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Potential use of super antioxidant astaxanthin and its role

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Abstract
A karotenoid called astaxanthin serves as a super antioxidant. Due to the fact that it has better antioxidant activity than many different carotenoids, it has potential as a cosmetic, nutraceuticals, pharmaceuticals and as food supplement and food additive. In nature, the substance is produced in one or two steps by *Haematococcus pluvialis*. Oxidative and free radical stress are greatly reduced when astaxanthin is used as a natural antioxidant. The application of astaxanthin as a nutraceutical for the prevention of cardiovascular illnesses, skin protection, anti-cancer, cosmetic ingredient, natural food colourant, and feed supplement for poultry and aquaculture is also discussed.

Keywords: Biological processes, a bio refining system, antioxidant, astaxanthin, microalgae

Introduction
Carotenoids are tetra-terpenoid pigment and naturally synthesized by higher plants, algae, fungi and some bacteria. Carotenoids can divide into the carotenes (having carbon and hydrogen), and xanthophylls (oxygenated derivatives). Astaxanthin, a karotenoid, functions as a powerful antioxidant. It has potential as a cosmetic, nutraceutical, pharmaceutical, food supplement, and food additive because it has stronger antioxidant activity than many different carotenoids. *Haematococcus pluvialis* produces the material in nature in one or two processes. Astaxanthin is a natural antioxidant that dramatically reduces oxidative and free radical damage. Carotenoids provide pigmentation and also have crucial role in the biological system such as, scavenging reactive oxygen (ROS), quenching of chlorophyll triplet state, light-harvesting, and dissipation of excess energy (Chen *et al.* 2020; Yang *et al.*2020) [8, 32] Xanthophylls are categorized under three group based on the presence of functional group: -OH group (i.e., zeaxanthin), the ═O group (i.e., canthaxanthin), or both –OH and ═O group (i.e., astaxanthin [ASX] and lutein). Astaxanthin (MW 596.8 Da) is a xanthophylls carotenoid and having the molecular formula $C_{40}H_{52}O_4$ (Shah *et al.* 2016) [8]. Astaxanthin is a fat soluble red-carotenoid and possesses an unusual antioxidant activity higher than vitamin C, beta carotene and α-tocopherol (Han *et al.* 2020) [16]. Due to higher antioxidant activity it help in prevention and cure of cancer, anti-inflammatory, atherosclerosis, antiaging, eye-related disorders, and cardiovascular disease (Farruggia *et al.* 2018; Eren *et al.* 2019; Sztretye *et al.* 2019) [11, 13, 31]. The current market of astaxanthin is dominated by the synthetic astaxanthin and is worth 1000 USD/kg (Lim *et al.* 2018) [21]. Natural astaxanthin is approved as a natural food additive for animals and fish feed and human diet by The US Food and Drug Administration (FDA) and European Commission, respectively (Brendler *et al.* 2019; Singh *et al.* 2019) [6, 29]. The sources of natural astaxanthin are mainly from microalgae, fungi, bacteria, some crustaceans and higher plant. Astaxanthin is primarily used in industries like food and feed (Lim *et al.,* 2018; Chronis *et al.* 2021) [21, 9], aquaculture (Yu W *et al.* 2020) [12], pharmaceutical (Araújo *et al.* 2021) [2], health and personal care [Borowiak *et al*. 2021; Gateau *et al.* 2017; Kusmayadi *et al*. 2021) [3, 15, 20]. Two factors that have paced up the synthesis of natural astaxanthin are the higher biological activities of the natural bioactive compound than synthetic astaxanthin and safety for human use (Capelli *et al.* 2019) [7]. However, there are certain limitations associated with natural astaxanthin production as it is a time- consuming process and involves intricated cultivation techniques. Microorganisms like algae, for instance, *Chlorella zofingiensis* , *Chlorococcum*, *Haematococcus*, and yeast-like Phaffia rhodozyma are the potential ASX producers (Ambati *et al.* 2014 Shao *et al.* 2021) [1, 30]. *Haematococcus pluvialis* has gained the worldwide attention of researchers. *H. pluvialis* accumulates ASX under stress conditions like high salt, nitrogen deficiency, low light intensity, and high temperature.

In 2019, the worth of the global market was assessed to be USD 1 billion by the Grand view research and predicted it to reach up to USD 3398.8 million by 2027 with an annual growth rate of 16.2% from 2019 to 2027, due to rising awareness, and associated health benefits (Market Analysis Report 2020–2027)

Importance and Health benefits of Astaxanthin

Some of each ionone ring's distinct properties are explained by the hydroxyl (OH) and keto (C=O) moieties that are present on them. highlights a stronger antioxidant activity (Dhankhar *et al.* 2012) [10].

In Numerous investigations on astaxanthin have been conducted recently. Its antioxidant action was demonstrated *in vitro* and *in vivo*, Examples include the effect of quenching on singlet oxygen, a significant hydrogen and superoxide scavenging effects hydroxyl radicals, peroxide, and an inhibitory effect on lipid peroxidation. Replace synthetic ASX with chemical ASX because consumers want safe, ecologically friendly products and are aware of the risks associated with synthetic ASX. As was already noted, algae, bacteria, yeast, shrimp, trout, crayfish, yeast, and salmon all contribute to the production of natural ASX. However, yeast (*Xanthophyllomyces dendrorhous*) and microalgae (*H. pluvialis*) are the primary sources for ASX production in the commercial sector. Only *Adonis annua* has been demonstrated to produce 1% of the dry weight of its petals in the chemical, excluding plants that produce ASX. The ASX producers' small petals still restrict them from being used in commercial production despite their increased toughness. The best organism for producing ASX for human consumption is *H. pluvialis*, which has been proven to gather up to 5% ASX on a DW. Due to inductive circumstances, salinity, intense light, high temperatures, salinity, and pH changes can all affect the ASX production life cycle of *H. pluvialis*. The noninductive alga *Chlorella zofingiensis* produces 50% of the naturally occurring carotenoid content. They found that monoester synthesis is decreasing.

Chemistry of ASX

In this molecule, a polyene chain links two terminal rings. The hydroxyl groups are asymmetrically linked at positions 3,3 and 3,3 on either end of an ionone ring. ASX diesters are 1.6 times more potent and twice as powerful than ASX monoesters and ASX free forms. Because each ionone ring has hydroxyl and keto groups attached, ASX has exceptional antioxidant capabilities and is susceptible to esterification. ASX is red as a result of its conjugated double bond. It is efficient in protecting cells because it contains fatty acid esters. It serves as a stabiliser as a result, maintaining the strong antioxidant properties in both situations. The ASX ring is located in the hydrophilic layer, as opposed to the polyene chain, which is located in the lipophilic zone (Boussiba *et al*. 1999). The interior and external cell membranes fusing together strengthens the cell's defences. ASX efficiently neutralises ROS because it contains both hydroxyl and keto groups in a single molecule. Free radicals and other reactive oxygen species, such as hydrogen peroxide, can be neutralised by antioxidants.

Bioavailability and safety of ASX

Asx has been tested on rats to determine the right dose for humans. Micelles produced in intestinal tissue are initially partially absorbed by a mucosal cell (Boussiba, 2000) [5]. By a process known as lipoprotein lipase, the ASX complex reaches tissues as the ASX complex is broken down by the lipoprotein lipase enzyme, which is often located on cells and removed by the liver and other organs. Xanthophyll ester absorption is directly regulated by structure; bioavailability and absorption are directly influenced by structure. In the small intestine, adults absorb and hydrolyze xanthophyll (Yuan *et al*. 2000) [33]. The slow-moving enzymatic esterification of ASX is controlled by enzymes in the intestinal cells after it has been absorbed from the gut. Carotenoids must be consumed along with other dietary components in order to be absorbed; for example, a diet high in cholesterol may facilitate absorption. In terms of boosting immune responses and reducing the risk of vascular and viral disorders, ASX has more biological advantages than fish oil. When taken with fish oil, ASX increases the activity of several enzymes, such as catalase, glutathione peroxidase (GSH-PX), and superoxide dismutase, which lowers the formation of oxygen (O2), nitric oxide, and hydrogen peroxide (SOD) (Higuera-Ciapara, 2006) [17].

Biosynthesis of ASX from microalgae

A number of steps are required for the production of ASX from microalgae, including microalgae cultivation, ASX induction, and biomass harvesting. The manufacturing of microalgae is now largely automated. Infected microalgae are initially grown in the best possible conditions for temperature, nutrients, light, and pH, which leads to the growth of biomass (Hussein *et al.* 2006) [18]. Once sufficient biomass is available, the cell is given the right conditions to stimulate ASX synthesis. ASX is being improved by a lot of states simultaneously promising to provide carbon supply and nitrogen shortage. To create the perfect environment for microalgae growth, carbon, phosphorus, and nitrogen are added to the media in the one-stage process. Proliferation of microalgae results in nutrient depletion and pH changes. Once the harsh environment is initiated, algal cells begin to grow into resting cysts and the ASX production process begins. Due to the changes in the microalgae's growing environment, the one-stage process is regarded as an ASX manufacturing procedure that develops on its own. Inducers are provided simultaneously with microalgae, even if they occasionally have a negative effect on their growth. The manufacturing of ASX can be cost-effective since only one manufacturing step is required. The two-step approach to cultivation of *Haematococcus* is usually adopted by companies to alleviate the problem of a one-step approach. The green stage consists of reproducing cells and biomass accumulation, while the red stage is characterized by loss of motility and reproduction. In the red stage, ASX begins to accumulate inside the cell and may contribute as much as 5% of the dry biomass weight (Hussein 2006) [18]. It is common for *Haematococcus* cells to be grown in enclosed photobioreactors under typical growth conditions, either mixotrophically or phototrophically. After biomass accumulation and cell growth, cells are transferred to raceway ponds or large-scale photobioreactors. As buildup and phototropic encapsulation occur under stress- and nutrient-deficient conditions. As a result, the red stage can be produced in stainless steel fermenters either by heterotrophic or mixotrophic means; however, phototrophic induction is more effective. The process of encrustment is initiated by ASX induction within 3 to 5 days, which results in the formation of aplanos-pores (Rao *et al*. 2010) [26].

It can be achieved by using renewable energy sources and reducing energy and water consumption. The process of gravitational settling is used to collect the generated aplanospores, and spray drying—which is more affordable than drum drying or freeze drying—is then used to dry them. Usually, after being cracked by high-pressure homogenizers or bead millers, biomass is dried using a belt or spray drier. Aplanospores must be cracked open in order to extract ASX because they are tough for both people and animals to digest. Safety and cost considerations for biomass collection should be part of the process (Peng *et al*. 2008) [25]. The cost of biomass harvesting makes between 20–30% of ASX's overall expenses. To reduce carbon footprints, the industrial method must be both economically and environmentally viable. Only one life cycle evaluation resulting from H. lacustris has been published on ASX thus far. Producers like Alga Technologies use solar energy, mostly in green stage production (250 W, 15% conversion efficiency, 1.65 m2), to fight environmental degradation. 1000–1500 tonnes of freshwater are required to generate H. lacustris biomass, however growing the red stage uses a lot less water. In addition, open ponds only use 30% of the water. For a sustainable product biorefinery technique, which is based on the principle of "high value product first," can be utilised to simultaneously manufacture ASX, phytosterols, and polyunsaturated fatty acids. Reusing leftover biomass can produce protein or biofertilizer. Environmental sustainability is made possible by waste from soft drinks, such as carbonates, and flue gases, such as carbon dioxide (Rise 1994) [27].

Practical application of ASX

ASX is a super antioxidant and lacks provitamin A activity. It is studied extensively due to its potent biological activities, including anticancer, antidiabetic, anti- inflammatory, antioxidative activities (Eren *et al*. 2019) [11]. At singlet oxygen quenching, ASX is 800 times stronger when compared to coenzyme Q, 550 times than green tea catechins, 6000 times than vitamin C and 11 times than β carotene up to 2.75 times than lutein (Nguyen 2019) [24]. ASX is considered a “super oxidant” as it spans the biological membranes and protects them, especially the lipids, including phospholipid, against peroxidation by scavenging the free radicals. Due to higher antioxidant activity other than any carotenoids, there is an increasing demand for the use of ASX in the nutraceutical, cosmetic, food, and pharmaceutical industries.

All conditions that affect the heart and blood vessels are referred to as having a "cardiovascular disease." ASX can reduce oxidative damage while increasing insulin and blood sugar levels because it is an antioxidant (Medhi *et al*. 2021) [23]. In a randomised controlled trial (RCT), 54 patients with type 2 diabetes received either 12 or 6 mg of ASX twice daily for eight weeks. As ASX consumption grew over time, interleukin-6 levels, HbA1c percentages, and tumour necrosis factor (TNF) levels all decreased. The levels of TG, LDL, clotting factors, total cholesterol, and plasminogen inhibitors may be decreased with a higher dose. In order to improve medication delivery in the kidneys. Chen *et al*. found that overexpressing GLUT1 made it possible for ASX liposomes loaded with glucose-PEG6-DSPE to be delivered directly to glomerular membranes. In addition to playing a part in the pathophysiology of these conditions, ROS also have a role in cardiomyopathy, ventricular remodelling, cardiac hypertrophy, heart failure, myocardial infarction, and ischemia/reperfusion injury. Among the many strategies used to treat and prevent CVD are carotenoids, antioxidants, polyphenols, vitamin E, and ascorbic acid (Kumar *et al*. 2021) [19].

Carotenoids lower the blood pressure, lessen pro-inflammatory cytokines, and increase the sensitivity of the liver and adipose tissue to insulin. Carotenoids can transform into retinoids, which have antioxidant properties. (Some carotenoids have anticarcinogenic properties that are more effective than beta-carotene, according to a study by Bertram *et al*. Additionally, the study showed that beta-carotene did not shield people with lung cancer; rather, it caused lung disease. Researchers suggested using carotenoids like ASX, which have no provitamin A effect and do not have retinoids' toxicity, to deal with such situations. When canthaxanthin and ASX were compared, it became clear that ASX had the largest impact on inhibiting connexin and changing its phosphorylation pattern, which in turn impacted its function.

Conclusion

As more people become aware of the risks associated with using synthetic colours, there is an increasing desire for natural and sustainable alternatives. The market for natural pigments derived from microalgal biomass is expected to grow as we learn more about the nutritional properties of that biomass. The availability of items with antioxidant characteristics as well as green and sustainable lifestyle choices has increased as a result of people's rising concern for and understanding of Mother Nature. Over the past few years, consumers have reduced their environmental footprint by making moral decisions. People are becoming more interested in natural and sustainable alternatives as they become more aware of the issues associated with synthetic colours. As we learn more about the nutritional benefits of microalgae, we anticipate a growth in demand for natural colours made from microalgal biomass.

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