

Astaxanthin: An algae-based natural compound with a potential role in human health-promoting effect: An updated comprehensive review

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ABSTRACT

Astaxanthin (ASX) is a xanthophyll carotenoid, naturally synthesized by Algae, Yeast, and bacteria. They are not just a powerhouse of antioxidant properties but also possess anti-inflammatory and other bioactive properties. *Haematococcus pluvialis* is the potential ASX source and shows powerful regulation on many health diseases. Over the decades, numerous studies have emphasized its importance in many human health diseases such as neurodegenerative disorders, cardiovascular diseases, Alzheimer, Parkinson, skin allergies, COVID-19, and many more. The present review discusses available evidence on the functional activities of ASX in various diseases and summarizes the potential factors involved in ASX response and highlights the potential implications.

1. INTRODUCTION

Astaxanthin (ASX) is a carotenoid, occurring naturally in some marine organisms such as microalgae, crustaceans, crayfish, shrimp, krill, trout, and salmon. The potential source of ASX was found in the *Haematococcus pluvialis* (Chlorophyceae, Volvocales) green microalgae [1]. It is 3,30-dihydroxy-b, b-carotene-4,40-dione and is ubiquitous in nature, belonging to a bright red secondary carotenoid from the same family as β -carotene, lutein, and lycopene. Microalgae/phytoplankton is mainly biosynthesized, gathering in crustaceans and zooplankton, and later in fish, from which it is introduced to greater levels in the food chain. Naturally, several stereoisomers ([3R, 3'S], [3R, 3'R], and [3S, 3'S]) found in ASX and that differ in the structure of the groups of two hydroxyl molecule's, whereas the 3S, 3'S stereoisomer, most commonly occurs in the salmon and *H. pluvialis* [1,2] [Figure 1].

ASX has a similar metabolic and physiological function as other carotenoids bear, such as Vitamin C, α -tocopherol, canthaxanthin, zeaxanthin, lutein, and β -carotene; however, ASX is considered as more bioactive compared to others. This is mainly due to the occurrence of hydroxyl and a keto group on each end of the molecule. However, unlike others, it does not convert into Vitamin A. The biosynthetic pathway of ASX was demonstrated in Figure 2.

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In marine animals, ASX possesses many important biological functions, including defense against macromolecular oxidation, stress tolerance, immune response, reproductive ability, ultraviolet (UV) light effects, communication, and pigmentation [3]. Due to its specific molecular structure, compared to the other carotenoids, the ASX possess higher antioxidant property [4] such as having both hydroxyl and a keto group, play an important role in neutralizing reactive oxygen species (ROS). ASX protects cell membranes' integrity by inserting themselves into their bilayers, mitochondria functional integrity, and redox state preservation [5]. Due to its "super-anti-oxidant" property, ASX provides various health benefits and nutraceutical applications to humans, including antidiabetic, kidney protection, atherosclerotic cardiovascular disease (CVD), prevention of liver damage, immunomodulator, neurodegenerative diseases, and many others [Figure 3].

1.1. Sources of ASX

ASX naturally originates from algae, crayfish, shrimp, krill, trout, salmon, and yeast [6]. ASX isolated from various microbial origins is demonstrated in Table 1. Besides, commercially, a large amount of ASX is derived from *Haematococcus*, *Phaffia* yeast, and through chemical synthesis. Recently, the study by Dave [7] recovered ASX content from Atlantic Shrimp. The potential natural ASX source is *H. pluvialis* (accumulate up to 5% DW) of ASX. In addition, from a genetically modified *Xanthophyllomyces dendrorhous* yeast, *Chlorella zofinginesis*, and *Chlorococcum*, a very small volume of ASX was isolated [6]. However, natural ASX seems to be more

powerful than its synthetic component due to its safety and functional property.

1.2. Effects of *H. pluvialis*-derived ASX

The secondary metabolite ASX is produced by *H. pluvialis* in several stress conditions, including enhanced salinity, a higher carbon-to-nitrogen (C:N) ratio and high light. Up to 5% of the ASX can be accumulated by *H. pluvialis*. Therefore, it is regarded as the potential natural source for the production of carotenoid pigment with high-value [8]. Due to the potential health benefits of naturally derived ASX from *H. pluvialis*, it is utilized as a dietary supplement from 3.8 to 7.6 mg dosages/day. For more than 15 years, the *H. pluvialis*-based ASX was frequently used as a nutraceutical supplement without any harmful events [9]. Table 2 represents

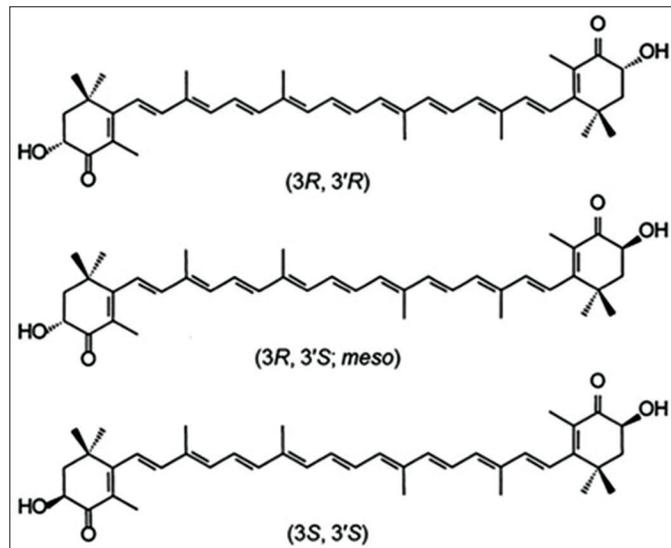


Figure 1: An image of structures of astaxanthin stereoisomers

the *H. pluvialis*-based ASX on different physiological systems in humans.

2. VARIOUS BIOLOGICAL PROPERTIES OF ASX

2.1. Antioxidant Property

In a polyene chain, the carotenoids possess long covalently-linked double bonds which are accountable for antioxidant properties. This property scavenges radicals for inhibition of chain reaction and quenching oxygen in a singlet. Compared to other antioxidants, ASX displays greater biological activity since it can bind from inside to outside within the cell membrane. ASX's polyene chain appears to trap radicals inside the membrane of a cell, whereas the terminal ring of ASX can eliminate radicals both at the interior and in the cell membrane surface. Recently, ASX has drawn much attention from researchers because of its greater antioxidant properties as compared to other naturally occurring carotenoids.

Extrinsic skin damage is caused by various factors, including environmental pollution, poor nutrition, and psychological and physical stress. However, out of all the factors, exposure to UV radiation contributes to 80% and is an important factor for the damage of the skin. UV radiation exposure causes the generation of ROS through oxidative metabolism, leading to skin ageing. It has been established that oxidative stress initiated by ROS depletes the activity of catalases (CAT) in the skin and increases the oxidation of proteins. Further, it initiates the photochemical reactions of ROS by the formation of superoxide anion (O_2^-), singlet oxygen (O_2^1), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH). UV radiation penetrates the skin and is absorbed by the cells causing the dysfunction of DNA, resulting in the development of photoproducts that inactivates the DNA function, thereby leading to premature skin photoaging. There are many naturally occurring sources available that act as antioxidants which include carotenoids and polyphenols [10]. Recently, Dai *et al.* [11] investigated the differences of antioxidants between J-aggregates and ASX H-, J-ADC, and H-aggregate-embedded DNA/Chitosan nanoparticles

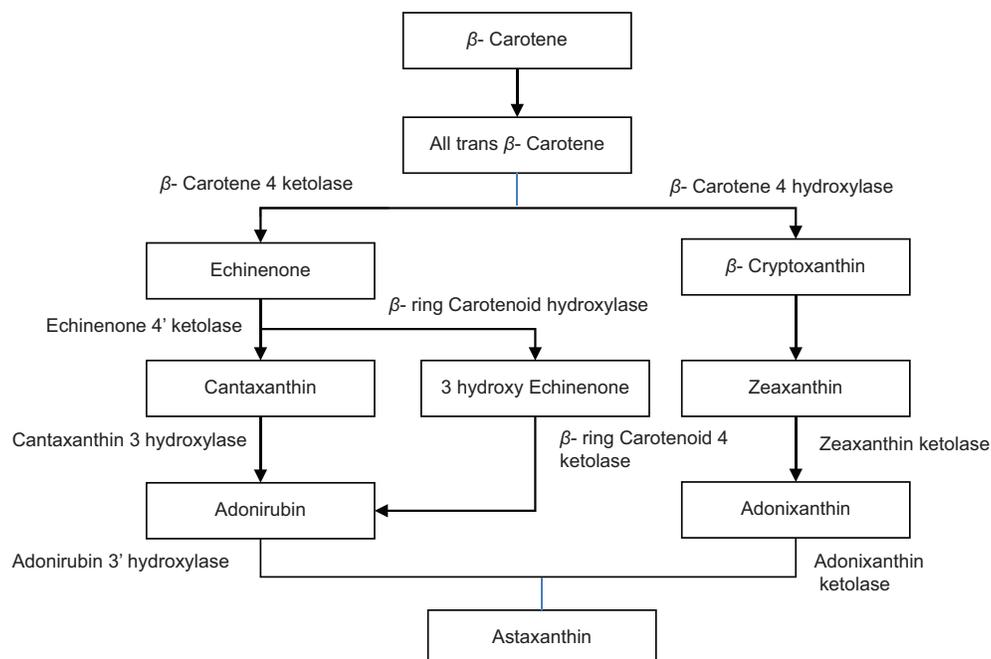


Figure 2: Astaxanthin synthesis pathway

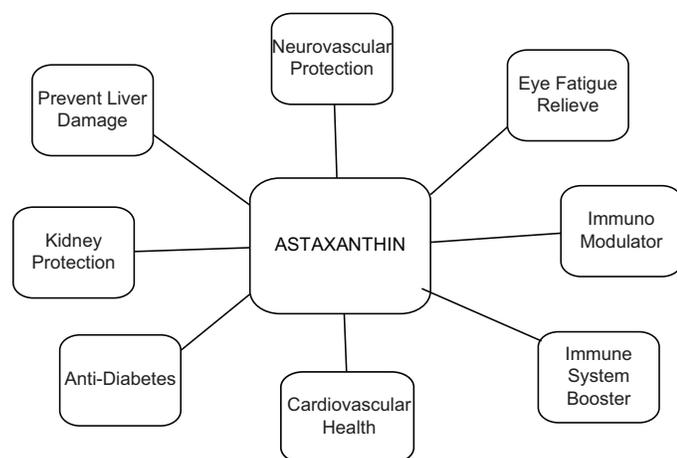


Figure 3: Health benefits of astaxanthin

Table 1: Natural microbial sources of astaxanthin

| Sources | Astaxanthin (%) on the dry weight basis | References |
|---|---|------------|
| Malacostraca | | |
| <i>Pandalus clarkia</i> | 0.015 | [2] |
| <i>Pandalus borealis</i> | 0.12 | [7,55] |
| Labyrinthulomycetes | | |
| <i>Thraustochytrium</i> sp. CHN-3 (FERM P-18556) | 0.2 | [56] |
| Tremellomycetes | | |
| <i>Xanthophyllomyces dendrorhous</i> (VKPM Y2476) | 0.5 | [57] |
| <i>Xanthophyllomyces dendrorhous</i> (JH) | 0.5 | [58] |
| Alphaproteobacteria | | |
| <i>Paracoccus carotinifaciens</i> (NITE SD 00017) | 2.2 | [55] |
| <i>Agrobacterium aurantiacum</i> | 0.01 | [59] |
| Floriideophyceae | | |
| <i>Catenella repens</i> | 0.02 | [60] |
| Ulvophyceae | | |
| <i>Ulva lactuca</i> | 0.01 | [59] |
| <i>Enteromorpha intestinalis</i> | 0.02 | [60] |
| Chlorophyceae | | |
| <i>Neochloris wimmeri</i> | 0.6 | [61] |
| <i>Chlorella zofingiensis</i> | 0.001 | [62] |
| <i>Chlorococcum</i> | 0.2 | [63,64] |
| <i>H. pluvialis</i> (K-0084) | 2.7 | [65] |
| <i>H. pluvialis</i> (AQSE002) | 3.4 | [66] |
| <i>H. pluvialis</i> (Local isolation) | 3.6 | [67] |
| <i>H. pluvialis</i> (K-0084) | 3.8 | [68] |
| <i>H. pluvialis</i> | 3.8 | [69,70] |

H. pluvialis: *Haematococcus pluvialis*

were exposed to H₂O₂-pretreated Caco-2 cells. H-aggregates had a stronger cytoprotective effect compared with ASX monomers and J-aggregates by facilitating the scavenging of intracellular ROS.

ASX has been recommended to provide beneficial antioxidant protection for people with over-oxidant stress, for example, smokers and obese people [12]. Seventy-eight individuals (39 non-smokers and 39 heavy smokers) were randomly allocated to obtain ASX for 3 weeks at either 5, 20, or 40 mg/day and oxidative stress markers were evaluated. Among smokers, relative to baseline, the oxidative markers isoprostane (ISP) and malondialdehyde (MDA) reduced at all doses. Total antioxidant capacity (TAC) and superoxide dismutase (SOD) ability-assessed antioxidant performance, enhanced, indicating that ASX can help compensate for some of the oxidative damage related to smoking [13]. Various researches have indicated several health benefits from the use of natural ASX in both *in vivo* and *in vitro* models based on its chemistry, antioxidant effects, and mechanism of action [14-16].

ASX particularly inhibits the formation of ROS and regulates the oxidative stress-responsive enzymes expression, including heme oxygenase-1 (HO-1). HO-1 is a regulatory mechanism and an oxidative stress marker for the adaptation of cells to oxidative damage [17]. HO-1 is regulated by many factors of transcription, such as nuclear factor erythroid 2-related factor (Nrf2), which enters into the detoxifying mechanism of the enzymes promoter region [4]. Furthermore, ASX has shown to upregulate in irradiated cells of glutathione peroxidase 1, CAT, antioxidative enzymes SOD2, and Nrf2-targeted proteins HO-1. Therefore, ASX has an extensive antioxidant property not only through direct radical scavenging but also through the Nrf2 pathway modulation by activating the cellular antioxidant defense mechanism [18]. Overall, studies conducted by various researchers have shown a significant role of ASX in multiple health benefits based on its mechanism of actions.

2.2. Anti-cancerous Property

Multiple studies have revealed the important role of ASX as anti-oxidative properties without any side effects and toxicity. However, much evidence has suggested its anti-cancerous effects in several cancers types, including leukemia [19], colon carcinogenesis, oral cancer [20], bladder carcinogenesis, and hepatocellular carcinoma [20]. ASX has mediated its effects on different pathways, including cell junction, inflammation, and apoptosis.

The rapid proliferation of cancerous cells results in the formation of tumors. Cancerous cell proliferation facilitates its adhesion to the target tissues, migration, and invasion. These measures differentiate the tumor cell for a metastatic phenotype. Many studies conducted till now shows the effect of ASX on cell proliferation. ASX has an antiproliferative effect on Lewis (mouse lung) lung carcinoma cells, CBRH- 7919 (human hepatoma), and SH-88 (rat breast) [21]. CBRH-7919, however, was a cell line that was most susceptible to ASX with a 39 μM IC₅₀ value.

As compared to other carotenoids, including capsanthin, bixin and, β-carotene on K562 leukemia cells, the growth inhibitory effects of ASX have shown the most effective inhibitory role [19]. ASX has a negative effect on the multiplication of the cancerous cells in oral cancer by controlling the cyclin D1 expression and proliferating cell nuclear antigen [20]. But it decreases the viability of cells in human colon cancer cells HCT-116 [19].

In multicellular organisms, the programmed cell death mechanism that takes place is apoptosis and involves several cellular events such as ultimately cell death, chromosomal DNA fragmentation, cell blebbing, and nuclear fragmentation [22]. However, in tumor cells, if apoptosis

Table 2: *Haematococcus pluvialis* derived astaxanthin derived from role in human health-promoting effect

| Physiological system | Subject | Effect followed | Main outcome | References |
|------------------------|---|--|---------------------------------|------------|
| Male fertility | Twenty four healthy male. | Idiopathic infertility | Reduced | [39] |
| | Thirty sub-fertile male | Pregnancy rate; sperm velocity; oxidation markers | Increased; decreased; Increased | [71] |
| | Twenty sub-fertile male | Pregnancy rate, semen quality | Increased | [72] |
| Central nervous system | Male and female (Elderly and middle aged) | Cog Health battery scores | Increased | [73] |
| | Ten healthy male | Time of response and accuracy of many assignments | Increased | [74] |
| Muscle endurance | Sixteen non-trained male | Accumulation of lactic acid after a run | Decreased | [75] |
| | Nineteen non-trained male | Activities of the respiratory and sympathetic nervous systems | Increased | [76] |
| | Twenty non-trained male | Explosiveness/strength/test; Endurance/strength/test | Improved; Nil effect | [77] |
| | Twenty resistance-trained male | Skeletal muscle damage markers | Nil effect | [78] |
| Cardiovascular system | Male | Levels of blood plasma | Decreased | [38] |
| | Twenty male | Time of blood flow | Increased | [79] |
| Gastric ulcer | Forty-four functional dyspepsia patients | Gastrointestinal discomfort; Inflammatory markers | Nil effect; Nil effect | [80,81] |
| Immune response | Fourteen healthy female | Immune response; inflammation and oxidative stress markers | Increased; Decreased; | [82] |
| Skin | Forty-six healthy female | Moisture and skin elasticity | Increased | [83,84] |
| | Healthy male or female | Dermis, corneocyte layer, epidermis, and skin wrinkle | Increased | [85] |
| Eye function | | Tiredness, blurred vision dryness and eye soreness, and | Decreased | [86] |
| | Eighty-seven male | Amplitude of eye accommodation | Increased | [87] |
| | Forty-nine healthy male | Far visual acuity uncorrected | Increased | [88] |
| | Forty patients with asthenopia | Potency for eye accommodation | Increased | [89] |
| | Ten healthy male | Function of eye | Increased | [90] |
| | Eighteen healthy male | Deep vision | Increased | [75] |
| Anti-oxidation | Male (bilateral cataract) | The development of hydroperoxide in aqueous humor; antioxidative effects by modifications in the activity of superoxide scavenging | Suppressed; Increased | [91] |

occurs, the cancer cell volume tends to decrease. In this case, ASX has shown great importance in the process of apoptosis and thus attracted the interest of many researchers. As the tumor cells are exposed to ASX, it induced modifications in transmembrane potential, respiratory chain, and mitochondrial morphology, and thus regulated the apoptotic mitochondrial proteins such as Bcl-2 associated X protein (Bax) and B-cell lymphoma 2 (Bcl-2) [19].

ASX is of great importance in oral cancer [20]. By up-regulating pro-apoptotic p-Bcl-2-associated death promoter and BAX, down-regulating the anti-apoptotic Bcl-2 expression, it induces mitochondrial apoptosis mediated by caspase, followed by the movement of cytochrome c and Smac/Diablo into the cytosol and polymerase (ADP-ribose) polymerase cleavage. However, in hepatocellular carcinoma, ASX has regulated the apoptosis pathway by increasing the non-metastasis 23-1 and BAX level while decreasing the B-cell lymphoma-extra-large, c-Myc, and Bcl-2 expression [21]. Thus, this reveals an efficient role of ATX in inducing mitochondria-mediated apoptosis in cells of cancer.

2.3. Cardiovascular Health Diseases

ASX also offers great support for CVD in that its antioxidative and anti-inflammatory properties can significantly shorten blood transmit times. Oxidative stress has appeared as a widespread mechanism for atherosclerosis in particular [23]. It helps in reducing inflammation

and improves lipid and glucose metabolism. In a 12-week dose-response randomized clinical trial (RCT), the use of ASX derived from natural algae doses of 6, 12, and 18 mg/day demonstrated a substantial reduction in levels of serum triglycerides (TG), while an increase in serum adiponectin and serum high-density lipoprotein (HDL)-cholesterol levels among adults with mild hyperlipidemia [15]. The effects of a 3-month supplementation period of 8 mg/day of ASX on ASX absorption and lipid peroxidation were examined in a randomized study of healthy men aged 19–33 years. The findings showed that compared to the placebo group, ASX supplementation led to an increase in levels of plasma ASX ($P < 0.001$). This study indicated that bowel encapsulated ASX absorption was well-tolerated and effective and that ASX supplementation in healthy men reduced *in vivo* oxidation of selected fatty acids [15].

In another research, 5 and 20 mg/day of ASX ingestion for 3 weeks showed increased SOD and TAC blood levels while decreased MDA and ISP levels among obese and overweight adults. In addition, regular consumption of ASX led to a significant decrease in the levels of LDL-cholesterol and apolipoprotein B [12]. A pilot clinical study conducted by Kato *et al.* [24] on 16 patients with a risk of heart failure who were taking 12 mg of ASX supplementation daily for 3 months [24]. Researchers have assessed 6-min walk distance, blood pressure, BMI, left ventricular ejection fraction, heart rate, and numerous oxidative stress markers, including urinary 8-hydroxy-2-deoxyguanosine,

biological antioxidant potential, and the diacron-reactive oxygen metabolites (d-ROM). Throughout the study, levels of plasma ASX increased significantly. As a result, it decreased the oxidative stress levels demonstrated by a decrease in dROM levels. This research showed improvements in cardiac contractility and exercise tolerance in left ventricular systolic dysfunction patients.

As discussed earlier, ASX does not act as a pro-oxidant, and therefore it is an effective antioxidant. Similarly, in another study, ASX concentration has significantly decreased the serum TG and increased serum HDL-cholesterol levels along with an increase in adiponectin levels in adults with milk hyperlipidemia [25]. However, the mechanism behind the relationship between adiponectin and ASX is unclear. Some researchers have suggested that the ASX's anti-inflammatory properties can be due to the presence of an increased level of adiponectin as adiponectin itself have its own anti-inflammatory effects. Further studies are required, however, to define specific dosages and to evaluate overall efficacy as a potential preventive measure against CVD. Various bioactivities of ASX reported by several studies were demonstrated in Table 3.

2.4. Diabetes

A recent human epidemiological study indicates an inverse correlation between carotenoid content in plasma and diabetes mellitus (DM) incidence [26]. In an RCT, 54 Type 2 diabetes (T2D) patients received a placebo and ASX 12 or 6 mg daily for 8 weeks. Ingestion of daily ASX supplementation significantly reduced tumor necrosis factor- α (TNF- α) and plasma IL-6 levels and further decrease in HbA1c (%) and blood glucose levels. Specifically, a higher dosage supplementation significantly reduced the levels of LDL, total cholesterol, plasma TG, and clotting factors such as factor VII and plasminogen activator inhibitor [27]. Data from ten RCTs of the recent meta-analysis found that fasting blood glucose levels were significantly decreased by ASX supplementation [28]. Forty-four participants with T2D received 8 mg of ASX for 8 weeks or placebo in an RCT. Adiponectin, visceral fat, systolic blood pressure, serum TG, and very-low-density lipoprotein were significantly decreased in the group receiving ASX than placebo

Table 3: Bioactivities of astaxanthin demonstrated by various studies

| Biological activities | References |
|----------------------------|--------------------------------|
| Anticancer | [92] |
| Antiproliferative activity | [93] |
| Bone disease | [94] |
| Immunoregulatory activity | [95] |
| Antimicrobial activity | [92,96,97] |
| Cytotoxic activity | [98] |
| Antityrosinase activity | [98] |
| Neuroprotection | [99-101] |
| Immune response | [82,102] |
| Cardiovascular prevention | [15,103-105] |
| Anti-diabetes | [50,106,107] |
| Anti-hepatoprotective | [108] |
| Anti-gastric activity | [109,110] |
| Anti-inflammatory | [105,111-114] |
| Anti-skin cancer | [115-117] |
| Protection from UV rays | [117] |
| Antioxidant activity | [11,13,18,69,95,97,98,117-123] |

[29]. Studies conducted in the past revealed a positive association between carotenoids intake and decreased T2D risk [30]. Recently, a study by Chen *et al.* [31] reported, kidney-targeted evaluation showed that ASX liposomes modified by the glucose-PEG600-DSPE ligand could be transported directly to the glomerular mesangial cell membrane through overexpressed GLUT1 and achieved excellent delivery of kidney-targeted drugs. However, more human research is required to know the role of ASX in diabetes. The immune system, for instance, induces inflammation through releasing cytokines carotenoids and chemokines such as ASX modulate the function of the immune system through reducing cytokines and chemokines through their mechanisms of antioxidant. In addition, evidence indicates that ASX has protective effects against oxidative damage in other conditions, such as neurodegenerative diseases, cardiovascular diseases, diabetes, cancers and obesity [32].

2.5. Liver Function

The liver is vital to lipids and glucose metabolism [33]. There is multifactorial growth of liver stenosis and fatty liver, but oxidative stress is strongly involved in the pathogenesis [34,35]. Studies have confirmed that lipid oxidation products interact with the liver, which further increases the levels of ROS, insulin resistance, and accumulation of lipids and thereby causes liver damage [34]. To inhibit the lipid peroxidation level by ASX, female long-Evans rats were treated with carbon tetrachloride (CCl₄) orally (1 mg/kg) and subsequently treated with ASX (10 mg/kg) every day for 2 weeks. The findings of this experiment showed that CCl₄ administered in rats increased plasma alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities which were normalized by ASX treatment compared to control rats [36,37]. An RCT performed among obese Korean adults demonstrated that treatment of ASX significantly improved antioxidant markers, including the capacity of total antioxidant (by 121% and 125%) and SOD (by 193% and 194%) and further reduced the ASX blood oxidative stress markers including ISPs (by 64.9% and 64.7%) and MDA (by 34.6% and 35.2%) [12]. Another RCT among Finnish men (placebo [*n* = 20] vs. ASX, 8 mg/day, 3 months [*n* = 20]) demonstrated a significant reduction in plasma lipid peroxidation markers, such as 12-hydroxy fatty acids (by 36%) and 15-hydroxy fatty acids (by 60%) [38]. Such human studies have demonstrated beneficial effects of treatment dependent on ASX on oxidative stress, but the effects in the liver are hypothesis.

2.6. Male Infertility

To achieve potential oocytes fertilization, human sperms have to undergo a number of structural changes which is known as capacitation. ROS production demonstrates a major role in triggering a broad acrosome reaction (AR) to occur in the cells. There are many intrinsic and extrinsic factors which trigger the formation of ROS in semen such as activated leukocytes causing inflammation, immature spermatozoa, sertoli cells, exposure to radiation, and inactive lifestyle. The outer sperm membrane undergoes depletion of cholesterol during the capacitation phase [39], which increases both acrosome exocytosis and membrane fusibility followed by downstream signaling processes such as ROS generation, protein serine, and tyrosine phosphorylation (Tyr-P). Higher levels of ROS have induced oxidative stress on sperms, which is being correlated to reduced motility and damage of sperm DNA.

Further, ASX has been shown to enhance parameters of human sperm such as AR-pattern and Tyr-P head without influencing the cell redox

process [40]. It demonstrates the important role of a controlled ROS generation in the proper functioning of the sperm, thus providing ROS with the main role in the process of maturation, other than the detrimental factor previously evaluated by the sperm [10].

2.7. Skin Health

Because of its diverse roles in skin biology, collaborative evidence exists that ASX has substantial nutraceutical applications in the dermatology field. In damage and ageing to human skin, oxidative stress plays a significant role. The two factors that cause skin ageing and damage are the generation of ROS and exposure to solar UV radiation.

Oxidant skin ageing events include elastin in the dermal skin layer, the formation of matrix metalloproteinases (MMPs) which degrade collagen, reduced antioxidant production, inflammatory response, and DNA damage [4]. As discussed earlier, the expression of stress-responsive oxidative enzymes such as HO-1 was modulated by ASX and prevented the development of ROS. The latest study also reported in rats that ASX induces reepithelialization during the early burn wounds [41].

This process involves the decreased form of nicotinamide adenine dinucleotide phosphate oxidase (Nox) and free radical regulation of development through the influence of xanthine oxidase; both respond to the ROS generation [41]. It is well understood that by releasing pro-inflammatory mediators, keratinocytes play a significant role in response to photodamage after UV exposure. By reducing the inflammatory cytokine expression, development of UV-induced reactive nitrogen species, and apoptosis in keratinocytes, ASX therapy has been suggested to avoid the traumatic effects of UV. A potential reduction in cyclooxygenase-2 and inducible nitric oxide (iNOS) levels caused by ASX and reduced keratinocyte release of prostaglandin E2 after UV irradiation [15].

ASX's inhibitory impact on iNOS production has substantial consequences for anti-inflammatory development medications for skin diseases such as atopic dermatitis (AD) and psoriasis. A chronic inflammatory skin condition is called AD, and it is related to causative factors, including abnormalities in immunology that lead to skin lesions. The latest study showed that in an AD animal model, the gene expression of many pro-inflammatory biomarkers such as TNF- α , interleukin (IL)-6, and IL-1 β had been inhibited by ASX [42].

A variety of researchers investigated ASX's nuclear factor-kappa B (NF- κ B) inhibition. Specifically, ASX has been documented to have a powerful capacity to degrade of I π B α through its inhibitory effect on the activity of N κ B kinase (IKK) and inhibit the nuclear translocation of the NF- π B p65 subunit [43]. Recent research on 44 healthy individuals has demonstrated that a collagen hydrolysate (2 mg/day) and ASX (2 mg/day) combination for 3 months develops barrier integrity and elasticity in the skin of a human. These developments were specifically correlated with molecular changes, including lower levels in the collagen-degrading enzyme MMP-1 expression, elastin-degrading enzyme MMP-12, and induction of procollagen type I [4]. To further confirm the previous studies findings, a high-level evidence-based systematic review by Loke *et al.* [44] reported ASX substantially protects the skin without any adverse reactions from UV-induced skin damage.

2.8. Brain Health

ASX has also gained a lot of attention from researchers across the globe for its significant impact on neurological pathologies treatment

or prevention, including amyotrophic lateral sclerosis, dementia, Huntington's disease, Parkinson disease, and Alzheimer disease. Although various diseases have different causative agents, the characteristics are mostly same such as the redox metals release combining with oxygen and levels of ROS in cells of neuronal increasing caused by mitochondrial stress and the redox metals release combining with oxygen.

This can cause enhance in protein aggregation that activates cells of microglia. Neuroinflammation contributes to the release of activated cytokines and chemokine's, creating an oxidative stress environment within the neurons. Many researchers have revealed the role of ASX in delaying the ROS process and alleviating the pathophysiology of various neurodegenerative diseases. ASX induces nerve cell degeneration by increasing growth-associated protein 43, microtubule-associated protein 2, brain-derived neutrophil factor, and gene expression of a glial fibrillary acidic protein [45]. These proteins are responsible for brain recovery.

ASX has also shown its significant role in cognitive impairment. Chemobrain is a cognitive disorder which mostly occurs in cancer patients leading to inability to concentrate, memory impairment, and slow processing speed [46]. El-Agamy *et al.* have shown the significant effect of ASX as a protective shield to doxorubicin which induces the impairment of cognitive functions [46]. A systematic review of RCTs demonstrated that in middle-aged adults, ASX significantly improved verbal episodic memory performance [47].

ASX has shown neuroprotection and memory-enhancing effects by removing the oxidative stress and mitigating the enhanced activity of acetylcholinesterase.

2.9. Immune System

As discussed earlier, ASX role is an antioxidant, which helps to explain its effect in improving immunity and decreasing inflammation. In a recent study, the authors suggested the potent role of ASX to promote antibody production and oxidative and immune function balance. The study was conducted on a group of male soccer players who received either 4 mg of placebo or ASX for 90 days. Results revealed increased levels of immunoglobulin's A in salivary glands following ASX supplementation, accompanied by improved pro-oxidant-antioxidant balance [48]. Yet another study examined the effect of ASX compared to β -carotene on the production of antibodies by cells of the immune system (peripheral blood mononuclear cells). ASX enhanced antibody production in response to stimuli, whereas β -carotene did not show a potential impact on the production of human Ig [49].

2.10. Treatment of COVID-19

The algal derived - ASX has been potentially used for the treatment of certain viral infections. Chan *et al.* [50] reported that diet containing 0.05 percent ASX provided plasma-retained glutathione content for diabetic rats, significantly reduced plasminogen activator inhibitor-1, significantly decreased plasma CRP levels, and reduced MCP-1, TNF- α , IL-6, and ROS. These findings showed that ASX might potentially reduce oxidative, inflammatory, and coagulatory stress, which may have a similar useful impact in patients with COVID-19 who have comorbidities such as diabetes. Kubo *et al.* [51] reported that ASX prevents oxidative damage through Nrf2 pathway activation in mice model. Recently, Talukdar *et al.* [52] reported that ASX-derived naturally has considerable potential as a co-adjunctive supplement, desiring required clinical help against COVID-19 for its efficacy and benefit.

2.11. Safety Assessment

ASX has been consumed for nearly 20 years as a dietary supplement [53]. Novel Foods and Food Allergens (NDA) were requested to provide a suggestion on ASX safety with a limit of 8 mg/day when used as a food supplement, taking into account the total combined consumption of ASX from all sources of food. In 2014, in the form of an application submitted pursuant to regulation (EC) No 258/1997, the NDA Panel evaluated the protection of the new ASX-rich ingredient derived from *H. pluvialis*. In that view, the NDA Panel considered that 0.034 mg/kg body weight (bw) was the appropriate daily intake (ADI) for ASX set by the EFSA FEEDAP Panel in 2014. In 2019, the FEEDAP Panel adopted an opinion on the safety and efficacy of ATX-DMDS (dimethylidissuccinate (EFSA FEEDAP Panel, 2019), a colouring feed additive, for salmonids, crustaceans and other fish. In that assessment, a new ADI of 0.2 mg ASX/kg bw was extracted by the FEEDAP Panel that replaced 2014 ADI definition of 0.034 mg/kg bw [54].

2.12. Future Directions

A variety of compounds are produced by the microalgae, which is useful for human health. ASX is a reddish pigment group of chemicals known as carotenoids. At present, only a fraction of carotenoids is used commercially. There are many opportunities for future study, including isolation of ASX from the novel organisms with a high level of quantity and study into rare carotenoids. In addition, ASX is frequently isolated from the microalgae only. However, in the future, isolation of ASX from several macroalgae species can be attempted. The present market demand for natural ASX is not fulfilled. Therefore, we need to find out several optimization processes for the maximum production of ASX.

3. CONCLUSION

In the prevention and treatment of chronic health diseases such as CVD, cancers, skin diseases, neurological disorders, and COVID-19, ASX has shown an effective role. Several mechanisms of action have been discussed for human health-related diseases. Although there are still some voids in reproducing the efficient roles of ASX in human health as compared to animal studies, and therefore further development in these fields can have a profound effect on the commercial deployment of *H. pluvialis* ASX products.

4. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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6. CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

7. ETHICAL APPROVALS

Not applicable.

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