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Review

Astaxanthin: Unveiling biochemical mysteries, expanding horizons, and therapeutic opportunities in health science and biomedical research

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Abstract: This systemic study surveys the multifaceted nature of Astaxanthin (AXT), a member of carotenoid pigments broadly used in nutraceuticals and pharmaceuticals. Starting with an insight into its biological origin, the review proceeds to detail the complex chemical structure of AXT followed by considerations on its bioavailability, pharmacokinetics and safety as a dietary supplement. Foremost among these is the biological activities of AXT, especially its strong antioxidant activity which plays an important role in reducing oxidative stress (OS) damage to cells. The description of AXT as an anti-apoptotic and anti-inflammatory cytokine indicates its important role in cell protection and chronic inflammation improvement. Additional studies emphasize positive anti-obesity and anti-diabetic activities that could be exploited as therapy for metabolic disease. The review goes on to describe the immunomodulatory and neuroprotective effects of AXT, its role in cardiovascular protection, as well as hepatic health. The discussion of the anti-cancer activity of AXT is important, since it is related with its mechanisms for preventing and treating cancer. The broad perspective ends with an overview of the diverse biological activities of AXT, suggesting future research directions and its ability to be a multi-target ameliorator. Data compiled here aims to significantly help to improve knowledge on AXT, thus facilitating health and biomedical research progression.

Özet: Bu sistematik çalışma, geniş çapta nutrasötiklerde ve farmasötiklerde kullanılan karotenoid pigmentlerinin bir üyesi olan Astaksantinin (AXT) çok yönlü doğasını incelemektedir. İncelemede, öncelikle AXT'nin biyolojik kökenine dair bilgiler sunulmakta, ardından karmaşık kimyasal yapısı detaylandırılmakta ve diyet takviyesi olarak biyoyararlanımı, farmakokinetiği ve güvenliği ele alınmaktadır. Bunların başında AXT'nin biyolojik aktiviteleri, özellikle oksidatif stresin hücrelere verdiği hasarı azaltmada önemli rol oynayan güçlü antioksidan aktivitesi gelmektedir. AXT'nin anti-apoptoz ve anti-enflamatuvar sitokin olarak tanımlanması, hücre koruma ve kronik iltihaplanmanın iyileştirilmesindeki önemli rolünü göstermektedir. Ek çalışmalar, AXT'nin metabolik hastalıkların tedavisinde kullanılabilecek olumlu anti-obezite ve anti-diyabetik aktivitelerini vurgulamaktadır. Çalışma ayrıca AXT'nin immünomodülatör ve nöroprotektif etkilerini, kardiyovasküler korumadaki rolünü ve karaciğer sağlığı üzerindeki etkilerini ele almaktadır. AXT'nin anti-kanser aktivitesinin tartışılması önemlidir, çünkü bu, kanseri önleme ve tedavi etme mekanizmaları ile ilgilidir. Geniş kapsamlı perspektif, AXT'nin çeşitli biyolojik aktivitelerine genel bir bakış sunarak gelecekteki araştırma yönlerini ve çok hedefli bir iyileştirici olarak potansiyelini önermektedir. Bu derleme, AXT hakkındaki bilgileri önemli ölçüde geliştirmeyi, böylece sağlık ve biyomedikal araştırmaların ilerlemesine katkıda bulunmayı amaçlamaktadır.

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Introduction

Astaxanthin (AXT) is a lipid-soluble red-orange oxycarotenoid pigment belonging to the xanthophylls group of carotenoids, which also contains β-cryptoxanthin, canthaxanthin, lutein, and zeaxanthin. AXT was first developed for aquaculture pigmentation purposes, and was approved as a food supplement in 1991 due to the strength of its antioxidant properties, physiological effects and vitamin A precursor ability

shown in both rats and fish. The increasing need for natural AXT has attracted research interest particularly for human nutrition (Fakhri *et al.* 2018). Various sources like microorganisms, phytoplankton, marine animals, and seafood are natural providers of AXT. While wild salmon acquire AXT through the food chain, farmed salmon obtain their characteristic color from AXT feed supplements. *Haematococcus pluvialis* (Flotow), a green microalgae, is a prominent naturalsource of AXT for human consumption. Under stress conditions such as nitrogen deprivation, elevated salinity, and temperature fluctuations, *Haematococcus pluvialis* exhibits enhanced AXT accumulation. Other sources include the yeast *Xanthophyllomyces dendrorhous* (Phaff, Carmo Souza & Starmer), certain plants, fungi, microalgae, i.e. *Chlorococcum* (Geyler) species and *Chlorella zofingiensis* (Dönz), and the marine bacteria *Agrobacterium aurantiacum* (Sahin, Ladha & Young) (Sajilata & Singhal 2008). AXT shares structural similarities with β-carotene, having oxygen groups distinguishing it from other carotenoids. Its extended structure features polar ends and a nonpolar middle, with 13 conjugated double bonds-unique properties contributing to its antioxidant efficacy and light absorption. AXT's hydroxyl and keto groups enhance its polarity and membrane functionality. This polar-nonpolar-polar structure enables precise integration into cell membranes (Martínez-Cámara *et al.* 2021). AXT exhibits common carotenoid-related physiological and metabolic activities. It is present in micro-organisms and marine life as a xanthophyll carotenoid. It is a red, lipid-soluble pigment that lacks pro-Vitamin A functionality within the human body. Nevertheless, certain studies have indicated that AXT exhibits greater biological efficacy compared to other carotenoids (Pérez-Rodríguez *et al.* 2020). United States (US) Food and Drug Administration (FDA) has approvedAXT as an animal feed colorant, while the European Commission categorized it as a food dye. *Haematococcus pluvialis*, who accumulates AXT under stress conditions, is a primary human consumption source and also used for pigmentation in salmon, trout, and shrimp feed. AXT consumption offers preventive and therapeutic benefits for diverse disorders in humans and animals (Fig. 1). Its use as a supplement is burgeoning across various sectors including food industry, feeds, nutraceuticals, and pharmaceuticals (Ambati *et al.* 2014). In the present review, various biological sources, chemical profile and various pharmacological aspects of AXT are summarized.

Biological Sources of AXT

The sources of AXT found in nature encompass algae, yeast, aquatic organisms such as salmon, trout, krill, shrimp, and crayfish. Predominantly, commercially available AXT is obtained from the Phaffia yeast, *Haematococcus* microalgae, or synthesized chemically.

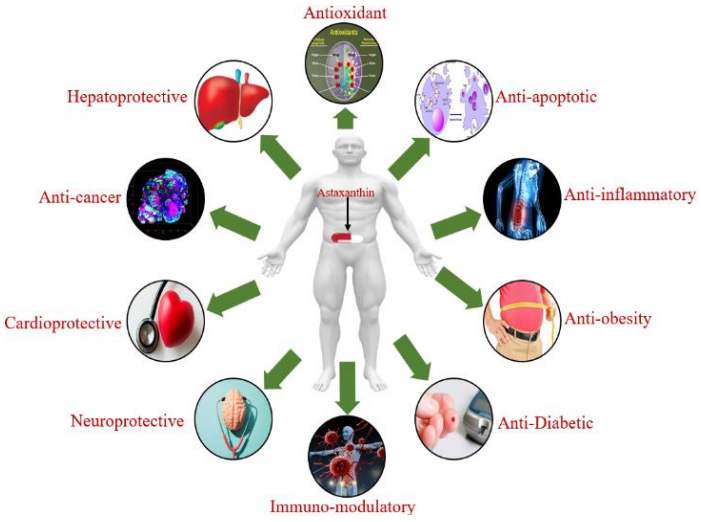

Fig. 1. Graphical representation showing pharmacological activities of AXT.

Among these, *H. pluvialis* stands out as a best natural source of AXT (Capelli *et al.* 2019). Among various species of wild salmon, the highest levels of AXT content have been recorded in sockeye salmon, ranging from 26 to 38 mg/kg of flesh, while comparatively lower content has been observed in chum salmon. Farmed Atlantic salmon has been noted to contain around 6 to 8 mg/kg of flesh (Torrissen *et al.* 1995). Sizable trout derived source produce 6 mg/kg of flesh in the European market while 25 mg/kg of flesh in the Japanese market. Dietary reservoirs of AXT encompass shrimp, crab, and salmon, with wild-caught salmon standing out as a noteworthy natural source. Consuming 165 grams of salmon per day would yield approximately 3.6 mg of AXT. Alternatively, a daily supplement of 3.6 mg of AXT could potentially confer health benefits (Shah *et al.* 2023). The diversification of microorganism-derived AXT sources is outlined in Table 1 and percentage content of AXT present in various biological sources are summarized in Fig. 2 (Ambati *et al.* 2014).

Chemical structure of AXT

AXT possesses a distinct planar structure, featuring two terminal cyclic rings designated as ring A and ring B. Ring A, known as the β-ionone ring, forms a hexagonal framework accommodating asymmetrical carbon atoms at positions 3 and 3', each bonded to hydroxyl groups (-OH) (Fig. 3). These groups contribute to molecular reactivity and stereochemistry of AXT (Brotosudarmo *et al.* 2020). A polyene chain, composed of alternating single and double bonds, links the terminal rings. This chain contains conjugated double bonds, creating interconnected p-orbitals responsible for AXT's light absorption and crimson coloration. The presence of additional functional groups in AXT depends on its molecular form, whether esterified or free. This intricate planar arrangement influences AXT's behavior in optics, chemistry, and biology. AXT's structural distinctiveness aligns with its classification as a xanthophyll. Its composition includes carbon, hydrogen, and oxygen (Seabra & Pedrosa 2010).

Table 1. Biological sources of AXT.

Source	Scientific/Common Name	AXT Content	Notes	Reference
Algae	*Haematococcus pluvialis*	High	Microalgae known for producing high levels of AXT.	(Boussiba & Vonshak 1991)
Algae	*Chlorella zofingiensis*	Moderate	Green microalgae capable of synthesizing AXT.	(Ip & Chen 2005)
Algae	*Nannochloropsis* sp.	Low to Moderate	Microalgae that can produce AXT under specific conditions.	(Fithriani *et al.* 2019)
Algae	*Isochrysis* sp.	Low to Moderate	Microalgae capable of AXT production, often used in aquaculture.	(Crupi *et al.* 2013)
Algae	*Tetraselmis* sp.	Low	Microalgae that can produce small amounts of AXT.	(Binti Ibnu Rasid *et al.* 2014)
Algae	*Dunaliella salina*	Low	Contains a mixture of carotenoids including AXT.	(Chen *et al.* 2020)
Algae	*Chlorococcum* sp.	Moderate	Green microalgae containing AXT pigment.	(Liu & Lee 1999)
Bacteria	*Agrobacterium aurantiacum*	Low	Certain bacteria can be engineered to produce AXT.	(Yokoyama & Miki 1995)
Crustaceans	Shrimp	Moderate	Shrimp accumulate AXT from their diet.	(Yaqoob *et al.* 2022)
Crustaceans	*Brachyura*	Moderate	Certain crab species contain AXT due to their diet.	(Ribeiro *et al.* 2001)
Crustaceans	*Cambarus* sp.	Moderate	Crayfish can possess AXT based on their food intake.	(Song *et al.* 2024)
Crustaceans	Lobster	Low to Moderate	Some lobster species can contain AXT due to their diet.	(Wade *et al.* 2005)
Crustaceans	Prawn	Low to Moderate	Prawns can accumulate AXT from their food sources.	(Zhang *et al.* 2021)
Fish	*Salmo salar*	Variable (high in sockeye)	Wild salmonids, especially the sockeye salmon, acquire AXT from their diet.	(Ytrestøyl & Bjerkeng 2007)
Fish	*Oncorhynchus mykiss*	High	Large trout species are noted for their AXT content.	(Pulcini *et al.* 2021)
Fish	*Euphausiacea*	High	Krill are an abundant source of AXT due to their diet.	(Ibrahim *et al.* 1984)
Fish	Chum Salmon	Low	Chum salmon exhibit lower AXT content compared to other species.	(Kitahara 1983)
Fish	Atlantic Salmon (farmed)	Moderate	Farmed salmon's AXT levels are influenced by their diet.	(Storebakken *et al.* 1987)
Fish	Rainbow Trout	Moderate	Rainbow trout can accumulate AXT, especially when fed AXT-rich diets.	(Foss *et al.* 1987)
Fish	Mackerel	Low	Certain fish species like mackerel can possess AXT.	(Roy *et al.* 2020)
Fish	Herring	Low	AXT content varies in different fish species.	(Bjerkeng *et al.* 1999)
Fungi	*Penaeus monodon baculovirus*	Low	Used in genetic engineering for AXT synthesis.	(Supamattaya *et al.* 2005)
Fungi	*Xanthophyllomyces dendrorhous*	High	Yeast-like fungus used for commercial AXT production.	(Rodríguez-Sáiz *et al.* 2010)
Fungi	*Phaffia rhodozyma*	High	Anamorphic yeast known for its AXT-rich pigment.	(Mussagy *et al.* 2023)
Fungi	*Neurospora crassa*	Low	Fungus capable of AXT production through genetic manipulation.	(Gmoser et al. 2017)
Fungi	*Paracoccus carotinifaciens*	Moderate	Bacterium capable of AXT production, used in research.	(Hayashi *et al.* 2021)

Table 1. Biological sources of AXT (Continued).

Source	Scientific/Common Name	AXT Content	Notes	Reference
Fungi	*Blakeslea trispora*	Moderate	Mucoralean fungus that can synthesize carotenoids, including AXT.	(Choudhari *et al.* 2008)
Insects	*Bombyx mori*	Low	AXT synthesis achieved through genetic modification.	(Chieco *et al.* 2019)
Microalgae	*Chlamydomonas* sp.	Low to Moderate	Green microalgae capable of AXT synthesis under certain conditions.	(Perozeni *et al.* 2020)
Microalgae	*Scenedesmus* sp.	Low to Moderate	Microalgae that can produce AXT as part of their carotenoid profile.	(Aburai *et al.* 2015)
Microalgae	*Spirulina* sp.	Low	Blue-green algae containing AXT in small quantities.	(An *et al.* 2017)
Microalgae	*Botryococcus braunii*	Low to Moderate	Green microalgae with potential for AXT production.	(Indrayani *et al.* 2022)
Microbes	*Escherichia coli*	Low	Genetic engineering can enable AXT synthesis in bacteria.	(Park *et al.* 2018)
Yeast	*Phaffia rhodozyma*	High	Widely used commercial source for AXT production.	(Sedmak *et al.* 1990)
Yeast	*Saccharomyces cerevisiae*	Low	AXT production possible through genetic engineering.	(Ukibe *et al.* 2009)

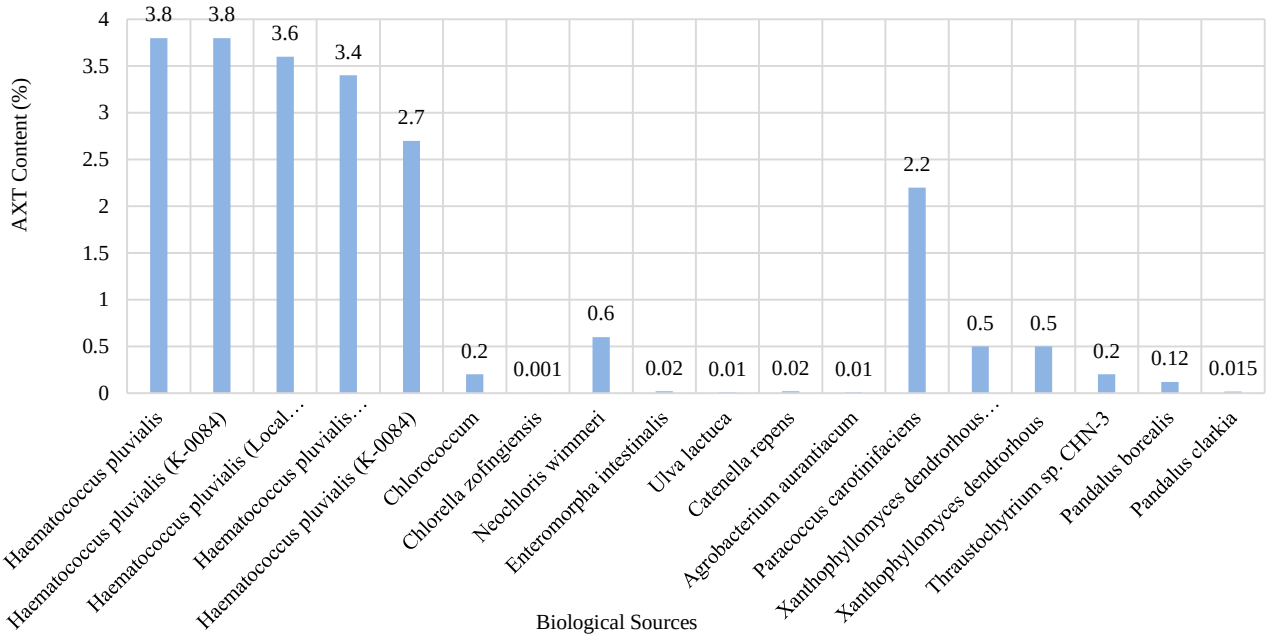

Fig. 2. Biological sources containing AXT. Values were given based on dry weight.

Structurally, AXT comprises paired terminal rings connected by a polyene chain. The β-ionone ring holds significance, hosting asymmetrical carbon atoms at positions 3 and 3', bonded to hydroxyl groups (-OH). This configuration is significant, leading to mono- and di-ester formations upon reaction with fatty acids. AXT's polymorphism is seen in stereoisomers and geometric forms, including liberated and esterified versions, found in natural sources (Yang *et al.* 2011).

In nature, prominent stereoisomers include 3S, 3′S and 3R, 3′R, synthesized by *Haematococcus pluvialis* and *Xanthophyllomyces dendrorhous*, respectively. Synthetic AXT comprises various isomers, including (3S, 3′S), (3R, 3′S), and (3R, 3′R). 3R, 3′R is the dominant stereoisomer found in the Antarctic krill *Euphausia superba* primarily in esterified form. In wild Atlantic salmon, the prevailing form is 3S, 3′S, existing as the free form. The molecular formula AXT is $C_{40}H_{52}O_4$, with a molar mass of 596.84 g/mol. These insights reveal AXT's intricate structure and diverse forms, impacting its behavior and interactions across natural and synthetic realms (Sun *et al.* 2023).

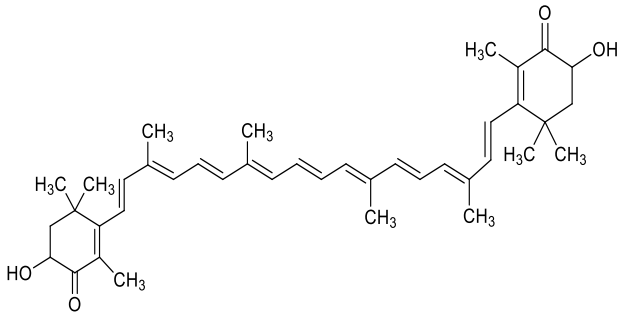

Fig. 3. Chemical structure of AXT.

Bioavailability, Pharmacokinetics and Safety of AXT

Bioavailability

Once released from the food matrix, carotenoids are amassed inside lipid droplets in gastric juices, where they are then incorporated into micelles. These micelles then diffuse into enterocyte plasma membrane. Carotenoids, such as AXT, are carried in circulation via high- and low-density lipoproteins (HDL and LDL, respectively) (Liu *et al.* 2023). AXT and other carotenoids fate relies on their biochemical properties, whereas dietary and non-dietary factors affect their absorption. The content of 3–37 mg/kg of AXT in salmon flesh converts to an intake of approximately 1-7 mg of AXT in a 200-g portion of salmon. The common natural form of AXT in wild salmon is the 3S, 3′S isomer (Odeberg *et al.* 2003). Absorption is affected by dietary habits and smoking; concurrent food consumption tends to enhance absorption, while smoking appears to decrease AXT's half-life. Studies on various animal species, such as mice, rats, dogs, and humans, have investigated AXT absorption from diverse sources (Madhavi *et al.* 2018). In a double-blind trial involving healthy men, daily consumption of 250 g of wild or aquacultured salmon for four weeks yielded differing plasma AXT concentrations. Plasma AXT levels stabilized at 39 nmol/L after consuming wild salmon (3S, 3′S isomer) for six days, and at 52 nmol/L after aquacultured salmon (3R, 3′S) consumption. Interestingly, aquacultured salmon intake led to significantly higher AXT concentrations in plasma on days 3, 6, 10, and 14, though not on day 28. This suggests that AXT intake pattern in plasma mirrors the ingested salmon and that maximal concentrations can be attained within the initial week, regardless of the source (Rüfer *et al.* 2008). Bioavailability and isomer distribution pattern of AXT in human plasma have been investigated while comprehensive studies on AXT's pharmacokinetics and tissue distribution in human skin remain lacking. AXT's lipid-solubility implies improved absorption in the presence of dietary lipids. Oil-based formulations enhance AXT bioavailability; an open parallel study revealed that lipid-based formulations, particularly those with higher hydrophilic synthetic surfactant content, yield the highest bioavailability (Odeberg *et al.* 2003).

It is recommended to consume AXT alongside dietary fats to optimize bioavailability. Future research should replicate these finding using dose aligned with regulatory recommendations. Current literature suggests a lack of significant focus on enhancing AXT bioavailability, especially for skin tissue. Novel delivery methods like nanoparticles, topical creams, and specific phospholipid complexes show promise and warrant further exploration to enhance AXT bioavailability (Lima *et al.* 2021). Different forms of AXT and other factors affecting its bioavailability are represented in Fig. 4.

Pharmacokinetics

Carotenoids undergo absorption akin to lipids, subsequently traversing the lymphatic system to reach the hepatic locale. The efficiency of carotenoid absorption is contingent upon the concurrent dietary constituents. A diet abundant in cholesterol possesses the potential to augment carotenoid absorption, in contrast to a low-fat diet which tends to attenuate it. Following ingestion, AXT interacts with bile acids, leading to the formation of micellar structures within the small intestine.

These AXT-containing micelles experience partial uptake by enteric mucosal cells, thereby effectuating their integration into chylomicra within these cells. Following their release into the lymphatic circulation, chylomicra containing AXT undergo enzymatic hydrolysis by lipoprotein lipase. The subsequent swift clearance of chylomicron remnants by the hepatic organ and other tissues ensues. AXT becomes encompassed within lipoproteins, facilitating its systemic transport to various tissues. Among the diverse repertoire of endogenous carotenoids, AXT is distinguished for its exceptional capacity to shield cells, lipids, and membranous lipoproteins against oxidative impairment (Ambati *et al.* 2014).

Safety

Microalgae-derived AXT (i.e. AXT of *H. pluvialis*) has been authorized as color additives in feed for salmon and as a dietary supplement for human consumption in Western countries, Europe, Japan, and the USA. As part of its regulatory framework, the European Food Safety Authority (EFSA), and specifically its Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), recommends an acceptable daily intake (ADI) for AXT at 0.034 mg/kg body weight (bw), or 2.38 mg/70-kg individual per day. Later on, the EFSA's Panel on Dietetic Products, Nutrition and Allergies (NDA) reaffirmed this scientific position maintaining that a conclusion of establishing the safety for 4 mg/day (0.06 mg/kg bw) of AXT was still to be determined (Agostoni *et al.* 2014, Aquilina *et al.* 2014). Notably, studies involving individuals who were administered more than 4 mg of AXT per day reported no adverse effects (Spiller & Dewell 2003, Res *et al.* 2013). First and foremost, even an acute administration of 40 mg of AXT over 48 hours in 32 healthy people was reported to be largely harmless, with only three mild cases (Odeberg *et al.* 2003). Chronic intake of AXT at 16 and 40 mg per day is safe for patients with functional dyspepsia (Kupcinskas *et al.* 2008). FDA has granted approval for direct human consumption of AXT from *H. pluvialis*, permitting dosages up to 12 mg

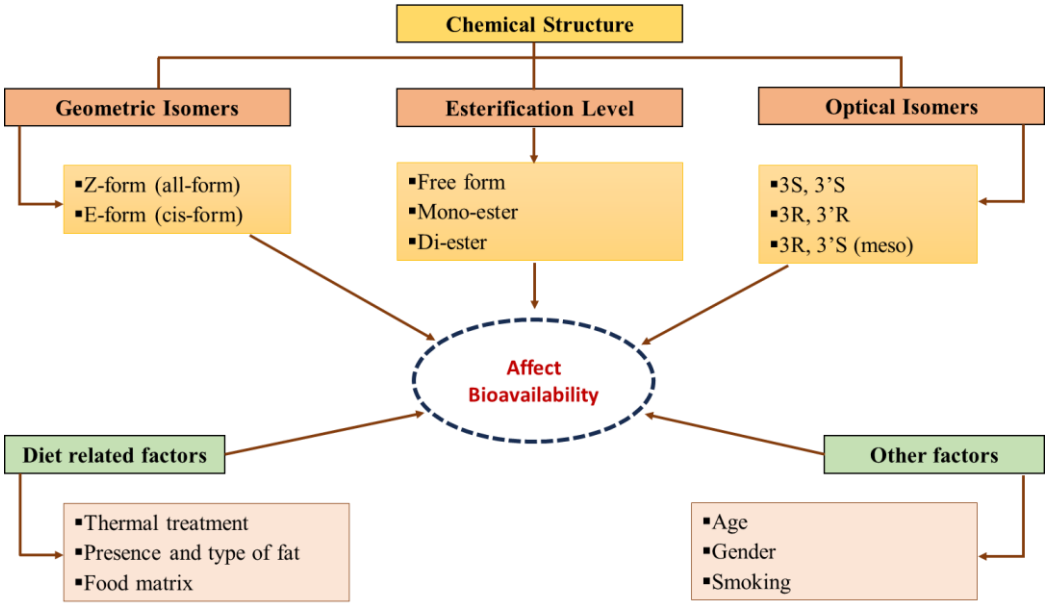

Fig. 4. Representation of different forms of AXT and other factors affecting its bioavailability.

per day and up to 24 mg per day for a duration not exceeding 30 days (Visioli & Artaria 2017). Furthermore, supercritical CO_2 extracts sourced from *H. pluvialis* have obtained "novel food" designation from FDA and are acknowledged as having "GRAS" (generally recognized as safe) status (Shah *et al.* 2016).

Common mechanism of action and biological activities of AXT

Disease progression is a complex phenomenon influenced by a myriad of factors, each exerting a significant impact on the intricate interplay of health and well-being. A suboptimal diet, characterized by nutritional deficiencies or an excess of detrimental components, compromises the body's immune system and overall functionality, fostering an environment conducive to the development of diseases (Childs *et al.* 2019). Infections, initiated by pathogenic microorganisms, have the potential to overpower the body's defense mechanisms, initiating detrimental cascades that contribute to the progression of diseases (Heinzelmann *et al.* 2002). Smoking, a well-established risk factor, introduces harmful chemicals that promote inflammation and OS. Dysfunctional mitochondrial respiration, along with chronic or acute inflammation, disrupts normal cellular activities, acting as influential forces in disease pathogenesis (Winiarska-Mieczan *et al.* 2023). Environmental factors, encompassing pollution, toxin exposure, radiation, drug metabolism, and ischemia-reperfusion injury, collectively contribute to the intricate network influencing disease progression (Heinzelmann *et al.* 2002). AXT, as a potent antioxidant, assumes a pivotal role in this context by modulating the activities of essential antioxidant enzymes at the cellular level, including superoxide dismutase (SOD), catalase, and glutathione peroxidase. Through the neutralization of free radicals and the reduction of OS, AXT augments the cellular antioxidant defense system, presenting potential in the prevention of diseases associated with OS (Kim *et al.* 2009). Scientific investigations revealed that AXT supplementation has shown beneficial effects at doses of 6–18 mg/day for 12 weeks, improving HDL (6 & 12 mg), reducing triglycerides and increasing adiponectin (12 & 18 mg). An 8 mg/day dose for 8 weeks lowered visceral fat, triglycerides, and systolic blood pressure. 12 mg/day for 12 weeks improved insulin resistance and reduced LDL, HbA1c, and OS markers. Studies also reported enhanced antioxidant capacity and lipid profile regulation, with no significant impact on BMI or total cholesterol in some cases (Dansou *et al.* 2021). The common mechanism of action of AXT is summarized in Fig. 5.

Antioxidant activity of AXT

An antioxidant is a molecule that combats oxidation by neutralizing free radicals and reactive oxygen species (ROS). These highly reactive molecules stem from normal aerobic metabolism, causing oxidative damage to proteins, lipids, and DNA, linked to various disorders (Gutteridge & Halliwell 2010). Endogenous and exogenous antioxidants like carotenoids counter this OS. Carotenoids, with their conjugated double bonds, exhibit antioxidant properties by quenching singlet oxygen and halting chain reactions. These benefits likely result from carotenoid interactions with cell membranes (Mohd Aijaz *et al.* 2023). Compared to other carotenoids including lutein, lycopene, α-carotene, and β-carotene, AXT holds superior antioxidant activity. AXT found in *H. pluvialis* offers robust protection against radicals in rats. Its distinctive molecular structure, featuring hydroxyl and keto groups, contributes to its potent antioxidant abilities. AXT's antioxidant potency surpasses zeaxanthin, lutein, canthaxanthin, β-carotene, and α-tocopherol. The polyene chain in AXT traps radicals in cell membranes, while its terminal ring scavenges both inner and outer membrane

radicals (Rao *et al.* 2015). AXT's antioxidant role extends to boosting enzyme activities, as seen in rabbits' diets and ethanol-induced gastric ulcer rats. OS disrupts pro-oxidant/anti-oxidant balance, yielding ROS and free radicals (Augusti *et al.* 2012). Xanthophylls, including carotenoids, counteract this by interrupting radical chain reactions or reacting harmlessly. AXT safeguards against oxidative damage by neutralizing singlet oxygen, scavenging radicals, inhibiting lipid peroxidation, enhancing immune function, and regulating gene expression. Its high antioxidant capacity and polarity make it a promising nutraceutical (Seabra & Pedrosa 2010). *In vivo*, carotenoids like AXT need appropriate tissue transfer and concentration proportional to the oxidizing agent. AXT's antioxidant prowess surpasses vitamin E, neutralizing singlet oxygen and outperforming other photochemical agents (Kogure 2019).

Age affects AXT activity, being more effective in youth due to enhanced antioxidant enzymes. AXT also enhances membrane fluidity, impeding diffusion and bolstering antioxidant efficacy. Scientific investigations revealed that AXT is highly effective to protect against inflammation, cancer, aging, and age-related macular degeneration, along with promoting overall health. It shields the retina from impairment induced by NMDA and antagonizes OS, activating pathways that trigger antioxidant responses (Kandy *et al.* 2022). AXT activates the PI3K/AKT and ERK pathways, facilitating Nrf2 activation and enhancing enzyme expression for protection against OS (Kavitha *et al.* 2013). SOD, catalase,

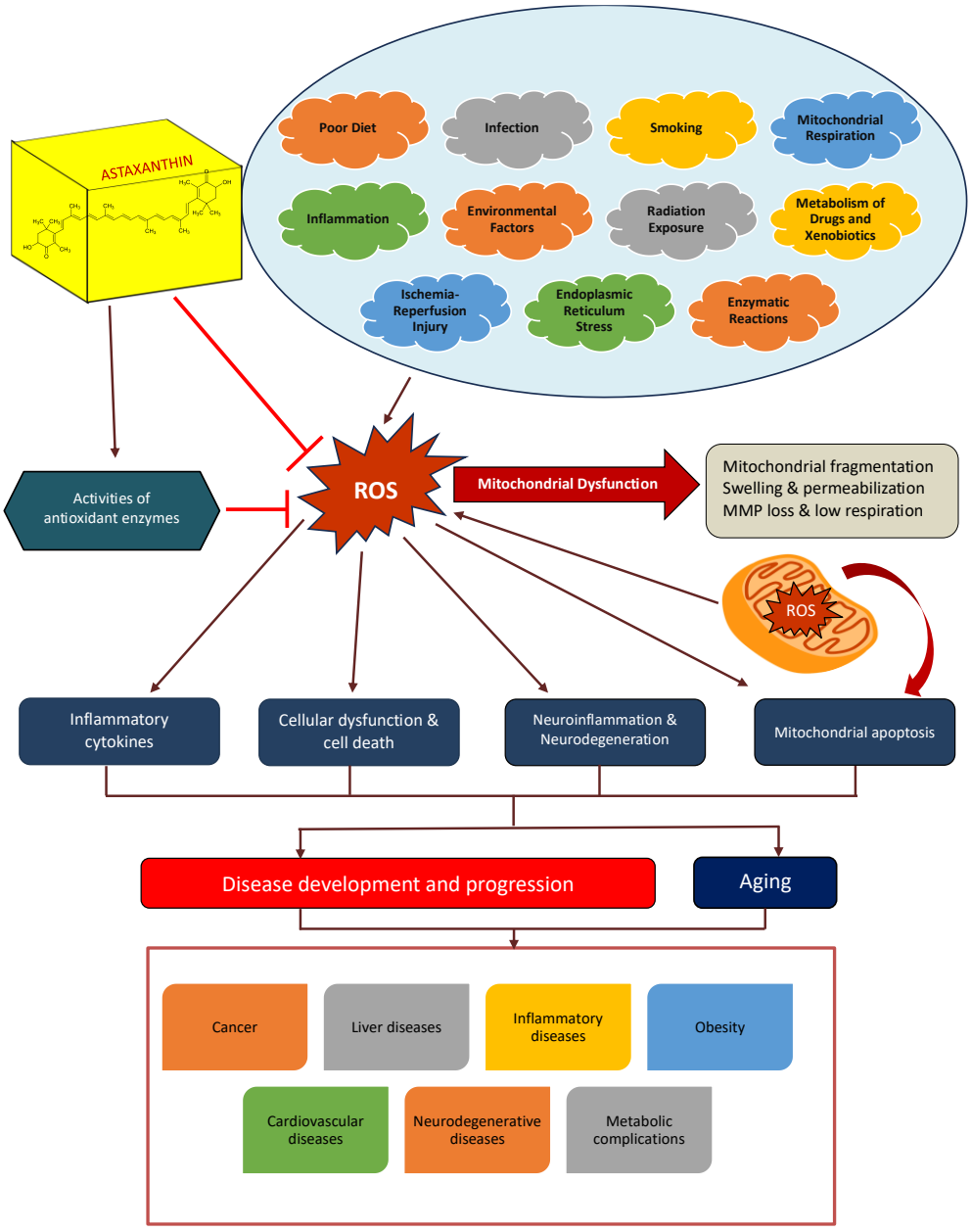

Fig. 5. Diagrammatic illustration of disease development and progression through various factors and common mechanism of action of AXT for their prevention.

TBARS, and peroxidase are elevated in rat liver and plasma after AXT supplementation (Polotow *et al.* 2014). In essence, antioxidants like AXT combat oxidative damage by neutralizing radicals and ROS, offering multifaceted protection against various disorders and promoting overall health (Rodriguez-Ruiz *et al.* 2018). In a study by Dansou *et al*. (2021), laying hens were supplemented with AXT at doses of 0, 21.3, 42.6, and 213.4 mg/kg of feed. The results indicated that while AXT improved antioxidant activities, such as enhancing SOD and glutathione peroxidase (GSH-Px) activities and reducing malondialdehyde (MDA) content in both liver and serum, the highest dose (213.4 mg/kg) did not provide additional antioxidant benefits compared to the moderate doses (21.3 and 42.6 mg/kg). Therefore, for optimal antioxidant activity in laying hens, a supplementation range of 21.3 to 42.6 mg/kg of feed is recommended (Dansou *et al.* 2021).

Antiapoptotic activity of AXT

Neurodegenerative disorders, ischemic stroke, heart ailments, sepsis, and syndromes involving dysfunction in multiple organs are associated with cell death through apoptosis (Sanz *et al.* 2008). Several treatment approaches are available to manage apoptosis. Depending on the specific disease context, AXT may either inhibit or promote apoptosis (Hormozi *et al.* 2019). Intrinsic (mitochondrial) and extrinsic (death receptor) pathways are two primary pathways involved in apoptosis which are influenced by crucial apoptotic proteins (Sanz *et al.* 2008). By influencing these proteins, AXT could modify the course of apoptosis and mitigate associated diseases. AXT has been observed to have a dual impact on apoptosis regulation. It can enhance the phosphorylation of Bcl-2-associated death promoter, while the activation of cytochrome c and caspase 3 and 9 reduces. These effects are mediated through the control of mitogen-activated protein kinase/p38 (p38 MAPK), thereby influencing apoptosis (Li *et al.* 2015). Additionally, AXT activates the survival pathway PI3K/AKT, leading to the improvement of mitochondrial-linked apoptosis (Kim & Kim 2019). Interestingly, AXT has been documented to induce intrinsic apoptotic signaling in a model of oral cancer in hamsters. This is achieved by deactivating ERK/MAPK and PI3K/AKT cascades, ultimately inhibiting NF-κB and Wnt/β-catenin pathways (Kavitha *et al.* 2013). Furthermore, AXT's protective effects extend to retinal ganglion cells, reducing apoptotic cell death and ameliorating conditions like diabetic retinopathy by counteracting OS (Harada *et al.* 2017, Fang *et al.* 2023).

Anti-inflammatory activity of AXT

Inflammation is a complex series of immune responses that activate as a protective mechanism in response to injuries, to initiate the tissue repair process (White & Mantovani 2013). However, when inflammation becomes excessive or uncontrolled, it can be harmful to the host, causing damage to cells and tissues. In both acute and chronic neurodegenerative conditions, inflammation plays a pivotal role (Liu *et al.* 2012). AXT effectively intervenes in biological systems to curb the initiation of inflammation (Moh Aijaz *et al.* 2024). The anti-inflammatory properties of AXT hold significance in halting the advancement of central nervous system disorders (Masoudi *et al.* 2021). AXT acts by blocking the NF-κB-dependent signaling pathway, thereby decreasing expression of downstream inflammatory mediators such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). NF-κB remains inactive in the cytosol under the influence of inhibitory kappa B (IκB) which is a major inhibitor in normal circumstances. Activation of NF-κB triggers a cascade involving IκB phosphorylation by IκB kinase β (IKKβ), IκB degradation through the ubiquitin proteasome pathway, and dissociation of IκB from NF-κB. This exposes NF-κB's nuclear localization signal, thereby regulating the transcription of inflammatory genes (Chang & Xiong 2020). Additionally, AXT displays its anti-inflammatory effects by inhibiting cyclooxygenase-1 enzyme (COX-1) and nitric oxide (NO) in lipopolysaccharide-stimulated BV2 microglial cells. *In vivo* studies have demonstrated AXT's capacity to effectively diminish inflammation in tissues and organs (Pereira *et al.* 2021). AXT's anti-inflammatory prowess extends to diverse conditions, including arteriosclerosis, inflammatory bowel disease, sepsis, rheumatoid arthritis, gastric inflammation, brain inflammatory diseases, and the reduction of bacterial load in mice infected with *Helicobacter pylori* (Bennedsen *et al.* 2000). AXT functions as a potent antioxidant to counteract inflammation's initiation within biological systems (Chang & Xiong 2020). For instance, extracts from algal cells, i.e. of members of the genera *Haematococcus* and *Chlorococcum*, have shown promising results in reducing bacterial load and gastric inflammation in *H. pylori*-infected mice (Wang *et al.* 2000). Studies indicate that AXT can reduce oxidative damage to DNA, thereby enhancing immune responses in healthy human subjects (Park *et al.* 2010). Other research has found that AXT, when combined with *Ginkgo biloba* extract and Vitamin C, leads to reduced inflammation in lung tissues and improved levels of cAMP and cGMP (Haines *et al.* 2011). Furthermore, AXT has demonstrated gastro-protective effects on acute gastric lesions induced by ethanol, possibly due to its influence on various factors such as ATPase inhibition and antioxidant activities (Lee *et al.* 2022). AXT has also been proven effective in mitigating OS, inflammation, and apoptosis caused by high glucose in proximal tubular epithelial cells (Kim *et al.* 2009). Japanese researchers have highlighted AXT's potential for treating ocular inflammation, while its capacity to prevent skin thickening and to reduce collagen loss makes it a promising agent against UV-induced skin damage (Harada *et al.* 2017). In endotoxin-induced uveitis (EIU), a dose-dependent anti-inflammatory effect was observed, with 100 mg/kg AXT showing comparable efficacy to 10 mg/kg prednisolone. AXT improves immune function and reduces inflammation, particularly in individuals with excessive OS, making it a promising candidate for managing inflammatory conditions (Abdelazim *et al.* 2023).

Anti-obesity activity

Obesity stands as a prominent and widespread public health concern impacting diverse age cohorts globally. Its deleterious outcomes encompass a range of severe ailments such as type 2 diabetes, hypertension, hyperlipidemia, and cardiovascular disorders, mediated by assorted mechanisms (Suhel Alam 2024). The pursuit of alternative, safe agents for combating obesity has spurred considerable attention towards AXT due to its promising anti-obesity attributes (Radice *et al.* 2021). Incorporating AXT into the diet as a supplementary component demonstrates the capacity to thwart weight gain, curtail plasma cholesterol levels, diminish plasma and hepatic triacylglycerol (TAG) content, amplify the expression of endogenous antioxidant genes within the liver, mitigate myeloperoxidase and NOS levels, and render splenocytes less responsive to lipopolysaccharide (LPS) stimulation. Furthermore, it holds potential to preempt obesity-linked disruptions in metabolic processes and inflammatory responses (Xia *et al.* 2020). A study by Aoi *et al*. (2008) unveiled that AXT fosters heightened lipid utilization during physical exercise, culminating in a reconfigured muscular metabolism, heightened physical performance, reduced body adiposity, and enhanced efficacy in muscular activities during exercise (Aoi *et al.* 2008). In a randomized double-blind study involving 23 overweight and obese adults (BMI > 25 kg/m²), participants were administered either 5 mg or 20 mg of AXT daily for 3 weeks. The study found significant improvements in OS biomarkers, suggesting potential benefits in managing obesity-related OS (Choi *et al.* 2011). Another study examined the combined effects of high-intensity functional training and AXT supplementation (20 mg/day) over 12 weeks in obese men. Results indicated reductions in body weight, body fat percentage, and improvements in lipid profiles, highlighting the potential of AXT in weight management when combined with exercise (Saeidi *et al.* 2023). AXT emerges as an innovative selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), operating as an antagonist or agonist to exert its beneficial impacts on obesity and insulin resistance (Taghiyar *et al.* 2023).

Anti-diabetic Activity

OS levels are notably elevated in diabetes mellitus patients, primarily attributed to hyperglycemia-induced dysfunction of pancreatic β-cells and concurrent tissue damage (Yang *et al.* 2011). AXT holds promise in mitigating hyperglycemia-induced OS within pancreatic β-cells, while concurrently enhancing glucose and serum insulin levels. AXT's protective influence extends to shielding pancreatic β-cells against glucose toxicity, and it demonstrates immunomodulatory potential in the context of lymphocyte dysfunction associated with diabetic rats (Kanwugu *et al.* 2022).

In tandem, AXT combined with α-tocopherol exhibited the ability to counter OS and ameliorate its effects in streptozotocin-induced diabetes in rats (Yeh *et al.* 2016). This versatile compound also impedes glycation and cytotoxicity induced by glycated proteins in human umbilical vein endothelial cells through the inhibition of lipid and protein oxidation (Mashhadi *et al.* 2018). In metabolic terms, AXT effectively enhances insulin sensitivity in models of high-fat/high-fructose diet-induced obesity, both in spontaneously hypertensive corpulent rats and mice. This effect is attributed to its stimulation of the insulin receptor substrate (IRS)–PI3K–AKT signaling pathway, achieved through a reduction in serine phosphorylation of IRS proteins. Consequently, this leads to improved glucose metabolism through the regulation of metabolic enzymes, particularly in insulin-resistant mice (Naito *et al.* 2004, Zhuge *et al.* 2021). Notably, AXT demonstrates a multifaceted approach to combatting diabetes-associated complications. It effectively decreases urinary albumin levels and exhibits potential in preventing diabetic nephropathy by diminishing OS and curtailing renal cell damage. This encompasses the restoration of enzyme activities in salivary glands and the attenuation of glycation-induced cytotoxicity in human umbilical vein endothelial cells (Zhang *et al.* 2021). Animal studies investigated the effects of AXT on metabolic syndrome features in SHR/NDmcr-cp rats. The rats were administered AXT at a dose of 50 mg/kg body weight per day for 22 weeks, leading to improved insulin sensitivity and lipid metabolism parameters (Hussein *et al.* 2007). A clinical study involving healthy volunteers with prediabetes, participants were administered 12 mg of AXT daily for 12 weeks. The results indicated improvements in glucose metabolism and reductions in modified low-density lipoprotein levels (Urakaze *et al.* 2021). Another randomized clinical, placebo-controlled trial assessed the effects of 12 mg/day AXT over 24 weeks in individuals with prediabetes and dyslipidemia. The study found that AXT improved lipid profiles and reduced markers of cardiovascular disease risk, with trends toward improved insulin sensitivity (Ciaraldi *et al.* 2023). Overall, AXT emerges as a versatile therapeutic candidate, addressing hyperglycemia-induced OS, enhancing insulin sensitivity, and potentially mitigating diabetic complications.

Immuno-modulatory activity

Immune cells are highly vulnerable to damage from free radicals, particularly due to the presence of polyunsaturated fatty acids (PUFAs) in their cell membranes (Das 2011). The protective role of antioxidants, particularly AXT, in safeguarding immune defenses from free radical harm is significant. While animal studies under laboratory conditions have explored AXT's impact on immunity, clinical research in humans remains limited (Fakhri *et al.* 2018). In comparison to β-carotene, AXT has demonstrated more potent immuno-modulating effects in mouse models. Notably, older animals displayed improved antibody production and reduced humoral immune responses following dietary AXT supplementation. Laboratory investigations

revealed that AXT prompted immunoglobulin production in human cells (Jyonouchi *et al.* 1994). Notably, an eight-week AXT supplementation regimen in humans resulted in heightened blood AXT levels, improved activity of natural killer cells targeting virus-infected cells, increased counts of T and B cells, reduced DNA damage, and significantly lower C-reactive protein (CRP) levels in the AXT-supplemented group (Sekikawa *et al.* 2023).

Both *in vivo* and *in vitro* studies on rats have unveiled AXT's influence on immunity, while human clinical research remains scarce. AXT's heightened immuno-modulating effects compared to β-carotene have been evidenced in mouse models. Additionally, aged animals witnessed enhanced antibody production and diminished humoral immune responses through dietary AXT supplementation (Ohgami *et al.* 2003, Donoso *et al.* 2021). Further investigations demonstrated AXT's ability to activate humoral immune and cell-mediated reactions in canines and felines, regulate lymphocytic immune responses *in vitro*, and partly exert *ex vivo* immunomodulatory effects by elevating interferon-gamma (INF-γ) and interleukin-2 (IL-2) production without cytotoxicity (Lin *et al.* 2016). In various *in vitro* settings, AXT showcased the potential to elevate antibody secretory cell production, T-helper cell antibodies, and various immunoglobulins (IgM, IgG, IgA) in response to T-dependent stimuli (Fan *et al.* 2021). An *in vivo* study by Jyonouchi *et al.* (2000) indicated that dietary supplementation with AXT could potentially restore immune responses. In the face of stress, AXT effectively counteracts the decline in immunological functions by boosting immune responses mediated by natural killer (NK) cells and T lymphocytes, while also reducing DNA damage and CRP levels (Jyonouchi *et al.* 2000).

Neuroprotective activity

Neurological disorders encompass a range of conditions leading to disability, including both acute injuries and chronic neurodegenerative diseases. The underlying pathogenesis of many of these disorders involves inflammation, OS, and apoptosis (Suescun *et al.* 2019). A compound of particular interest in this context is AXT, which possesses the unique ability to traverse the Blood Brain Barrier (BBB) due to its fat-soluble nature. Given its diverse activities, AXT holds considerable promise as a potential therapeutic option for both acute and chronic neurological diseases (Si & Zhu 2022).

Recent investigations conducted in the laboratory have delved into the biological properties of AXT using an *in vivo* model. The findings from these studies underscore the favorable neuroprotective attributes of AXT in animal models of spinal cord injury (SCI). The heightened metabolic activity within the brain renders it susceptible to OS (Bahbah *et al.* 2021). However, AXT demonstrated the capability to enhance the activities of antioxidant enzymes and mitigate OS markers in distinct central nervous system (CNS) regions. Additionally, AXT exhibited a dampening effect on pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), and NOS (Yook *et al.* 2016). In a study on pilocarpine-induced status epilepticus in rats, AXT was administered at a dose of 30 mg/kg body weight every other day for two weeks. The treatment improved cognitive function and reduced neuronal apoptosis, OS, and inflammation in the hippocampus (Deng *et al.* 2019). Furthermore, as alluded earlier, AXT has demonstrated its neuroprotective potential across experimental models of diverse neurological disorders. This efficacy is attributed to its multifaceted mechanisms, including anti-oxidative, anti-inflammatory, and anti-apoptotic actions (Fakhri *et al.* 2019). Notably, AXT's efficacy spans conditions such as Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, traumatic injuries, inflammatory-induced injuries, and age-related dementia. The broad spectrum of functionalities exhibited by AXT in the context of neurological disease treatment underscores its role as a versatile and multi-target pharmacological agent (Fakhri *et al.* 2018).

Cardioprotective activity

Elevated generation of reactive oxygen and nitrogen species stimulates transcriptional agents, propelling the development of atherosclerosis, disruption of endothelial function, and harm subsequent to ischemic reperfusion and arrhythmia (Xiang *et al.* 2021). The likelihood of cardiovascular ailments is positively linked to cholesterol concentrations, specifically focusing on low-density lipoprotein (LDL), inflammation and OS form the basis of numerous cardiovascular symptoms (Yang *et al.* 2018). AXT exhibits cardioprotective effects by enhancing inflammation, lipid and glucose metabolism, and antioxidant activity. AXT inhibits free radicals and 7-ketocholesterol formation, curbing atheroma. It prevents arteriosclerosis by inhibiting LDL oxidation, lowering macrophage infiltration, apoptosis, and plaque rupture, enhancing plaque stability via adiponectin (Zaafan & Abdelhamid 2021). AXT reduces pro-inflammatory cytokines, Matrix Metalloproteinase (MMP) activation, and scavenger receptor upregulation in macrophages, regulating atherogenesis related functions. It counters inflammation and OS, curbs lipid peroxidation, thrombosis, and protects against cardiovascular damage in animal models and human cells (Derias *et al.* 2021). AXT ameliorates diabetes-related coagulation by its anti-oxidative and anti-inflammatory effects, increasing red blood cell concentrations. It safeguards against isoproterenol cardiotoxicity through free radical scavenging and antioxidant activity, a potential adjuvant therapy. AXT's impact on coronary disease prevention is underexplored (Krestinina *et al.* 2020). It reduces blood pressure by attenuating the renin-angiotensin system, angiotensin-II, and ROS-induced vasoconstriction, enhancing NO bioavailability and endothelial function, primarily in resistant arteries. AXT improves vascular elastin, arterial wall thickness, and blood fluidity in hypertension. It augments heart mitochondrial function,

reduces pro-inflammatory markers, suggesting a role in cardiac protection (Gao *et al.* 2021). OS and inflammation characterize atherosclerotic cardiovascular disease, making AXT a potential therapeutic due to its antioxidant and anti-inflammatory potential (Kara & Kilitçi 2023). Disodium disuccinate astaxanthin (DDA) shows promise in protecting myocardium, reducing infarct size and enhancing salvage. AXT is detected in myocardial tissues post DDA treatment (Adam Lauver *et al.* 2005). In hypertensive and normotensive rat models, AXT influences blood pressure, increases basal arterial blood flow, elevates nitric oxide, and reduces peroxynitrite levels (Kara & Kilitçi 2023). In mice, AXT elevates heart mitochondrial potential and contractility index. AXT prevents hypercholesterolemia-induced protein oxidation in rabbits through paraoxonase and thioredoxin reductase activity maintenance at dosages of 100 mg and 500 mg/100 g (Augusti *et al.* 2012).

Anti-cancer activity

Aerobic metabolism generates reactive species like superoxide, hydroxyl radical, and hydrogen peroxide, while photochemical reactions and lipid peroxidation produce singlet oxygen and peroxyl radicals (Martemucci *et al.* 2022). These processes contribute to aging, carcinogenesis, mutagenesis, and degenerative diseases by oxidizing proteins, DNA, and lipids. Antioxidants mitigate oxidative damage, decreasing carcinogenesis and mutagenesis (Sun *et al.* 2020). Carotenoids, notably AXT, attract attention for their anticancer potential due to their inverse correlation with cancer prevalence (Ramamoorthy 2020). AXT surpasses other carotenoids like β-carotene and canthaxanthin in antitumor efficacy. Gap junctional communication is impaired in human tumors due to absent cell-to-cell connections, but AXT's promotion of connexin-43 protein via gene upregulation restores this communication, curbing tumor proliferation (Demirel & Tuna 2021).

AXT exhibits antitumor effects in various cancers, restraining growth and inducing cell death. Moreover, AXT curbs metastasis, inhibits 5-α-reductase to suppress prostate cancer, and triggers anti-invasive pathways (e.g., NF-κB, STAT3, PPARγ). Downregulating MKK1/2-ERK1/2-mediated thymidylate synthase expression enhances non-small cell lung carcinoma sensitivity to pemetrexed-induced cytotoxicity (Faraone *et al.* 2020). AXT demonstrates preventive effects in carcinogenesis models, including large bowel and tongue cancers. It suppresses bladder and oral cancers, regulates immunity, and delays tumor initiation, implying optimal blood AXT levels safeguard against tumorigenesis. However, AXT supplementation post-tumor initiation may be counterproductive ROS from aerobic metabolism. Singlet oxygen and peroxyl radicals arise from photochemical events and lipid peroxidation, contributing to aging and degenerative diseases via DNA, protein, and lipid oxidation (Yasui *et al.* 2011, Immacolata Faraone *et al.* 2020). Antioxidants counteract ROS-induced mutagenesis and carcinogenesis. Natural carotenoids and retinoids enhance gap junctional communication between the cells. For instance, AXT derivatives improve intercellular communication in primary human skin fibroblasts. AXT exhibits potent antitumor activity compared to canthaxanthin and β-carotene, restraining fibrosarcoma, breast, and prostate cancer growth (Rivera-Madrid *et al.* 2019).

AXT's impact extends to inhibiting cell death, proliferation, and mammary tumors in chemically induced rodents. *Haematococcus pluvialis* extract, rich in AXT, hinders human colon cancer cell progression via cell cycle arrest, apoptosis, and cytokine suppression (Lim & Wang 2020). Nitroastaxanthin and 15-nitroastaxanthin, products of AXT and peroxynitrite, demonstrate anticancer effects. AXT treatment inhibits Epstein-Barr virus and mouse skin papilloma carcinogenesis (Ambati *et al.* 2014).

Hepatoprotective activity

AXT, as a potent antioxidant, has demonstrated remarkable preventive and therapeutic effects on various liver conditions. It addresses liver fibrosis, tumors, ischemia-reperfusion injury, and non-alcoholic fatty liver disease by modulating crucial signaling pathways (Li *et al.* 2015). It curtails JNK and ERK-1 activity to enhance liver insulin sensitivity, suppresses PPAR-γ expression to reduce hepatic fat synthesis, and inhibits TGF-β1/Smad3 to counteract HSC activation and fibrosis. It also targets JAK/STAT3 and Wnt/β-catenin pathways to impede liver tumor progression, and safeguards against ischemia-reperfusion injury by mitigating apoptosis and autophagy (Jannel *et al.* 2020). AXT's benefits extend to lipid accumulation, insulin resistance, ROS, and lipid oxidation products in the liver. It mitigates these issues by reducing lipid buildup and insulin resistance. It curbs lipid peroxidation (LPO), augments cellular antioxidants like TBARS, glutathione, and SOD, and emerges as a hepatoprotective agent (Li *et al.* 2020). Following liver ischemia-reperfusion injury, AXT treatment maintains hepatic xanthine dehydrogenase and curbs protein carbonyl levels (Bernabeu *et al.* 2023). AXT also intervenes in hepatic stellate cell (HSC) activation and extracellular matrix formation. It accomplishes this by downregulating NF-B and TGF-1 expression, preserving MMP2/TIMP1 balance, and influencing energy production in HSCs through autophagy modulation and apoptosis stimulation (Zheng *et al.* 2023). AXT effectively counteracts apoptosis and autophagy induced by hepatic IR injury by neutralizing ROS and inflammatory cytokines, attributed to MAPK family inactivation (Wei & Guo 2022). In mouse models, AXT (80 mg/kg) significantly alleviates liver fibrosis through the suppression of profibrogenic factors, possibly via downregulation of NF-κB p65 and Wnt/β-catenin pathways, achieved by inhibiting ERK and PI3K/AKT activation (Zhuang *et al.* 2021). Overall, AXT emerges as a versatile agent for liver protection and treatment, acting on various pathways to address a spectrum of liver-related conditions (Azadian *et al.* 2024).

Conclusion and future perspectives

AXT represents an exciting and promising nutraceutical and pharmaceutical with innumerable biological activities and health benefits. As a powerful antioxidant, it performs a key function to lower OS, improve inflammation, and prevent cell damage. Its therapy use is widespread in neuroprotection, cardiovascular diseases, metabolic disorders, and cancer prevention. AXT is effective, however, it depends heavily on the dosage, because not all these health problems require the same dosage of AXT to work properly. For general signals of health and antioxidant support, some studies suggest 4–12 mg doses per day while for neuroprotective and cognitive enhancement, clinical results show greater efficacy with higher doses between 6–16 mg per day. In metabolic diseases like diabetes and obesity, AXT has improved insulin sensitivity, glucose metabolism, and lipid regulation when supplemented at 8–12 mg/day. Doses of 5–20 mg daily were shown to inhibit body fat accumulation and improve lipid metabolism for weight management. Cardioprotective effects like decreasing LDL oxidation and improving circulation are noticed in doses of 8–12 mg daily. For instance, AXT has successfully inhibited tumor growth, mediated apoptosis, and prevented metastasis in preclinical studies using higher doses of 10–50 mg/kg body weight in cancer model systems. Indeed, additional clinical trials will be needed to establish accurate cancer-dosage levels for humans. One of the main obstacles in AXT research is guided by its bioavailability, despite its many health benefits. It is usually poorly absorbed in human body, as it is a lipid-soluble compound. In the future, advanced delivery systems, such as nano-emulsions, lipid-based carriers, and phospholipid complexes, should be developed in order to facilitate the absorption and effectiveness of AXT. Moreover, large-scale human clinical trials are warranted to develop dosage guidelines and confirm long-term toxicity. Exploration of synergistic effects of AXT with other bioactive compounds represents another encouraging area of research. Incorporating AXT with other polyphenols, flavonoids, or conventional medicines may yield higher therapeutic effects, especially for chronic diseases like cancer, cardiovascular diseases, and neurodegenerative diseases. Biotechnological approaches regarding the future AXT production may offer a sustainable and cost-effective alternative for the commercial availability of AXT in the near future. As the global demand for this potent carotenoid is ever-increasing, optimizing microalgae-based biosynthesis together with improving the extraction methods can help to scale up the production of AXT. Moreover, the role of AXT in healthy aging and longevity represents a fascinating research avenue within and beyond the realm of DI diseases. This is important because its ability to resist oxidative damage, optimize mitochondrial function, and modulate inflammatory pathways, indicate that it may help prevent many age-related diseases which include Alzheimer's, Parkinson's, and cardiovascular diseases as well.

Summarizing, AXT appears to be a very promising natural compound with pleiotropic health applications. However, more research is required to fine-tune dosing and enhance bioavailability, along with larger scale clinical trials, in order to capitalize on its potential to do so. With continuous advancements in biotechnology, formulation science, and clinical research, AXT could become a key player in modern medicine, offering innovative strategies for disease prevention, treatment, and overall health improvement.

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