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PHARMACOTHERAPEUTIC POTENTIAL OF ASTAXANTHIN: HUMAN AND ANIMAL TARGETING ROLES – A REVIEW

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Abstract

The recent pandemic stress and the impacts of climatic changes on humans' and animals' health status and well-being resulted in severe drawbacks. Initially, stress-induced oxidation resulting from the generation of free radicals led to the impairment of cellular function and a high possibility of attack with infection. Astaxanthin is a bioactive material derived from fish, crustaceans, and algae with high antioxidative potential. Astaxanthin is a lipid-soluble carotenoid that can easily cross through the cellular membrane layers to catch the reactive oxygen metabolites. Astaxanthin also has pigmentation properties making it suitable for pharmaceutical, cosmetic, nutraceutical, agriculture, and aquaculture sectors. Recently, astaxanthin is suggested as a natural scavenger for free radicals induced by COVID-19. Besides, using astaxanthin as antioxidative and immunostimulant agents is well-reported in several clinical studies. The output of these investigations should be simplified and presented to the scientific community to utilize the available information and fill the gap of knowledge. Also, it is necessary to update the researchers with the recent recommendations of applying astaxanthin *in vivo* and *in vitro* to help in proposing new horizons for engaging natural antioxidative agents to protect human and animal health. Herein, this review article tackled the nature, sources, potential roles, applicable sides, and availability of astaxanthin to fortify the scientific community with the required knowledge for further research efforts.

Key words: astaxanthin, human health, animal welfare, well-being, immuno-therapy, immuno-nutrition

Astaxanthin is one of the carotenoids with bioactive natural substances and sourced from plants, photosynthetic microorganisms, and crustaceans (Brotosudarmo et al., 2020; Raza et al., 2021). Many carotenoids play a vital role in the photosynthetic reactions while some other play a role in protection of organisms from photooxidation (Brotosudarmo et al., 2020). Astaxanthins are among the most abundant xanthophyll pigments, which are responsible for the characteristic red to pink color of salmon, crustaceans and some birds (Galasso et al., 2017). Astaxanthin was first isolated from lobsters in 1938 (Lorenz and Cysewski, 2000). Naturally, many organisms are a natural source of astaxanthin including green algae, bacteria, fungi, crawfish, shrimp, crabs, Antarctic krill, marine copepoda, and salmonids (Ambati et al., 2014; Dominguez-Bocanegra et al., 2004; Kusdiyantini et al., 1998). Several marine organisms are abundant in astaxanthins which are responsible for the coloration of skin and flesh of fish, shells, and crustaceans (Breithaupt, 2007). Astaxanthins are known for their

pigmentation effects which are required for the coloration of some aquatic animals (Lim et al., 2018). Further, astaxanthin is consumed by the ornamental fish species to enhance the coloration of egg yolk and skin. In the poultry industry, astaxanthin can also enhance coloration and reduce lipid peroxidation in birds' meat (Akiba et al., 2001). Astaxanthin inclusion enhanced the antioxidative capacity in aging roosters, leading to high semen quality (Gao et al., 2021). Further, astaxanthin addition did not affect the titer of antibodies to Newcastle disease, infectious bronchitis, avian rhinotracheitis, and egg drop syndrome in the serum of vaccinated laying hens (Shevchenko et al., 2021). In fact, fishes, and animals are unable to synthesize astaxanthin, while the color of these animals is the result of bioconcentration of the pigment due to consumption of algae and other microorganisms (Fitton et al., 2015; Shekarabi et al., 2020).

Haematococcus pluvialis is the most prevalent and promising producer of astaxanthin, it can produce 10–15% d.w. under certain stress conditions (Ambati et al.,

2014). Astaxanthin has a lot of health benefits including its strong antioxidant effects, anti-lipid peroxidation effect, anti-inflammatory effect, anticancer, antidiabetic effects in addition to the protection from heart diseases (Lauver et al., 2005; Park et al., 2010; Rao et al., 2013; Uchiyama et al., 2002). Many patents are available for the use of astaxanthin in pharmaceutical applications (Lu et al., 2021; Ng et al., 2021; Radice et al., 2021). Recently, astaxanthin have been produced commercially in many forms including for instance tablet, capsule, soft gel, biomass powder, cream, and oil in the market (Table 1). The global market of astaxanthin was estimated to be USD 600 in 2018 and it is expected to reach USD 880 million by 2024 with the increasing awareness of the various nutritional and pharmaceutical roles and the safety of its use (Donoso et al., 2021). While chemically synthesized astaxanthin is most cost effective, pharmaceutical, food, and cosmetics industries use exclusively the natural one (Fakhri et al., 2020).

Table 1. Pharmaceutical products of astaxanthin

Product	Form	Component
Astaxanthin Ultra	Soft gel	4 mg (astaxanthin)
Best Astaxanthin	Soft gel	6 mg (astaxanthin & canthaxanthin)
Physician Formulas	Soft gel/Tablets	2–4 mg (astaxanthin)
Astavita ex	Capsules	8 mg (astaxanthin)
Zanthin Xp-3	Soft gel capsules	2–4 mg (astaxanthin)
Pure Encapsulations	Capsules	(astaxanthin)
AstaREAL	Oil	(astaxanthin, astaxanthin ester)
AstaTROL	Oil	(astaxanthin)

The COVID-19 pandemic has recently threatened humanity, and massive efforts were made to counteract its fatal consequences (Brendler et al., 2021; Hamulka et al., 2021). Antiviral drugs were prepared and offered to people with the hope of inhibiting this fatal pandemic (Butters and Whitehouse, 2021). However, these antivirals are not fully approved as treatments against COVID-19 (Chowdhury et al., 2021). The possibility of infection with COVID-19 varies among people due to the differences in immune responses and health status (Feng et al., 2021). The resistance against infection with COVID-19 relies on natural immunity, which can be activated by using natural functional substances such as astaxanthin (Bogan-Brown et al., 2021). Although no investigations confirmed the possible protective roles of astaxanthin against COVID-19 infection, astaxanthin can be proposed as a natural supplement involved in the protection against oxidative stress, immunosuppression (Lu et al., 2021; Oslan et al., 2021), and features associated with COVID-19 infection.

The potential effects of marine-derived astaxanthins on the health and well-being of ruminants, birds, and aquatic animals as leading sources for animal protein are presented in this review. The antibacterial, antiviral,

antioxidative, anticancer, anti-inflammation, and immunostimulant effects are also investigated. Comprehensively, herein we present an optional supplement that may relieve the negative impacts of COVID-19 infection.

Sources, structure, and bioavailability of astaxanthin

Astaxanthin pigment (3,3'-dihydroxy- β,β -carotene-4,4'-dione) is a 40 carbon tetraterpenoid with molecular weight of 596.8 g/mol and density of 1.081 g/L (Stachowiak and Szulc, 2021). The xanthophyll pigment which is a metabolic product of zeaxanthin and/or canthaxanthin consists of two terminal β -ionone-type rings joined by a polyene chain with two asymmetric carbons located at the 3,3'-position of the β -ionone ring and hydroxyl group of both ends of the molecule (Higuera-Ciagara et al., 2006). Astaxanthin may be present in free form inside the cell or esterified form as the hydroxyl group (OH) of one or both rings can bind to a number of fatty acids such as oleic, palmitic, stearic, and linoleic acid and form mono- or diesters (Udayan et al., 2017). Three geometrical isomers are known for astaxanthin, two of them are enantiomers (3R,3' R) and 3S,3' S) and one is a meso form (3R,3' S) (Figure 1). The green alga *Haematococcus* in addition to wild salmon are famous for synthesizing the 3S,3' S isomer, while the *Euphausia superba* (Antarctic krill) produce the 3R,3' R as the primary isomer (Ambati et al., 2014). Unlike the natural astaxanthin which exists in esterified or in complex with proteins or lipids, the synthetic one is never esterified and contains the three isomers 3S,3' S, 3R,3' S, and 3R,3' R in a 1: 2: 1 ratio, respectively (Higuera-Ciagara et al., 2006).

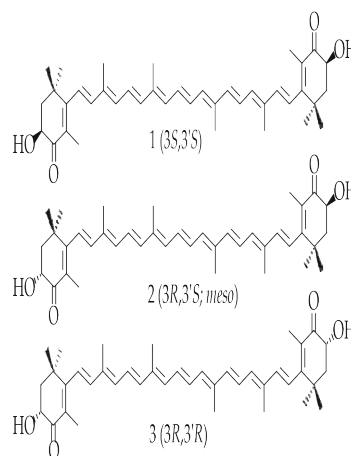


Figure 1. Stereoisomers of astaxanthin (Donoso et al., 2021)

As a lipophilic compound astaxanthin absorption increases when combined in dietary oils. Bioavailability of astaxanthin in human plasma was confirmed after consumption of a single dose of 100 mg of *H. pluvialis* as a source of astaxanthin (Okada et al., 2009). Interestingly, the bioavailability of astaxanthin was enhanced with the use of lipid base formulation (Olson, 1994). In another study 28 volunteers were given either 250 mg

of wild salmon or aquaculture salmon, the astaxanthin levels in plasma were higher at 3, 6, 10, and 14 days during the farming season rather than wild salmon, with the (3-S, 3'-S) isomer of astaxanthin showing the higher level in plasma (Rüfer et al., 2008). The bile salt plays a crucial role in the absorption of different carotenoids as carotenoids should be hydrolyzed before absorption (Olson, 1994). The absorption of the carotenoids is enhanced with fat-based diet and reduced in the low-fat diets. After ingestion, astaxanthin with the bile salt makes micelles in the intestinal lumen. The astaxanthin is finally assimilated via lipoprotein lipase and then distributed into different tissues (Olson, 1994). In general, the half-life of plasma elimination of astaxanthin from blood is 52 ± 4 h (Coral-Hinostroza et al., 2004).

Mode of action

Although astaxanthin has been linked to various health advantages, they have been proven to differ depending on the astaxanthin source (natural or synthetic), its isomeric variation, and even the consumer's diet (Donoso et al., 2021). This might be one of the reasons why various research obtained inconsistent findings when analyzing the same parameters and pharmacokinetics of astaxanthin (Nagao, 2009). Hence, we included astaxanthin's main mode of action based on the *in vivo* and *in vitro* studies in the following lines.

Immunomodulation

Carotenoids, especially astaxanthin, offer very good protection for the immune system from free radicals which affect the immune system badly (Lu et al., 2021; Oslan et al., 2021). Although there are many reports about the effect of astaxanthin on animals, there is limited clinical research on humans. Jyonouchi et al. (1995) concluded that astaxanthin enhances the production of immunoglobulins *in vitro* by peripheral blood mononuclear cells in response to T-dependent recall antigen (Ag). In

another study, Park et al. (2010) reported that supplementation of astaxanthin for 8 weeks increases natural killer cell cytotoxic activity and increases generally the total T and B cell subpopulations. Additionally, they reported a lower rate of DNA damage and significantly lower levels of CRP proteins in the astaxanthin supplemented group.

Antimicrobial activity

A number of studies, although few, indicate antimicrobial activity of astaxanthin especially against bacterial organisms (Table 2). Ushakumari and Ramanujan (2013) proved moderate antibacterial activity of astaxanthin when compared to chloramphenicol antibiotic against bacterial pathogens including *Bacillus subtilis*, *Salmonella typhi*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In another study, high antimicrobial activity was noticed via the carotenoid pigment extracted from *Sporobolomyces* sp. against *Escherichia coli* and *S. aureus* (Manimala and Murugesan, 2014). In the same context, Suganya and Asheeba (2015) concluded high antibacterial activity of crab isolated astaxanthin against *E. coli* isolated from spoiled milk and rotten meat. In a recent study Rather et al. (2021) studied the antimicrobial activity of astaxanthin against *E. coli*, *S. typhi*, *Vibrio cholera* and *S. aureus*. The highest antibacterial activity was observed against *E. coli* with inhibition zone of 10.2 ± 0.20 mm, while the lowest activity was displayed against *V. cholera* with inhibition zone of 6.1 ± 0.0 mm. Astaxanthin was also found to have an antimicrobial effect against *Helicobacter pylori* and protect from gastric ulcers (Wang et al., 2000). In fact, there are few studies that explain the mechanism of antimicrobial activity of astaxanthin, but the antimicrobial effect may be due to many factors including for instance alteration of the composition of the bacterial cell wall and cell membrane (Devine and Hancock, 2002).

Table 2. Models of antimicrobial activity studies of astaxanthin

Type of study	Organisms	Dose	Activity	References
<i>In vitro</i>	<i>Bacillus subtilis</i> , <i>Salmonella typhi</i> , <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i>	1–100 µg/ml	Maximum inhibition was attained against <i>Pseudomonas aeruginosa</i> with inhibition zone of 24 mm.	Ushakumari and Ramanujan (2013)
<i>In vitro</i>	<i>Enterococcus</i> sp., <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>	100 µg/ml	Antimicrobial activity against <i>E. coli</i> with inhibition zone of 29 mm and <i>S. aureus</i> with inhibition zone of 26 mm.	Manimala and Murugesan (2014)
<i>In vitro</i>	<i>E. coli</i> isolated from spoiled milk and rotten meat	50 µg	Antimicrobial activities against <i>E. coli</i> with inhibition zone range of 10.05 ± 0.53 mm to 12.11 ± 0.95 mm	Suganya and Asheeba (2015)
<i>In vitro</i>	<i>Escherichia coli</i> , <i>Salmonella typhi</i> , <i>Vibrio cholera</i> and <i>Staphylococcus aureus</i>	10 µl	Antibacterial activity was against <i>E. coli</i> with inhibition zone of 10.2 ± 0.20 mm using acetone extract of astaxanthin. The lowest activity was against <i>Vibrio cholera</i> with inhibition zone of 6.1 ± 0.0 using hexane extract of astaxanthin.	Rather et al. (2021)

Table 3. Models of antioxidant and anti-lipid peroxidation activities of astaxanthin

Type of study	Subjected population (n)	Dose	Duration	Health effect	References
<i>In vivo</i>	n=24	1.8 21.6 mg /day	2 weeks	Decrease LDL oxidation	(Iwamoto et al., 2000)
<i>In vivo</i>	n=40 (healthy non-smokers)	mg/ day	12 weeks	Decrease the oxidation of fatty acids	(Karppi et al., 2007)
<i>In vitro</i>	human umbilical-vein endothelial cells (HUVEC)	0–100 µg	24–72 h	Inhibit glycation and and glycated protein induced cytotoxicity in HUVEC	(Nishigaki et al., 2010)

Antioxidant and anti-lipid peroxidation activity

Antioxidants are molecules with a protective function against free radicals, which has a determinable effect on human body (Dawood et al., 2021 a). Free radicals are molecules with one or more unpaired electrons so as to have a high chemical reactivity (Bolarin et al., 2016). These radicals are normally produced through normal aerobic metabolism or through exposure to ionizing radiation, cigarette smoking, drug ingestion, chemicals such as acetyl phenyl hydrazine and hydrogen peroxide (Ekpe et al., 2018). The presence of excessive free radicals reacting with proteins, lipids and DNA molecules causes damage of these molecules which result in a number of disorders (Flaman et al., 2001). Antioxidants which may be either enzymes like superoxide dismutase, catalase, and glutathione reductase or dietary antioxidants such as vitamins A, C, E play a vital role in the inhibition of these free radicals (Table 3). Carotenoids are mainly composed of polyene chain in addition to long conjugated double bonds, which are responsible for the antioxidant activity (Naguib, 2000). Comparing to other carotenoids, astaxanthin is considered to have higher antioxidant activity as well as lowering lipid peroxidation (Naguib, 2000). Astaxanthin adjusts the redox state within the cellular mitochondrial membrane via lipophilic property (Ge et al., 2013). Karppi et al. (2007) assessed that the astaxanthin supplementation for three months decreased the *in vivo* oxidation of fatty acids in healthy non-smoking men. In another study, Iwamoto et al. (2000) concluded that consumption of astaxanthin from marine sources inhibited LDL oxidation. Astaxanthin is showed also to inhibit glycation in human umbilical vein endothelial cells though preventing lipid/protein oxidation (Nishigaki et al., 2010).

Anti-inflammatory activity

Astaxanthin is a potent antioxidant playing a vital role in the inhibition of inflammation in the biological

systems, especially human (Ambati et al., 2014). Haines et al. (2011) concluded that a combination of astaxanthin, vitamin C, and *Ginkgo biloba* extract suppressed inflammation with efficiency superior to Ibuprofen (widely used non-steroidal anti-inflammatory drug, NSAID). Park et al. (2010) observed the reduction in DNA oxidative damage biomarker inflammation, which improved young women's immunity. Additionally, astaxanthin plays a vital role in minimizing inflammation at local and systematic levels (Bhuvaneswari et al., 2010).

Astaxanthin for human health

Although there are many studies that evaluated the medical and pharmacological importance of astaxanthin, studies on humans are very few and most of them conducted on healthy volunteers. Majority of these studies are performed to assess the perfect dose, bioavailability, and safety of astaxanthin (Table 4).

Cancer represents the second cause of mortalities globally and was encountered to be responsible for about 8.8 million deaths in 2015 (McGuire, 2016) and reached around 10 million deaths in 2020 (Ferlay et al., 2020). Healthy cells are controlled by signals that manage the cell division and discriminate into another cell or die. These signals give cancer cells a sense of autonomy, resulting in unregulated differentiation and division (Weinberg, 2013). Antioxidants, especially carotenoids, are known for their ability to decrease carcinogenesis (Chatterjee et al., 2012). The anticancer activity of carotenoids may be a result of enhancing cell to cell communication as the carotenoids increase the synthesis of the gap-junction protein and connexin-43 (Woolfe, 1992). Astaxanthin induced apoptosis and inhibition of growth and proliferation of LS-180 colorectal cancer cells through increasing expression of BAX and caspase-3 and decreasing Bcl-2 expression (Hormozi et al., 2019). Similarly, the different stereoisomers of astaxanthin induce apoptosis of HCT-116 and HT-29 colon cancer cells (Liu

Table 4. Clinical studies about astaxanthin

Type of study	Population (n)	Dose	Duration	Health effect	References
<i>In vivo</i>	n=3	100 mg	2 weeks	Proved that astaxanthin taken up via VLDL chylomicrons.	(Østerlie et al., 2000)
<i>In vivo</i>	n=35	6 mg/day	8 weeks	Prove the safety of astaxanthin through measuring of blood pressure and blood biochemistry parameters.	(Spiller and Dewell, 2003)
<i>In vivo</i>	n=27	4 mg/day	12 months	Improve the retinal function.	(Parisi et al., 2008)
<i>In vivo</i>	n=20	6 mg/day	10 days	Improve the blood rheology.	(Miyawaki et al., 2008)

et al., 2016 b). It also inhibits the growth and the proliferation of breast, embryonic fibroblasts and prostate cancer cells (Palozza et al., 2009). It is found that astaxanthin inhibits STAT3 protein which is activated in the cancerous cells and plays a vital role in inhibiting the expression of crucial immune response, STAT3 is greatly accompanied to prostate cancer in addition to breast cancer and human leukemia, multiple myeloma, head and neck squamous cell carcinoma (Franceschelli et al., 2014; Zou et al., 2020).

Animals responses to astaxanthin

Livestock and poultry

A limited number of studies on the potential of astaxanthin in ruminants were reported (Raza et al., 2021). Kumar and Singh (2019) described positive Karan Fries heifers' responses to the daily dietary astaxanthin at 0.25 mg/kg body weight under heat stress conditions in terms of enhanced weight, feed efficiency, Bcl-2 (B-cell lymphoma 2), adipose leptin hormone, and lowered skin temperature, plasma cortisol, interleukins, and nuclear factor-kappa B (NF- κ B), and caspase-3 expression patterns. In the same line, dietary astaxanthin increased the glucose and reduced plasma prolactin, non-esterified fatty acids, and respiration rate in the Egyptian buffalo (Carballo et al., 2019). Zenteno-Savín et al. (2002) explained that feeding newborn lambs on a milk substitute enhanced with astaxanthin (6 mg/day) led to an improvement in the quality of meat by boosting meat and fat redness, stability of lipid, and reduced the accumulation of butylated hydroxytoluene (BHT) in meat.

The effect of using astaxanthin in the poultry industry has been studied at all stages e.g. broiler chicks, laying hens, and egg quality. Hosseindoust et al. (2020) investigated astaxanthin dietary implementation at levels of 0, 20, 40, and 80 ppm on heat-stressed broiler chickens,

and trial results showed reduced hyperthermic stress while also improving meat quality (increased redness and yellowness of breast meat) and antioxidant status in muscle (increased total antioxidant capacity, 2,2-diphenyl-1-picrylhydrazyl radical scavenging, and 3-ethylbenzothiazol-6-sulfonate reduction activity as well as reduced malondialdehyde, MDA) and plasma (increased catalase, superoxide dismutase). Moreover, astaxanthin downregulates expressions of hepatic heat shock protein (HSP 27, 70), tumor necrosis factor (TNF), and interleukin 6. Similarly, Gao et al. (2020) observed affirmative impacts of dietary astaxanthin on lipid/sterols metabolism genes, heat shock proteins (HSP90, HSP70, and P38MAPK), tumor necrosis factor (TNF), interleukin-6, diacylglycerol acyltransferase 2 (DGAT2), c-Jun N-terminal kinase 1 (JNK1), and P38 mitogen-activated protein kinase (P38MAPK). Liang et al. (2009) stated that dietary astaxanthin increased the egg quality, yolk color, and storage time were positive, with no effect on the yolk index, Haugh units, yolk pH, weight loss, and eggshell strength in laying hens. In the same context, Goto et al. (2001) reported that dietary astaxanthin can help in the improvement of egg storage and reduce the lipid peroxidation leading to high quality eggs.

Aquaculture

The role and applications of astaxanthin in aquaculture are well-reviewed by Lim et al. (2018). Owing to the positive impacts of astaxanthin and the inability of aquatic animals to synthesize it, it is fundamentally important to provide an external supply of astaxanthin (Lim et al., 2018). The focus has been on the various stages of production, starting with brood stock, reproductive efficiency (egg and sperm production and qualities), growth performance, survival, resistance to diseases, and stressors (Paibulkichakul et al., 2008; Palma et al., 2017).

Table 5. Aquatic animal reproductive performances with astaxanthin

Species	Dose	Impacts	References
Sea horse (<i>Hippocampus guttulatus</i>)	75–125	+ Egg quality	(Palma et al., 2017)
Goldfish (<i>Carassius auratus</i>)	150	+ Spermatocrit value	(Tizkar et al., 2015)
		+ Sperm concentration	
		+ Motility	
		+ Osmolality	
		+ Fertilization rate	
		+ Egg survival rate	
Black tiger shrimp (<i>Penaeus monodon</i>)	500	+ Number of spermatozoa	(Paibulkichakul et al., 2008)
		+ Number of eggs	
Atlantic cod (<i>Gadus morhua</i>)	73.5	+ Egg quality	(Sawanboonchun et al., 2008)
		+ Larval production	
Rainbow trout (<i>Oncorhynchus mykiss</i>)	0.07–92.91	+ Egg quality	(Ahmadi et al., 2006)
		+ Fertilization rate	
		+ Hatching rate	
		+ Survival rate	

+ (Enhanced)

Reproductive performance was boosted with astaxanthin application (Tables 5, 6, 7) at different levels in goldfish, *Carassius auratus* (150 mg astaxanthin/kg diet) (Tizkar et al., 2015), shrimp, *Penaeus monodon* (500 mg astaxanthin/kg diet) (Paibulkichakul et al., 2008), rainbow trout, *Oncorhynchus mykiss* (0.07–92.91 mg astaxanthin/kg diet) (Ahmadi et al., 2006). The functional role of astaxanthin may rely on its ability to accumulate within different tissues, including sex organs, which may indicate maturity and readiness for mating (Foote et al., 2004; Nie et al., 2011; Nordeide et al., 2006). Moreover, the major benefits of astaxanthin are due to its powerful antioxidant potential to quench immoderate levels of harmful free radicals, avoiding peroxidation or oxidative damage to reproductive cells and tissues, as well as developing eggs (Dufossé et al., 2005). Also, astaxanthin boosts the immunity system by heightening antibodies and proliferation of immune cells (Kiron, 2012; Magnadottir, 2010). Astaxanthin was suggested to be the first

source of retinoids in eggs which has a key role in cell signaling during embryo development (Kin Ting Kam et al., 2012).

Aquatic animals; growth and survival are a mirror of proper nutrition, of which a balanced feed is a basis (Dawood, 2021; Mohammadi et al., 2020 b). Astaxanthin impacts on growth and survival were remarkable in different studies (Hansen et al., 2016; Niu et al., 2014; Palma et al., 2017; Wade et al., 2017; Wang et al., 2019 a, b, 2018) and insignificant in others (Liu et al., 2016 a; Pham et al., 2014; Yi et al., 2014). Astaxanthin varied results may be linked to differences in aquatic animals (species, size, physiological condition), management, water characteristic, and dietary constituents (Lim et al., 2018). The role of astaxanthin in improving growth and survival is due to promoted nutrient assimilation, intermediary metabolism in cells, antioxidant potential, and hemolymph cells level (Amar et al., 2001; Kiron, 2012; Wade et al., 2017).

Table 6. Growth and survival responses in aquatic animals to astaxanthin

Species	Dose	Growth	Survival	References
Atlantic cod (<i>Gadus morhua</i>)	50–100 mg/kg diet	+	+	(Hansen et al., 2016)
Giant tiger prawn (<i>Penaeus monodon</i>)	0, 25, 50 or 100 mg/kg diet	+		(Wade et al., 2017)
Giant tiger prawn (<i>Penaeus monodon</i>)	0.1%	+	+	(Niu et al., 2014)
Red king crab (<i>Paralithodes camtschaticus</i>)	380 mg/kg diet	+	+	(Daly et al., 2013)
Pacific white shrimp (<i>Penaeus vannamei</i>)	80 mg/kg diet	+	+	(Zhang et al., 2013)
Giant tiger prawn (<i>Penaeus monodon</i>)	0.1%	+	+	(Niu et al., 2012)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	12.5–92.9 mg/kg diet	+		(Bazyar Lakeh et al., 2010)
Whiteleg shrimp (<i>Penaeus vannamei</i>)	100, 200 or 400	+	+	(Niu et al., 2009)
Pacific white shrimp (<i>Penaeus vannamei</i>)	80 mg/kg diet	+	+	(Flores et al., 2007)
Kuruma prawn (<i>Penaeus japonicus</i>)	50–100 mg/kg diet		+	(Chien and Shiau, 2005)
Red porgy (<i>Pagrus pagrus</i>)	40 mg/kg diet	+		(Kalinowski et al., 2005)

+ (Enhanced)

Table 7. Astaxanthin potent stress reliever and immunostimulant roles in aquatic animals

Species	Dose	Stress	References
Yellow catfish (<i>Pelteobagrus fulvidraco</i>)	80 mg/kg diet	Acute crowding stress	(Liu et al., 2016 a)
Oscar (<i>Astronotus ocellatus</i>)	200 mg/kg diet	<i>Aeromonas hydrophila</i>	(Alishahi et al., 2015)
Oriental river prawn (<i>Macrobrachium nipponense</i>)	50–150 mg/kg diet	Thermal shock (0°C), ammonia (0.75 mg/L), and reduced oxygen (0.5 mg/L)	(Tizkar et al., 2015)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	100 mg/kg diet	Infectious hematopoietic necrosis virus (IHNV)	(Amar et al., 2012)
Giant freshwater prawn (<i>Macrobrachium rosenbergii</i>)	0.67 and 1.34 nmol/g via injection	<i>Lactococcus garveae</i>	(Angeles Jr et al., 2009)
Pacific white shrimp (<i>Penaeus vannamei</i>)	100–400 mg/kg diet	Low dissolved oxygen	(Niu et al., 2009)
Pacific white shrimp (<i>Penaeus vannamei</i>)	80 mg/kg diet	Low salinity	(Flores et al., 2007)
Kuruma prawn (<i>Penaeus japonicus</i>)	50–100 mg/kg diet	Low dissolved oxygen	(Chien and Shiau, 2005)
Giant tiger prawn (<i>Penaeus monodon</i>)	200–300 mg/kg diet	Low dissolved oxygen White spot syndrome virus (WSSV)	(Supamattaya et al., 2005)
Giant tiger prawn (<i>Penaeus monodon</i>)	80 mg/kg diet	Thermal stress	(Chien et al., 2003)
Giant tiger prawn (<i>Penaeus monodon</i>)	71.5 mg/kg diet	Ammonia	(Pan et al., 2003)

Diseases and stresses in aquaculture are the main threats, which most recent studies seek to overcome using environmentally friendly approaches (Dawood et al., 2021 b; El Basuini et al., 2021; Gewaily et al., 2021; Mohammadi et al., 2020 a). Astaxanthin is a potent stress reliever and immunostimulant (Niu et al., 2014; Tizkar et al., 2015). The key function of astaxanthin is upris- ing functional components such as strengthening hepatic function (Chien et al., 2003), boosting antioxidants (Liu et al., 2016 a), enhancing hyper osmoregulatory ability (Flores et al., 2007), improving hemolymph (Wade et al., 2017), allowing them to mount a more effective defense against disease outbreaks and adverse or stressful situa- tions e.g. (hypoxic, ammonia, heat, and osmotic varia- tions).

Conclusion remarks

Astaxanthin offers broadly beneficial effects when delivered to animals, birds, and humans. In this regard, the antibacterial, anti-oxidative, anti-inflammation, anti- apoptosis, and anti-stressor effects are widely illustrated *in vivo* and *in vitro*. Besides, immunostimulant potential is confirmed in several animal and human-related stud- ies. Concurrently, astaxanthin is expected to enrich the entire body with high resistance and immunity against COVID-19 infection. However, no efforts were seen to confirm the anti-COVID-19 roles of astaxanthin. There- fore, further future studies are suggested to evaluate the possible antiviral roles of astaxanthin in humans.

Author contributions

Authors shared equally in this work. All authors have read and agreed to the published version of the manu- script.

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Conflicts of interest

The authors declare no conflict of interest.

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