enhancing mitochondria-mediated apoptotic signaling and inducing apoptosis.⁵⁷ Kim *et al.*⁵⁸ also reported that astaxanthin reduces ROS levels and promotes apoptosis in breast cancer cell lines, facilitated by activating the MAPK pathway and reducing the interaction between tumor-associated mutant p53 (mutp53) and Pontin. Furthermore, astaxanthin was also shown to inhibit the downstream NF- κ B, STAT3 and Wnt/ β -catenin signaling pathways by activating the MAPK pathway, which in turn induces apoptosis in hepatocellular carcinoma cells.⁵⁹ The pro-apoptotic effects of astaxanthin are primarily observed in cancer cells and appear to involve both ROS-dependent and ROS-independent mechanisms, which highlights the complexity of its biological actions. Future studies should clarify the specific conditions under which astaxanthin shifts from being a cytoprotective agent to being a pro-apoptotic compound, and explore how this context-dependent modulation could be exploited for therapeutic purposes.

Improved immunity

The modulation of immune cell activation by astaxanthin is closely linked to its anti-inflammatory effects, particularly in regulation of the phenotypic polarization of M1-type and M2-type (Figure 5A) macrophages. M1-polarized macrophages typically secrete several pro-inflammatory cytokines, such as Interleukin-1 Beta (IL-1 β), Interleukin-6 (IL-6), TNF- α , and Inducible Nitric Oxide Synthase, which play a pivotal role in driving inflammatory responses.⁶⁰ In distinction, M2-polarized macrophages release cytokines with anti-inflammatory properties, like IL-10.⁶¹ Astaxanthin exhibits the ability to modulate macrophage polarization through multiple mechanisms. For example, it inactivates the Notch signaling pathway by downregulating miR-31-5p expression, thereby inhibiting lipopolysaccharide (LPS)-induced macrophage polarization towards the M1 phenotype.⁶² Additionally, astaxanthin reduces R-spondin 2 (Rspo2) expression, alleviating its inhibitory effect on the Wnt/ β -catenin pathway, which in tandem diminishes M1 polarization and secretion of pro-inflammatory cytokine.⁶³ In LPS-induced rat models, astaxanthin suppresses IL-1 β expression in M1 macrophages by inhibiting mitochondrial succinate dehydrogenase (SDH) activity and modulating the SDH/ Hypoxia-inducible Factor 1- α (HIF-1 α) axis.⁶⁴ Furthermore, astaxanthin promotes the repolarization of M1 macrophages to the M2 phenotype. Li *et al.*⁶⁰ confirmed that in an osteoarthritis model, astaxanthin treatment successfully repolarized the M1 to M2 phenotype by restoring the mitochondrial membrane potential, increasing glutathione levels, and facilitating autophagy.

Astaxanthin inhibits inflammation through multi-target and multi-pathway regulatory mechanisms (Figure 5B). NF- κ B signaling is recognized as a vital pathway in regulating inflammation. Studies have demonstrated that astaxanthin inhibits the phosphorylation process of I κ B α and prevents the nuclear translocation of NF- κ B subunits (p50 and p65), thereby reducing the production of pro-inflammatory factors.⁶⁵ Furthermore, astaxanthin inhibits the Toll-

like Receptor 4 (TLR4)/MyD88/NF- κ B signaling axis to mitigate inflammatory reaction in ulcerative colitis mice.⁶⁶ Further studies have shown that astaxanthin not only inhibits TLR4 signaling by upregulating SIRT1 expression but also suppresses neuroinflammation induced by subarachnoid hemorrhage injury.⁶⁷ Astaxanthin also directly binds to SIRT1 and enhances its deacetylation activity, which subsequently promotes NF- κ B p65 acetylation and inhibits its phosphorylation, thereby suppressing cigarette-induced inflammation.⁶⁸ In addition, astaxanthin upregulates PGC-1 α , an upstream regulator of SIRT1, through the AMPK pathway, forming a multifaceted network for inflammation regulation.⁶⁹

An important role in inflammation is played by the PI3K/Akt pathway. In a high-glucose-induced retinal inflammation model, astaxanthin reduces PI3K and p-Akt levels and suppresses pro-inflammatory factors expression such as Tumor Necrosis Factor Alpha (TNF- α), thereby attenuating retinal cell damage.⁷⁰ Conversely, in a hyperosmolarity-induced dry eye model, astaxanthin promotes Akt phosphorylation while suppressing the levels of high-mobility group protein B1 and TNF- α and IL-1 β , thereby alleviating dry eye symptoms.⁷¹ This bidirectional regulation suggests that astaxanthin has the ability to flexibly regulate the activity of the PI3K/Akt pathway in a specific inflammatory context.

Astaxanthin also suppresses inflammation by modulating the MAPK pathway and NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome. For example, it reduces the phosphorylation of key kinases in the MAPK pathway, including ERK1/2, p38 Mitogen-Activated Protein Kinase (p38), and JNK, thereby reducing inflammation in neuropathic pain models.⁷² In arthritis models, astaxanthin suppressed inflammation by regulating the MAPK pathway and blocking the assembly of the NLRP3 inflammasome.⁷³ Similarly, in a rat model of status epilepticus, astaxanthin reduced neuroinflammation by suppressing the expression of the P2X7 receptor, an upstream regulator of NLRP3.⁷⁴

The JAK/STAT signaling pathway is pivotal in numerous inflammatory conditions. Astaxanthin binds directly to IL-6, thereby suppressing IL-6-mediated STAT3 activation and pro-inflammatory factors production.⁷⁵ It also interacts with the STAT3 DNA-binding domain and inhibits the JAK/STAT3 pathway to enhance its anti-inflammatory effects.⁷⁶ Zhu *et al.*⁷⁷ reported that astaxanthin treatment alleviates LPS-induced acute lung injury, a systemic inflammatory event, by activating the Suppressor of Cytokine Signaling 3 (SOCS3)/JAK2/STAT3 pathway.

ROS are key signaling molecules involved in immune cell activation during inflammation; however, excessive ROS accumulation exacerbates inflammation. Astaxanthin indirectly alleviates inflammation by activating the Keap1/Nrf2/HO-1 pathway to regulate ROS levels.⁷⁸ For example, in an LPS-induced dendritic cell model, astaxanthin activates the pathway of Nrf2/HO-1, suppresses the release of proinflammatory factors, and promotes immune cell activation and migration.⁷⁹ In addition, astaxanthin modulates inflammation at the epigenetic level. By activating SIRT1, it inhibits histone deacetylase 4 (HDAC4) expression, thereby diminishes the secretion of pro-inflammatory cytokines like IL-6 and TNF- α in macrophages exposed to alcohol.⁸⁰ Notably, the bidirectional regulation of PI3K/Akt signalling by astaxanthin in different pathological conditions demonstrates its ability to adapt to various situations, warranting further investigation into its mechanisms. Additionally, emerging evidence regarding the involvement of epigenetic regulators, such as SIRT1 and HDAC4, sheds new light on the immunomodulatory properties of astaxanthin. However, the epigenetic aspects of astaxanthin remain underexplored and require more in-depth study.

Regulated autophagy

Promoting autophagy. Autophagy is a material recycling process by which organisms remove dysregulated or misplaced proteins and damaged organelles. Astaxanthin is thought to exert beneficial effects by promoting cellular autophagy to prevent the onset and progression of spinal cord injury, cancer, aging, and neurological diseases (Figure 6).⁸¹ Autophagogenesis consists of the formation and fusion of autophagosomes with lysosomes and is regulated by a variety of Autophagy-related Proteins (Atg5, Atg7, LC3-II, Beclin-1, etc.).^{81,82} Wang *et al.*⁸³ described that astaxanthin treatment stimulated autophagosome formation by increasing the expression of ATG5 and ATG7 and LC3II/LC3I ratio. Co-localization results of LC3 and Lysosomal-

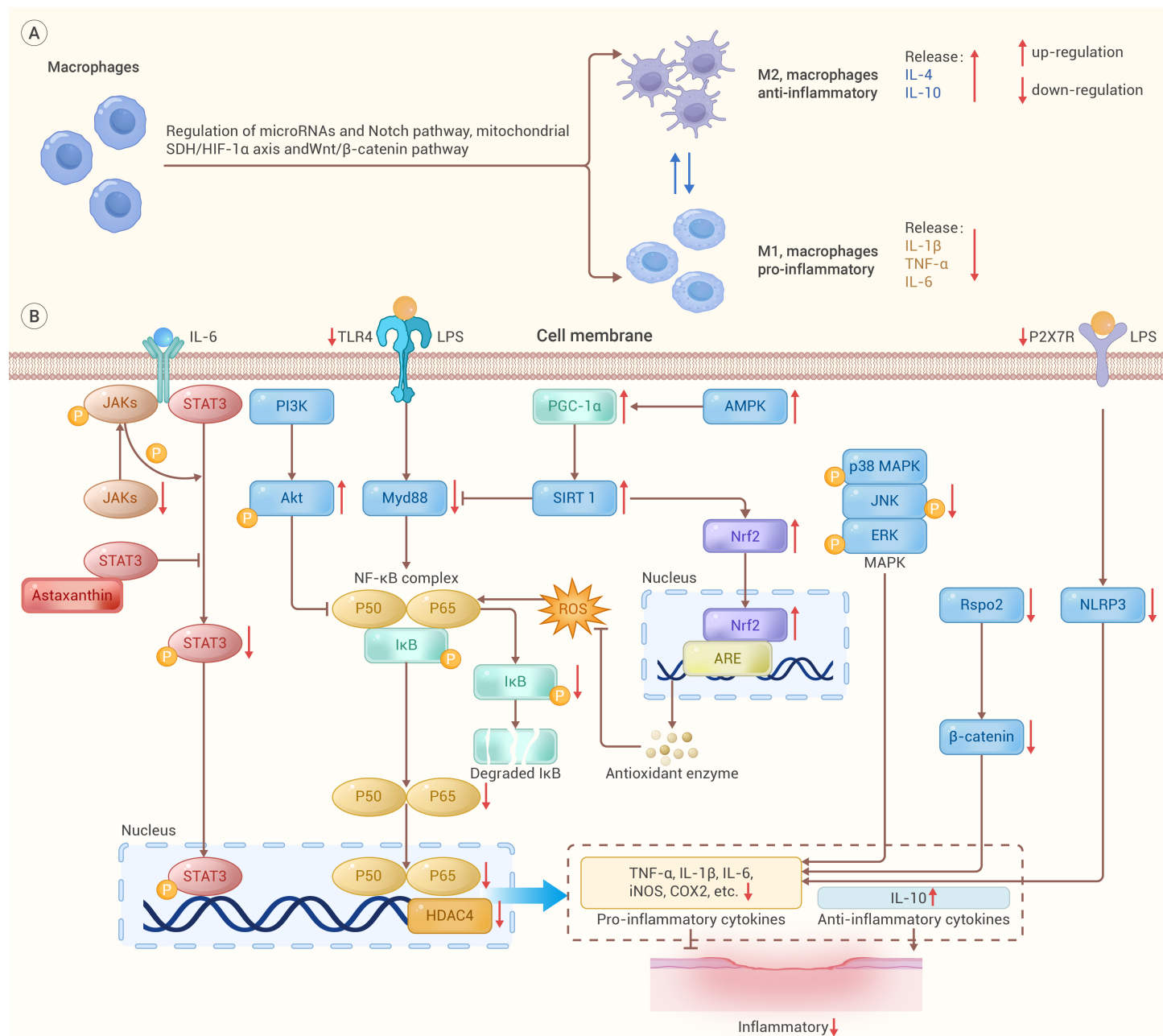


Figure 5. Regulatory mechanisms of astaxanthin on inflammation response (A) Astaxanthin inhibits the activation of M1 macrophages and their pro-inflammatory cytokines while promoting M2 macrophages and their anti-inflammatory cytokines. (B) Astaxanthin suppresses inflammation through multiple mechanisms, including inhibition of signaling pathways such as NF- κ B, upregulation of anti-inflammatory cytokines, flexible modulation of PI3K/Akt, inhibition of inflammasomes, direct suppression of STAT3, regulation of ROS, and epigenetic inhibition of HDAC4.

Associated Membrane Protein 1 (LAMP1) in mice fed a high-fat diet also suggested that astaxanthin regulates the autophagosome-lysosome fusion to inhibit autophagy. Unc-51-like kinase 1 (ULK1), an autophagy-essential kinase, is phosphorylated by AMPK at the S555 site of ULK1 (pro-autophagy) or by mTOR at the S757 site of ULK1 (anti-autophagy).⁸⁴ Some brain aging experiments have claimed that astaxanthin treatment may trigger autophagy by modulating Insulin-like Growth Factor 1 (IGF-1)/Akt/mTOR and IGF-1/Akt/Forkhead Box O3 (FoxO3a) signaling.⁸⁵ Previous research have proposed that astaxanthin delays aging by promoting autophagy dependent on the insulin/IGF-1 pathway but independent of the mTOR pathway.⁸⁶ In addition to inhibiting the Akt-mTORC1 axis, astaxanthin increases AMPK phosphorylation to promote autophagy in gastric epithelial cells treated with *H. pylori*.⁸⁷ In an acetaminophen-induced liver injury model, the role of astaxanthin in enhancing autophagy was shown to be related to regulating the Nrf2/HO-1 pathway.⁹

Inhibiting autophagy. Notably, astaxanthin exerts a protective effect by

reducing excessive autophagy (Figure 6). One study reported that gavage of astaxanthin in mice with hepatic ischemia-reperfusion inhibited hepatocyte autophagy, potentially due to inhibition of ROS production and phosphorylation of key proteins related to the MAPK family by astaxanthin.⁸⁸ Astaxanthin reduced the level of phosphorylated JNK by blocking the binding of TNF- α to TNF Receptor-Associated Factor 2 (TRAF2), which in turn inhibited the separation of Bcl-2 from Beclin-1, thereby exerting an inhibitory effect on autophagy.⁸⁹ Astaxanthin suppresses the phosphorylation of JAKs and subsequently lowers the phosphorylation of STAT3, which results in upregulation of Bcl-2 expression and downregulation of Beclin-1 activity, thus protecting mice with acute pancreatitis by inhibiting autophagy.⁵³ Furthermore, astaxanthin can alleviate bisphenol A-induced autophagy in human dermal fibroblasts via the ROS/p-ERK/NF- κ B pathway.⁹⁰ Research have shown that heat-induced mitochondrial autophagy can be inhibited by astaxanthin, which prevents the activation of Drp1 and PTEN-induced kinase 1 (PINK1)/ubiquitin ligase Parkin.⁹¹ Astaxanthin also exerts an anti-aging effect

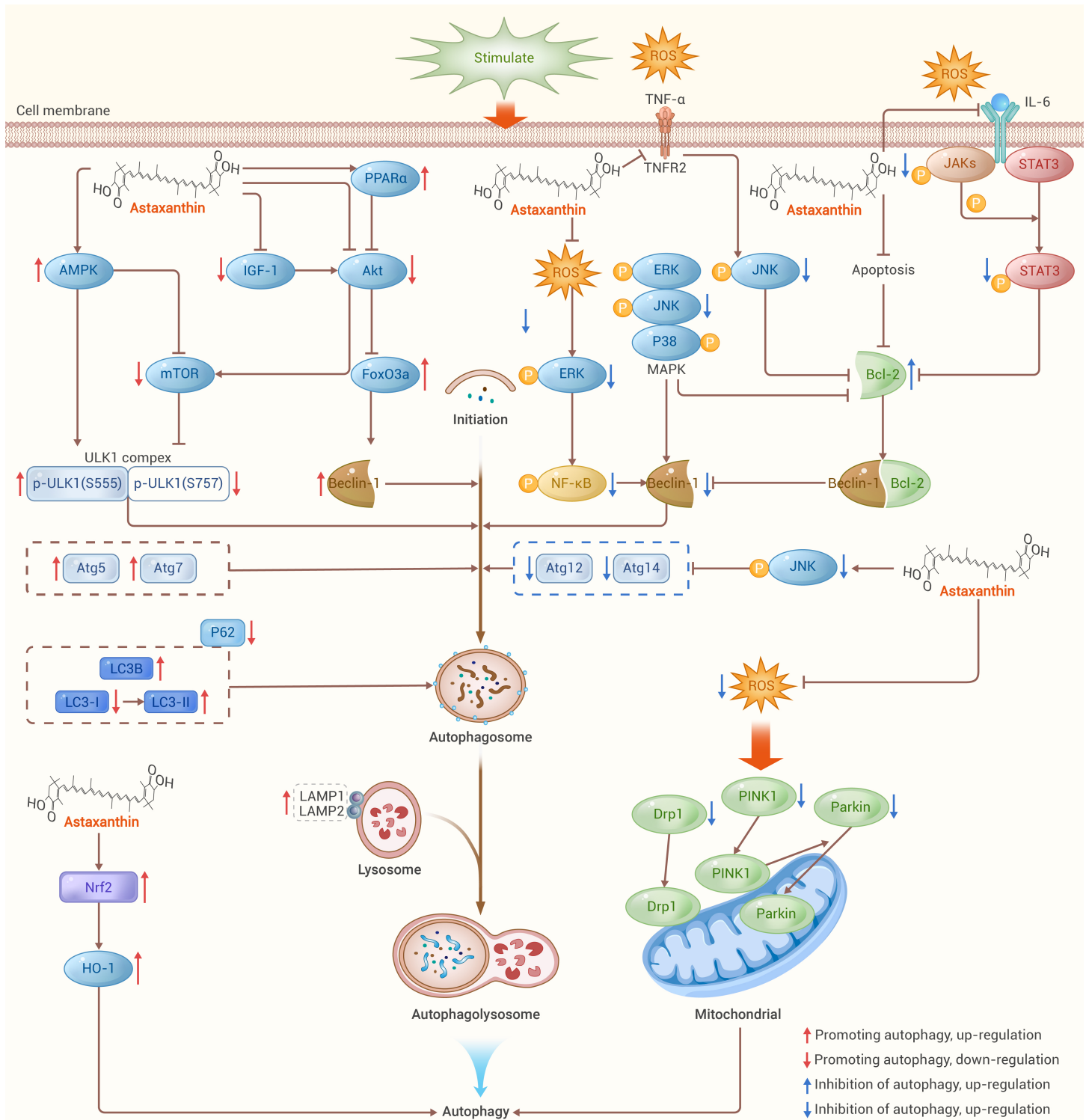


Figure 6. Regulatory mechanisms of astaxanthin on autophagy Astaxanthin promotes cellular autophagy by upregulating the expression of autophagy-related proteins (ATG5, ATG7, LC3-II, etc.), facilitating autophagosome formation and enhancing the autophagic process through mechanisms such as regulating Peroxisome Proliferator-Activated Receptor Alpha (PPARα), inhibiting the Akt-mTOR signaling axis and activating AMPK phosphorylation. Conversely, under certain conditions, astaxanthin inhibits autophagosome formation and function primarily by reducing ROS production, blocking the phosphorylation of key proteins in the MAPK family, and decreasing the phosphorylation of JNK and STAT3.

on porcine oocytes *in vitro* by inhibiting autophagy to rescue the functional state of organelles comprising mitochondria, Golgi apparatus, endoplasmic reticulum, and lysosomes.⁹² Astaxanthin plays a dual role in regulating autophagy, promoting it under certain conditions while inhibiting excessive autophagy in others. This context-dependent modulation involves multiple signaling pathways, such as AMPK, mTOR and Nrf2/HO-1. However, the precise mechanisms remain unclear. Further research is needed to clarify the circumstances in which astaxanthin activates or suppresses autophagy, in

order to better understand its therapeutic potential.

Astaxanthin modulates ferroptosis

Astaxanthin has been recognized as a potent lipophilic antioxidant capable of suppressing ferroptosis - an iron-dependent lipid peroxidation-driven programmed cell death - through multi-target mechanisms (Figure 7). Its core mechanisms involve regulation of GPX4-associated antioxidant systems, iron metabolism homeostasis, and mitochondrial function.⁹³ By

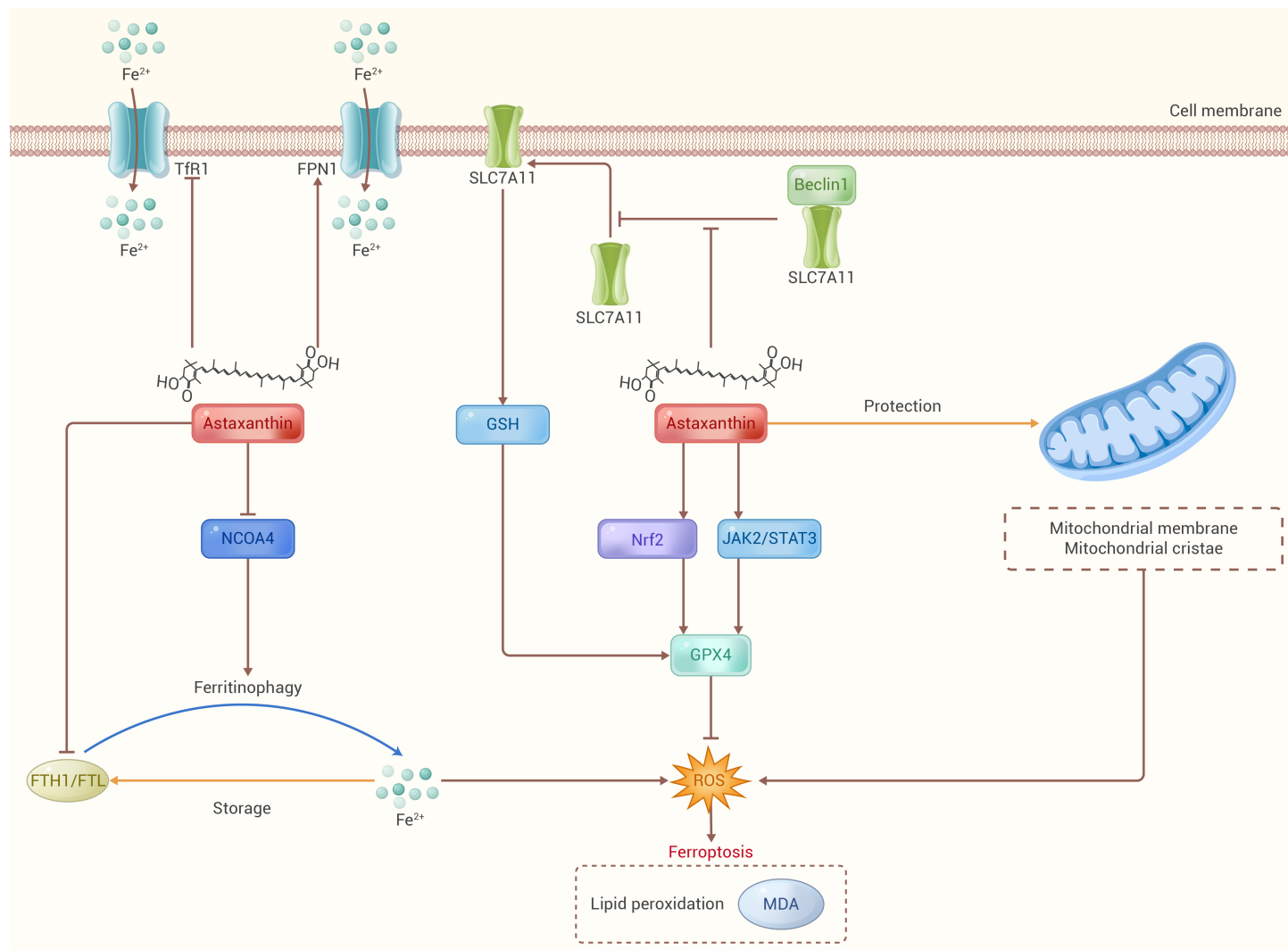


Figure 7. Mechanisms of astaxanthin in suppressing ferroptosis Astaxanthin modulates the Nrf2 and JAK2/STAT3 pathways and increases SLC7A11 membrane localization and GSH synthesis by inhibiting the formation of the Beclin1-SLC7A11 complex, which in turn up-regulates GPX4 and exerts an inhibitory effect on ferroptosis. Astaxanthin down-regulates TfR1 and FTH1/FTL to reduce iron influx, while up-regulation of FPN1 enhances iron efflux, and astaxanthin inhibits ferritinophagy through down-regulation of NCOA4, which down-regulates Fe^{2+} release, thereby inhibiting Fe^{2+} -driven ferroptosis. Astaxanthin maintains cristae integrity and stabilises membrane potential, which in turn inhibits ferroptosis.

promoting Nrf2 nuclear translocation, astaxanthin upregulates downstream targets GPX4 (directly neutralizing lipid peroxides) and SLC7A11 (enhancing cystine uptake for glutathione/ GSH synthesis), thereby restoring antioxidant defenses.^{94,95} For instance, studies demonstrate that astaxanthin inhibits macrophage ferroptosis and delays atherosclerotic plaque progression by activating the NRF2/SLC7A11/GPX4 pathway.⁹⁶ Astaxanthin modulates iron homeostasis to block iron-dependent lipid peroxidation. In doxorubicin (DOX)-induced cardiotoxicity models, it significantly downregulates transferrin receptor 1 (TfR1) and ferritin heavy/light chains (FTH1/FTL) to reduce iron influx, while upregulating ferroportin (FPN1) to enhance iron efflux, thereby decreasing free Fe^{2+} levels and suppressing Fenton reaction-driven lipid peroxidation.⁹⁷ A similar mechanism was observed in PM2.5-induced myocardial injury, where astaxanthin attenuated Fe^{2+} overload-mediated ferroptosis by coordinating the upregulation of SLC7A11/GPX4 with the down-regulation of TfR1/FTH1/FTL.⁹⁸ Beyond antioxidant pathway coordination (e.g., GPX4/SLC7A11), astaxanthin's mitochondrial protection constitutes another critical anti-ferroptotic mechanism.⁹⁹ Study reports that astaxanthin activation of the JAK2/STAT3 pathway upregulates GPX4 and restores mitochondrial membrane potential and reduces ROS-mediated ferroptosis in osteoblasts in a glucocorticoid-induced femoral head necrosis model.¹⁰⁰ For IL-1 β -induced osteoarthritis, astaxanthin repairs chondrocyte mitochondrial cristae structure, inhibits lipid ROS generation, and upregulates SLC7A11/GPX4 to delay joint degeneration.¹⁰¹ In age-related cataract models,

long-term astaxanthin intervention suppresses mitochondrial membrane potential collapse and ROS/ MDA accumulation in lens epithelial cells by upregulating GPX4, demonstrating efficacy comparable to the ferroptosis inhibitor ferrostatin-1.¹⁰² Notably, astaxanthin coordinately regulates the crosstalk between autophagy and ferroptosis. In acute pancreatitis models, it activates Nrf2-mediated autophagy to promote Beclin1-SLC7A11 complex dissociation, thereby enhancing SLC7A11 membrane localization for cystine uptake and GSH synthesis while upregulating GPX4 activity to inhibit acinar cell ferroptosis.¹⁰³ In LPS-induced acute lung injury (ALI), astaxanthin down-regulates nuclear receptor coactivator 4 (NCOA4) to inhibit ferritinophagy, reducing lysosomal Fe^{2+} release while upregulating ferritin expression to enhance iron storage capacity, ultimately restoring SLC7A11/GPX4 function and alleviating lipid peroxidation in pulmonary epithelial cells.¹⁰⁴ Astaxanthin effectively inhibits ferroptosis through multi-target mechanisms and modulates the interplay between autophagy and ferroptosis, thereby enhancing cellular defense against lipid peroxidation-induced cell death. However, further studies on its detailed molecular pathways and context-specific effects are needed to fully elucidate its therapeutic potential.

Improved gut microbiota

A growing area of research is exploring the interplay between astaxanthin and gut microbiota, suggesting new mechanisms for the regulation of organismal health by astaxanthin (Figure 8). Research indicates that astaxanthin actively regulates the composition and architecture of the microbiota, thereby

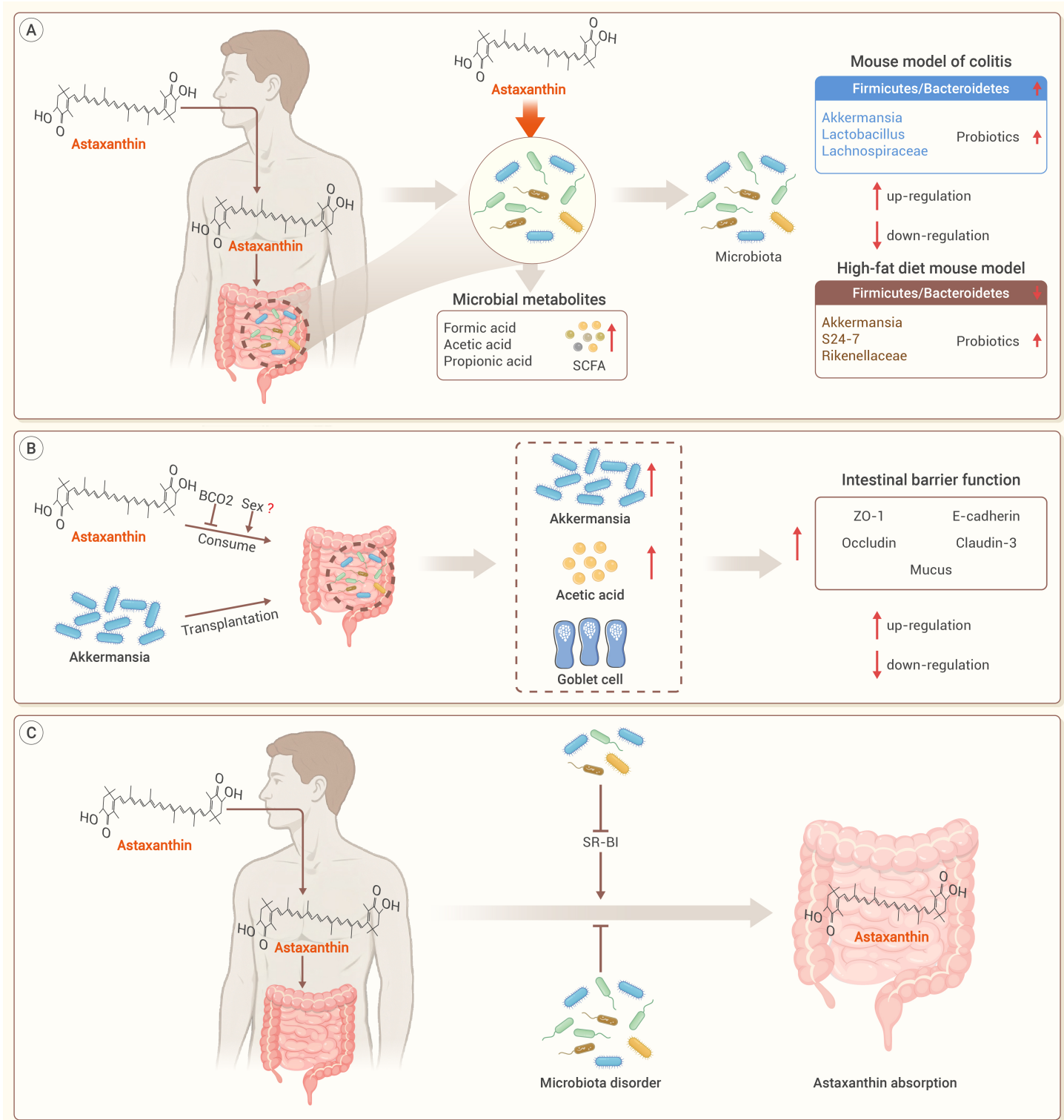


Figure 8. Astaxanthin modulates gut microbes (A) Dietary astaxanthin dynamically improves the intestinal microbiota, increasing the number of intestinal probiotics and increasing microbial short-chain fatty acid production. (B) Astaxanthin ingestion enhances intestinal barrier function as evidenced by increased *Akkermansia* abundance and short-chain fatty acid content, and increased intestinal tight junction protein expression and stimulation of goblet cell to increase mucus secretion; transplantation of *Akkermansia* is similar to the effects of astaxanthin ingestion. (C) Microbial disorders decrease astaxanthin absorption; a decrease in microorganisms leads to a decrease in astaxanthin absorption.

maintaining intestinal homeostasis. Furthermore, this regulation adjusts the concentrations of essential metabolites known as short-chain fatty acids (SCFAs), which are essential metabolites produced by gut microbes that contribute significantly to overall health.¹⁰⁵ Research has shown that astaxanthin supplementation effectively restores dextran sulfate sodium salt-induced intestinal flora abnormalities and alleviates colitis inflammation in mice. This was evidenced by an increase in the *Firmicutes/Bacteroidetes*

ratio, the abundance of probiotic bacteria like *Lactobacillus* and *Lachnospiraceae*.¹⁰⁶ Wang *et al.*¹⁰⁷ showed that adding astaxanthin to the food of mice fed a high-fat diet decreased the *Firmicutes/Bacteroidetes* ratio in the intestinal tract and upregulated the abundance of the probiotics *S24-7*, and *Rikenellaceae*, which related to glucose and lipid metabolism. These studies demonstrated the flexibility of astaxanthin in regulating the gut flora in different models and its adaptability to changes in the gut environment.

Table 1. Protective effects of astaxanthin in preclinical animal models of metabolic, neurodegenerative, and inflammatory diseases.

Species	Induction	Disease model	Astaxanthin outcomes	Target organ(s)	Reference
APPswe/PS1dE9 mice	Genetic model	Alzheimer's disease	Lowered fatty acids; improved antioxidant defense; reduced A β deposition; improved cognition	Brain	130
Mice	Hydrochloride/ethanol or aspirin administration	Gastric ulcers	Increased antioxidant capacity; reduced gastric injury	Stomach	131
C57BL/10ScSnDmdmdx/J mice	High-fat diet	Duchenne muscular dystrophy	Decreased body weight gain; improved muscle function and performance; reduced lipid/mitochondrial damage; increased gut probiotics	Skeletal muscle	111
Rats	Surgical induction	Osteoarthritis	Ameliorated oxidative stress-induced cell death; promoted extracellular matrix synthesis; reduced cartilage damage	Cartilage	132
C57BL/6J mice	Cigarette smoke exposure	Chronic obstructive pulmonary disease	Reduced oxidative stress, DNA damage, and apoptosis	Lung	29
BALB/c mice	Dextran sulfate sodium (DSS)	Inflammatory bowel disease	Improved colon morphology; reduced inflammation; restored gut microbiota and SCFA production	Colon	133
Sprague–Dawley rats	Particulate matter (PM _{2.5}) exposure	Cardiovascular disease	Enhanced cardiac antioxidant defense; reduced pathology and inflammation; inhibited ferroptosis	Heart	98
Wistar rats	Chronic alcohol administration	Alcoholic liver disease	Alleviated hepatic fibrosis and mitochondrial damage	Liver	28
Mice	High-fat diet	Non-alcoholic fatty liver disease	Reduced oxidative stress and steatosis; restored gut microbiota	Liver	34
Mice	High-fat diet	Atherosclerosis	Reduced obesity and dyslipidemia; protected retina and colon; remodeled gut microbiota	Retina, liver, colon	110
Sprague–Dawley rats	Streptozotocin	Diabetes mellitus and diabetic retinopathy	Improved glucose and lipid homeostasis; preserved islet and retinal function; enhanced mitochondrial antioxidant capacity	Liver, kidney, pancreas, retina	70

Several studies have suggested that *Akkermansia* are important astaxanthin-regulated probiotics. Studies have indicated that astaxanthin supplementation to the diet significantly increase *Akkermansia* abundance and slow disease progression in several disease models, including colitis, tumors,¹⁰⁸ alcoholic fatty liver disease, high-fat diet-induced obesity,¹⁰⁹ atherosclerosis,¹¹⁰ and Duchenne muscular dystrophy.¹¹¹ Furthermore, a recent study on a mouse model of experimental autoimmune prostatitis showed that either direct astaxanthin administration or *Akkermansia muciniphila* transplantation led to increased acetate production and improved colonic tight junction proteins expression, including ZO-1, E-cadherin, occludin, and claudin-3, which collectively contribute to the reversal of intestinal barrier damage.¹¹² Ren *et al.*¹¹³ also demonstrated that in germ-free tumor-bearing mice, the beneficial effects of astaxanthin in enhancing intestinal mucosal immunity are dependent on the existence of gut microbiota. They found that astaxanthin modulates the gut microbiome to increase antitumor cytokines (e.g., granzyme B) production and promotes the proliferation of *Akkermansia*, which in turn stimulates the production of goblet cells and mucus.¹¹³ Interestingly, research indicates that astaxanthin-based regulation of *Akkermansia* is influenced by beta-carotene oxygenase 2 (BCO2) and sex, with a higher abundance of intestinal *A. muciniphila* in male BCO2 knockout mice.¹¹⁴ This finding suggests that genetic factors influence an individual's response to astaxanthin and further broadens our comprehension of how astaxanthin interacts with the gut microbiota.

Importantly, the gut microbiota exerts a significant influence on the absorption and effectiveness of astaxanthin. Studies have shown that a reduction in microbial populations impairs the absorption of orally administered astaxanthin, probably because of microbial modulation of carotenoid transporters (such as SR-BI) in the gut and changes in the structure of astaxanthin itself.¹¹⁵ Compared with healthy individuals, obese individuals with dysbiosis have a significantly lower absorption rate of oral astaxanthin.¹¹⁶ Therefore, oral astaxanthin emulsions may be more appropriate than astaxanthin oils for obese individuals than astaxanthin oils.¹¹⁷ From the perspective of astaxanthin's dynamic regulation of intestinal microorganisms, astaxanthin not only regulates the overall structure and diversity of intestinal flora, but also flexibly adjusts the abundance of specific flora according to different

physiological and pathological environments, realizing the fine management of host intestinal homeostasis. This dynamic regulation reveals the complex role of astaxanthin in the intestinal ecosystem, suggesting that future research should focus on its regulatory mechanism in interaction with host genetic background, gender and dietary factors to realize precise nutritional intervention and disease management.

ASTAXANTHIN APPLICATION IN HUMAN HEALTH AND ANIMAL PRODUCTION

Astaxanthin metabolism application for human health

Astaxanthin has attracted attention for its potential health benefits in humans. Animal studies have demonstrated that administering astaxanthin orally can mitigate organ damage caused by various diseases and abnormal physiological conditions, offering promising therapeutic effects (Table 1). Experiments in mice have confirmed that taking large doses of natural astaxanthin has no toxic effects and improves antioxidant capacity and immunity.¹¹⁸ Although limited clinical evidence is available in humans, the findings suggest that astaxanthin supplementation improves several metabolic pathways. For example, studies in individuals with polycystic ovary syndrome have indicated that astaxanthin can alleviate endoplasmic reticulum stress, decrease insulin resistance, and mitigate oxidative stress.^{119–121} Astaxanthin also guards against UV-induced skin damage¹²² and improves the recovery from joint symptoms in individuals with mild osteoarthritis.¹²³ In particular, research has underscored the advantageous effects of astaxanthin in addressing obesity, with studies demonstrating synergistic benefits when combined with exercise, particularly in increasing resistance to oxidative stress among overweight and obese adults.^{124,125} Astaxanthin has also been shown to improve cognitive performance in adults aged 40–70 years and the oxidative status in older adults.^{126,127} Recent studies have shown that a combination supplement (Armolidip), containing red yeast rice, sucralose, coenzyme Q10, astaxanthin, and folic acid, significantly lowers total cholesterol, LDL cholesterol, and Apo B levels in children and adolescents with hypercholesterolemia, with stable and long-lasting effects observed at both 6 and 16 months of treatment.¹²⁸ However, studies have questioned the valid-

ity of astaxanthin supplementation due to its lack of effect on muscle damage biomarkers following exercise-induced muscle injury.¹²⁹ These mixed findings highlight the need for further investigations, particularly in elucidating astaxanthin's molecular mechanisms, validating its therapeutic effects through large-scale randomized trials, and establishing evidence-based guidelines for its clinical application in chronic diseases such as cardiovascular disorders, diabetes, and neurodegenerative conditions. Additionally, systematic evaluation of its long-term safety and synergistic potential with other interventions will be critical to translating preclinical promise into clinical practice.¹³⁰⁻¹³³

Astaxanthin application in aquaculture and livestock

Astaxanthin application in aquaculture. The U.S. Food and Drug Administration (FDA) first approved astaxanthin as a dietary supplement for use in aquaculture in 1987, and its approval has subsequently been extended to include other sectors of animal husbandry.¹³⁴ Astaxanthin was initially used in the aquaculture industry as a natural colorant to improve the color of aquatic products and thus increase their market value. However, with further research, its multiple benefits as an environmentally friendly functional feed additive have been increasingly recognized. Both the most commonly used synthetic astaxanthin and astaxanthin-enriched microalgae have been proven to improve the growth performance, immune response, antioxidant capacity, and digestive function of aquatic animals, thereby enhancing their survival in challenging aquaculture environments. For instance, a study demonstrated that supplementing the diet of coral trout with 1 g/kg *Haematococcus pluvialis* (astaxanthin content of 0.091 g/kg) increased the hepatic digestive enzyme (amylase, lipase and trypsin) activities, antioxidant capacity, immunity, and resistance to pathogenic bacteria such as *Vibrio harveyi*.¹³⁵ Similarly, supplementation of crustaceans, such as *Babylonia areolate*, with adequate levels (75–100 mg/kg) of astaxanthin shown to enhance growth performance, muscle composition, hepatopancreatic immunity, and ammonia-nitrogen stress resistance.¹³⁶ Moreover, studies on *O. mykiss* have reported that both natural and synthetic astaxanthin improve gut morphology, antioxidant capacity, muscle coloration, innate immune response, and growth performance, with synthetic astaxanthin resulting in better pigmentation in abdominal muscles and feed preservation compared with natural astaxanthin.¹³⁷ With respect to heavy metal contamination, although astaxanthin does not reduce the buildup of heavy metals like cadmium in the liver of *T. ovatus*, it can mitigate oxidative stress, inflammation, and intestinal barrier dysfunction induced by cadmium exposure.¹³⁸ Future research on astaxanthin in aquaculture could explore in greater depth the synergistic effects of astaxanthin with other nutrients or functional feed additives, and could provide valuable insights for optimizing feed formulations to improve aquatic animal health and performance.

Astaxanthin application in poultry and livestock

Astaxanthin application in poultry and livestock. As a highly effective natural antioxidant, astaxanthin finds diverse applications in poultry and livestock production. Specifically, astaxanthin improved the meat quality, antioxidant status, and reddening/yellowing of broiler breast and leg muscles in heat-stressed broilers.¹³⁹ Similarly, studies have reported that dietary astaxanthin supplementation improves antioxidant enzyme activity, meat quality, and growth performance in Pekin ducks.¹⁴⁰ Although astaxanthin has no direct effect on feed consumption, feed efficiency, egg weight, laying rate, Haugh units, or eggshell strength,¹⁴¹ it improves the yolk color and inhibits the decline in egg production in laying hens by preventing ovarian senescence in the advanced phases of egg-laying.¹⁴² Additionally, astaxanthin reduces the breakdown of DHA¹⁴³ and its deposition in eggs,¹⁴⁴ ultimately enhancing the eggs' nutritional. A short-term (28-day) supplementation of 16 ppm astaxanthin to the feed of laying hens produced astaxanthin-enriched eggs without affecting egg quality and taste.¹⁴⁵ In particular, hens fed free astaxanthin exhibited higher retention and color of astaxanthin in their eggs than those fed esterified astaxanthin, and hens fed Z-isomer astaxanthin (at a concentration of 8 mg/kg) exhibited better astaxanthin concentration and color of their yolks than hens fed the same concentration of the all-E isomer of astaxanthin.^{146,147}

Although astaxanthin is not yet widely used in pig nutrition, studies have

demonstrated its potential benefits. For example, incorporating 2.5% astaxanthin into the feed of weaned piglets did not affect average weight gain, feed utilization efficiency, or feed intake, although it reduced the piglets' susceptibility to pork fat oxidation and improved blood erythrocyte parameters.¹⁴⁸ In addition, astaxanthin supplementation (0.025 g/kg) reduced liver fibrosis caused by collagen deposition in weaned piglets.¹⁴⁹ Yang *et al.*¹⁵⁰ reported that dietary supplementation with astaxanthin (0, 1.5, and 3.0 ppm) did not alter meat quality and growth performance in finishing pigs but linear effects on backfat thickness, dressing percentage, and loin area were observed with ascending dietary astaxanthin concentration. A previous study reported that the addition of 5 ppm astaxanthin concentration of *H. pluvialis* to the sow diets significantly improved piglet survival rates and accelerated estrus recovery after weaning.¹⁵¹

Astaxanthin also exerts a notable influence on the reproductive health of animals. For example, astaxanthin alleviates the inhibitory impacts of metabolic stress triggered by high concentrations of palmitic acid on oocyte maturation, mitigates pesticide damage to oocytes, and improves the maturation and survival of frozen oocytes.¹⁵² The addition of astaxanthin during the cryopreservation of boar semen has been reported to improve semen quality by maintaining the motility and kinetics of sperm, morphology, viability, and functional integrity of sperm plasma membranes, and integrity of DNA under a variety of temperature conditions and increasing the antioxidant capacity of sperm.¹⁵³ In porcine embryo cryopreservation, astaxanthin treatment improved embryonic development and quality after vitrification.¹⁵⁴ In addition, feeding astaxanthin at 20.10 mg/kg body weight to buffalo heifers improved antioxidant enzyme activity, growth performance, and immune function and reduced inflammation and apoptosis in heat-stressed heifers.¹⁵⁵ Astaxanthin has a beneficial effect on reproductive health in heifers by improving bovine oocyte quality in vitro through its antioxidant effects and may have positive therapeutic effects on endometritis by activating the endometrial defensive barrier and promoting bovine endometrial cell activity.¹⁵⁶ Future studies should focus on establishing species-specific dosage standards for astaxanthin, exploring its synergistic effects with vitamin E, selenium, and other essential antioxidants in the human diet, and analyzing the core mechanisms of action, which not only enhance the nutritional quality of foods of animal origin (e.g., meat, dairy products) but also provide cross-species references for the discovery of metabolic regulatory mechanisms in the study of prevention of chronic diseases in human beings.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Astaxanthin has a significant effect on oxidative stress based on its antioxidant ability. Its roles in central energy and lipid metabolism, inflammation, apoptosis, autophagy, ferroptosis, gut microbiota, and epigenetic modifications allow it to modulate metabolic health via multiple mechanisms; thus, a variety of astaxanthin-associated targets are available for therapeutic intervention. A number of clinical and animal trials have performed astaxanthin supplementation, and the results show that this strategy improves antioxidant enzyme activity and antibody production. However, the relevance of many novel astaxanthin metabolic pathways in immune, cancer, and tumor cells remains unknown. Diverse cells and tissues are likely to respond differently to the structure and function of astaxanthin because different astaxanthin structures are best suited for uptake by different species. Furthermore, the regulatory mechanism of astaxanthin-mediated autophagy and apoptosis should be further investigated under different stress conditions because the findings in this study may present reverse results and clearly show that astaxanthin alone can affect disease or metabolic homeostasis. Further studies on combined therapies involving synthetic or natural astaxanthin with dietary interventions might provide additional insights on the effective use of astaxanthin in production and clinical settings, especially for treatments and interventions targeting aging, intestinal diseases, cancer, obesity, and fatty liver disease. The findings revealed that antioxidant properties driven by astaxanthin metabolism may be associated with disease occurrence in animal production and human health. Thus, a challenge for future research will be to describe the relationship between the changes in the structure and function of astaxanthin and various metabolic diseases. Additionally, future studies should assess the molecular mechanisms by which astaxanthin metabolism promotes the growth and development of livestock and aquaculture during critical windows of development.

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DECLARATION OF INTERESTS

Yulong Yin is an Editorial Board member of The Innovation Life and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

DATA AND CODE AVAILABILITY

No data was used for the research described in the article.