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Biological Targets and Pharmacology of Astaxanthin

Rubiya Farhaaz *Shalini Awasthi* and Cheenu Bhargava
Department of Pharmacology, Advance Institute of Biotech and Paramedical Sciences, Kanpur-209217, Uttar Pradesh, India

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ABSTRACT
Numerous studies have demonstrated the potential health benefits of astaxanthin in the prevention and treatment of a wide range of illnesses, including cancer, chronic inflammatory diseases, metabolic syndrome, diabetes, diabetic nephropathy, cardiovascular diseases, gastrointestinal disorders, liver disorders, neurodegenerative disorders, eye disorders, skin disorders, and Alzheimer's disease. This article summarises the most significant astaxanthin-related scientific research on its biological activities that is currently available.
Keywords: astaxanthin, skin, antioxidant, anti-inflammatory, oxidative stress

I. INTRODUCTION

The naturally occurring yellow, orange, or red colours of many vegetables and fruits are provided by carotenoids, which are the precursors to vitamin A. They are natural pigments that are regularly supplied with highly conjugated -bond systems. Carotenoids can be divided into two categories based on their structural similarities: (i) the sole elements in carotenes, also known as carotenoid hydrocarbons, are carbon and hydrogen; (ii) in contrast, xanthophylls, also known as oxygenated carotenoids, may contain a variety of functional groups (epoxy, methoxy, hydroxy, carbonyl, and carboxyl acid groups).

Along with the most well-known carotenoid, -carotene, astaxanthin, a marine xanthophyll carotenoid that was first isolated from a lobster, has recently drawn a lot of interest. Algal species such Haematococcus pluvialis (where it accumulates up to 3.8 percent on a dry weight basis), Chlorella zofingiensis, and Chlorococcum, as well as the yeast Phaffia rhodozyma, create large amounts of astaxanthin. Salmonids, crustaceans, and even certain non-aquatic species, like the flamingo, all exhibit the deep pink colour that astaxanthin gives them. Sea species must get astaxanthin from their meals, which include zooplankton and krill, as they are unable to make it on their own. The amount of astaxanthin in Krill oil ranges from 0.1 to 1.5 mg/mL, depending on the processing processes[1,2].

Astaxanthin (AST), which has three isomers, is derived from β-carotene. However, AST's two oxygenation groups on each of its rings set it apart structurally from -carotene. A minor quantity of AST is obtained by biological organisms, while the majority of AST comes from petroleum[3].

It is a red C40 molecule and one of the most prevalent aquatic carotenoids. It stands out within its chemical family since research has revealed that it has a 100–500 times greater antioxidant capacity than the well-known and widely utilised antioxidant -tocopherol (Vitamin EThe only natural astaxanthin source that has been approved for human consumption so far is H. pluvialis. Consuming crustaceans (such as copepods, shrimp, and krill) and Salmonidae (such as salmon, rainbow trout) species, whose diets contain astaxanthin natural sources, is another indirect way to consume astaxanthin.

The astaxanthin molecule has two asymmetric carbon atoms at positions 3 and 3'. As a result, three separate optical isomers or enantiomers are possible: 3S, 3'S, 3R, 3'R, and 3R, 3′S. The most prevalent isomers in nature are those with the chirality 3S, 3'S or 3R, 3'R; among these, the former has the highest known antioxidant activity. A combination of 3R,3'R, 3R,3′S, and 3R,3'R isomers make up synthetic astaxanthin (1:2:1). Astaxanthin has hydroxyl and keto groups as well as conjugated double bonds, and it exhibits both lipophilic and hydrophilic characteristics. Its red colour and, more importantly, its strong antioxidant capacity are both due to the conjugated double bonds in its centre, which donate the electrons needed to react with free radicals and turn them into more stable compounds, preventing the chain reactions caused by free radicals. The hydrogen atom at the C3 methine has been proposed as a radical trapping site in the terminal

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ring moiety of astaxanthin, which has the ability to trap free radicals as well. Astaxanthin is a molecule that may scavenge radicals from the surface of the cell and at the interior of the phospholipid membrane because it exhibits both lipophilic and hydrophilic characteristics. When compared to other antioxidants like -carotene or vitamin C, which can only exist inside or outside the lipid bilayer membrane, respectively, astaxanthin has this property that sets it apart from others[4].

Antioxidant Activity

The ageing process and cutaneous damage in humans are greatly influenced by oxidative stress. The production of reactive oxygen species (ROS) through oxidative metabolism and exposure to ultraviolet (UV) light from the sun, respectively, are the mechanisms of intrinsic (chronological) and extrinsic (photo-) ageing. Consequently, the generation of ROS is a key factor causing skin ageing. DNA damage, inflammation, decreased antioxidant synthesis, and the development of matrix metalloproteinases (MMPs), which break down collagen and elastin in the dermal skin layer, are all oxidant events of skin ageing. Because of its potent antioxidant activity and distinct molecular and biochemical messenger capabilities, ASX has recently attracted the attention of researchers due to its potential for treating and preventing skin diseases.

Comparative research on the photoprotective properties of carotenoids has shown that ASX is a better antioxidant than canthaxanthin and -carotene in human skin fibroblasts. As a sign of oxidative stress and a regulatory mechanism involved in the cell's defence against oxidative damage, heme oxygenase-1 (HO-1) is one of the oxidative stress-responsive enzymes that is modulated by ASX[5,6].

Oxidative stress

An imbalance between prooxidant and antioxidant species characterises oxidative stress, which causes macromolecular damage, disturbance of redox signalling, and loss of cellular control. It is a defining characteristic of a number of illnesses, such as the metabolic syndrome, chronic fatigue syndrome, neurodegenerative, cardiovascular, inflammatory, and age-related diseases. Astaxanthin's distinct molecular structure allows it to pass through the bilayer membrane and offer tenacious defence against oxidative damage. In both the inner and outer layers of the cellular membrane, it can scavenge and quench ROS and free radicals (superoxide anion, hydrogen peroxide, singlet oxygen, etc)[1].

Anti-Inflammatory Properties

It is widely known that UV exposure causes a rise in a number of proinflammatory skin indicators. By producing proinflammatory mediators, keratinocytes play a vital part in the photodamage response following UV exposure. It has been demonstrated that ASX therapy reduces UV-induced reactive nitrogen species generation, inflammatory cytokine expression, and apoptosis in keratinocytes, protecting against the harmful effects of UV. Inducible nitric oxide (iNOS) and cyclooxygenase (COX)-2 levels were significantly reduced by ASX, and keratinocytes released less prostaglandin E2 in response to UV light[7].

Immune-Enhancing Effects

There is strong evidence that, in both mouse models and people, immune system suppression plays a role in the development of cutaneous malignancies brought on by solar UV exposure, including melanoma and non-melanoma. In numerous in vitro and in vivo studies, ASX has a profound impact on immunological function. Studies conducted in vitro on human cells have shown that ASX increases the synthesis of immunoglobulin in response to T cell-dependent stimulation[8].

Effects on Skin Damage

Collagen, elastin, and glycosaminoglycans are the dermal extracellular matrix's (ECM) most significant and numerous structural components (GAGs). These structures alter with ageing, both intrinsic and extrinsic. These alterations include wrinkle formation, dryness, and impaired wound healing in addition to the loss of tensile strength and rebound capacity. In addition, UV-induced ROS promote the synthesis of MMPs, which are in charge of breaking down the ECM. MMPs, in particular, have the ability to completely break down collagen. In vitro, ASX successfully reduces free radical-induced cell damage and MMP-1 production in skin after UV exposure[5].

Inflammatory bowel disease (IBD)

A range of diseases known together as inflammatory bowel disease (IBD) can result in colorectal cancer. By lowering the expression of inflammatory-related cytokines such IL-1, IL-6, and COX-2, AST therapy has been demonstrated to somewhat inhibit the development of colonic mucosal ulcers and adenocarcinoma[3].

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Skeletal muscle atrophy

Skeletal muscle atrophy can happen as a result of both physiological and pathological circumstances, including immobility, ageing, chronic illnesses (including heart failure and kidney failure), and cancer. It has been established that there is a link between oxidative stress and muscle mass, that an increase in reactive oxygen species production accelerates the atrophy of inactive muscles by increasing protease activation,[9] and that the activation of oxidative stress pathways in wasting muscles may result in apoptosis. In many animal models, astaxanthin administration before and/or during hind limb unloading avoided muscle atrophy[1].

Neuropathic pain (NP)

When the somatosensory nerves are injured or ill, neuropathic pain (NP) develops. By lowering the expression of the inflammatory signalling modulators NR2B and p-p38MAPK and the inflammatory cytokine TNF-, decreasing ERK1/2, and activating AKT, AST has also been demonstrated to lessen neuroinflammation and mechanical allodynia. This lessens mechanical and thermal pain[3].

Effects on DNA Repair

DNA damage results from skin exposure to UV light. Defects in DNA repair, which can result in oncogenic mutations, are largely to blame for the medically damaging effects of exposure to UV radiation. According to reports, ASX enhances the ability of cells exposed to UV light to repair DNA. ASX was particularly effective at reducing DNA damage and affecting the speed of DNA repair[5].

Diabetes mellitus (DM)

High blood sugar is a symptom of diabetes mellitus (DM), which is also linked to inflammation and oxidative stress. Activating the NF-B pathway, generating VEGF to prevent microvascular damage, and modulating the MAPK and PI3K/Akt pathways all contribute to the effectiveness of AST in the treatment of diabetic retinopathy and diabetic neuropathy[3].

According to various research done on type 1 and type 2 DM animal models, ASX administered orally or parenterally decreases hyperglycemia, improves insulin resistance and insulin secretion, and protects against retinopathy, nephropathy, and neuropathy[10].

Neuroprotective activity

AST has been demonstrated to provide defence against Parkinson's and Alzheimer's diseases (PD). In a double-transgenic mouse model of AD called APP/PSEN1 (APP/PS1), supplementation with docosahexaenoic-acid-acylated astaxanthin diesters (AST-DHA) reduced cognitive impairment through controlling oxidative stress and reducing neuroinflammation. In order to determine the anti-apoptotic efficiency of DHA-astaxanthin treatment, researchers added DHA-AST (DHA-acylated AST ester), non-esterified AST, and DHA + AST (the combination of non-esterified AST and DHA) to a PD murine model. JNK and P38 MARK pathway activation served as a mediator for this impact[3].

Anticancer Effects

Through a number of mechanisms, including the reduction of cell growth, the activation of apoptosis, and the disruption of cell cycle progression, ASX has proven anticancer potential. NF-B, Janus kinase (JAK)/STAT-3, phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt), MAPK, Nrf2, and PPAR are suggested molecular targets for combating ASX-induced cancer[11].

Overall, this study's findings demonstrate that, in contrast to other encapsulation techniques and the drug's free form, astaxanthin liposomally encapsulated exhibits good in vitro anticancer activity in HepG2 Cell Lines and is non-toxic to Vero (Normal) Liver Cell Lines[12].

Detoxification And Liver Function

When defending the mitochondria of rat liver cells against lipid peroxidation, astaxanthin is significantly more effective than vitamin E. Additionally, astaxanthin stimulates the rat liver's production of xenobiotic metabolising enzymes, which may help prevent the development of cancer. In the kidney and lung, astaxanthin can activate enzymes that metabolise xenobiotics. Recent research on astaxanthin's effects in obese mice fed a high-fat plus high-fructose diet revealed that it prevented weight gain, improved insulin sensitivity, and protected against liver injury by lowering levels of cytochrome P450 2E1, myeloperoxidase, and nitro-oxidative stress and increasing antioxidant status.

Additionally, astaxanthin eliminated the high calorie diet-induced fat accumulation and elevated transforming growth factor-b expression. According to these research, astaxanthin may be useful in avoiding obesity, the metabolic syndrome,

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and liver disease brought on by insulin resistance and obesity in wealthy nations[13].

Antimicrobial Activity

Numerous techniques, including the agar well diffusion method, were used to study antimicrobial activity. Tests were conducted on each of the six extracts on gramme positive and gramme negative bacteria. In comparison to other extracts, methanolic extract had the highest zone of inhibition against all of the bacteria (E. coli, Bacillus, Staphylococcus, and Pseudomonas)[14].

II. CONCLUSION

A number of disorders, such as malignancies, hypertension, diabetes, cardiovascular, gastrointestinal, hepatic, neurological, and skin conditions have been linked to astaxanthin. Its antioxidant qualities protect sick cells from oxidative damage. Astaxanthin esters (mono-di) and their metabolic routes in biological systems are not well studied. Future studies should concentrate on how astaxanthin esters affect various biological processes and how they are used in pharmaceutical and nutraceutical products. This natural substance has the ability to alter a wide range of molecular targets and cellular signalling pathways. For their use in commercial applications, additional study on their metabolic pathways and molecular studies in in vitro and in vivo models are required.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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