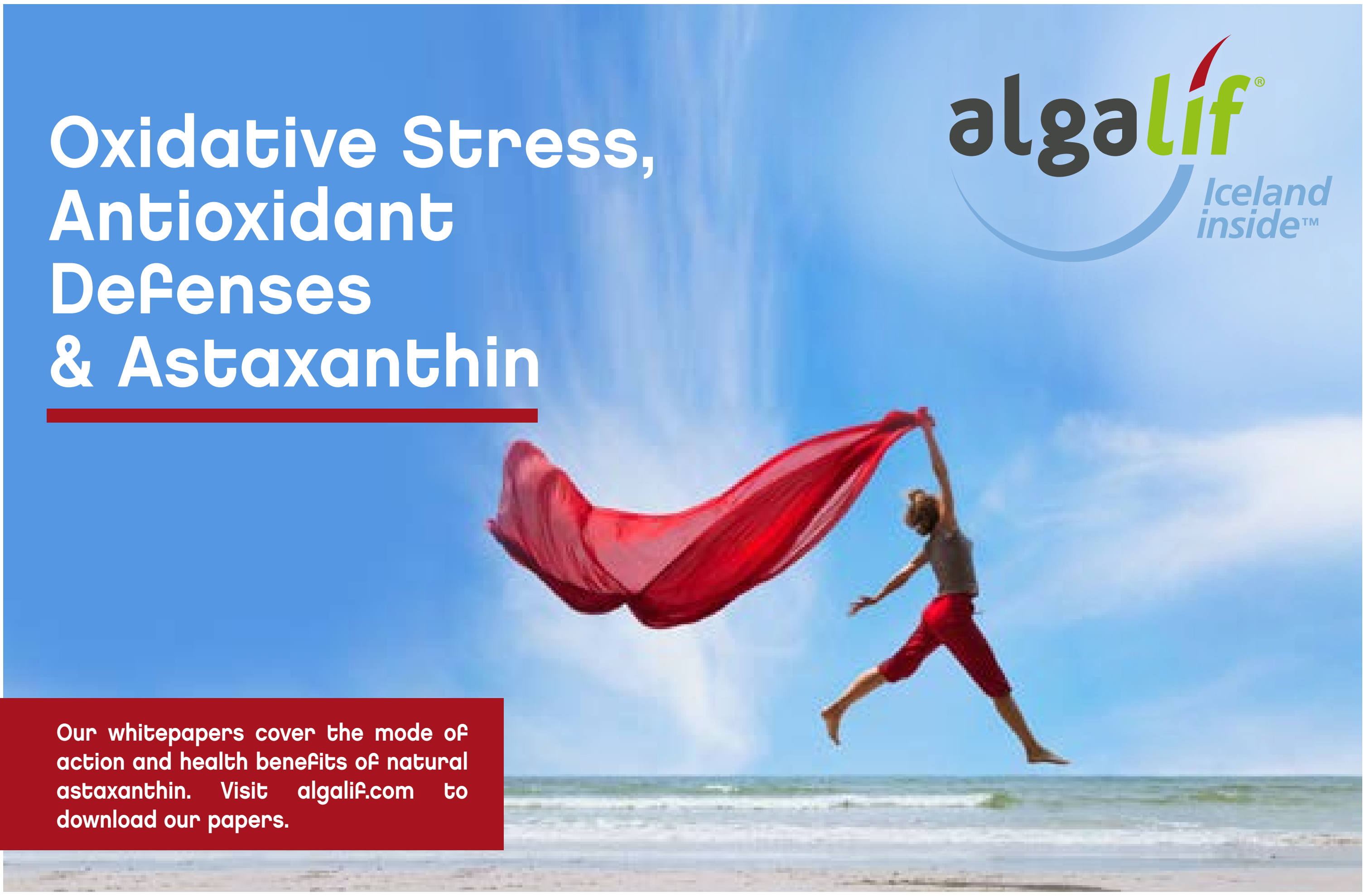
Oxidative Stress, Antioxidant Defenses & Astaxanthin



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Abstract

Antioxidants help to keep a healthy oxidative balance. A diverse range of oxygen free radicals and other reactive oxygen species (ROS) can be formed in the human body. The interplay between ROS and anti-oxidants is critical in maintaining good health. If the ROS generated exceeds the protective effects of antioxidants, it can cause oxidative stress – a deleterious process, damaging cell structures, including lipids, proteins, and even DNA. Many people do not get adequate levels of antioxidants from food alone. Supplementation with dietary antioxidants helps support the body's own antioxidant defenses, and control the harmful effects of excessive ROS.

Astaxanthin is a naturally occurring carotenoid with a unique chemical structure and cell membrane actions. It is a powerful antioxidant and highly effective at counteracting ROS. Astaxanthin has the unique ability to span the cellular membrane and trap ROS within the membrane's interior, and along its surface boundaries. Astaxanthin neutralizes ROS without becoming a pro-oxidant in the process. Clinically, astaxanthin has shown diverse health benefits, while also demonstrating excellent safety and tolerability.

How do Antioxidants Support Health and Well-being?

Balanced nutrition is a key lifestyle factor that helps support general wellness. Antioxidants are natural substances that help to prevent the harmful effects of excessive ROS activity, and combat or delay cell damage. Nonetheless, the calorie-rich and nutrient-poor diets of many people today, can make it challenging for them to get enough of essential micronutrients, such as vitamins, minerals, and antioxidants. Malnutrition and poor diet are the biggest drivers of the global burden of disease.[1] Furthermore, exposure to pollutants, excessive sunbathing, tobacco smoke, stress, sedentary lifestyle, extreme exercise, and the use of certain medications can all contribute to an excess of ROS,[2] and potentially have a destructive impact on health and wellbeing. To understand the mechanism of antioxidant action, it is necessary to define ROS and their damaging reactions via oxidative stress.

What are Reactive Oxygen Species and How Do They Cause Oxidative Stress?

Reactive oxygen species (ROS) is a collective term that includes not only oxygen-centered free radicals, but also some non-radical derivatives of oxygen. ROS, otherwise known as pro-oxidants, are formed as by-products of normal metabolism in our body when food is converted into energy.[3] Immune cells fighting bacterial infections also release ROS.[4] Additionally, we encounter ROS in many other aspects of our daily lives in response to the aforementioned lifestyle and environmental factors.

There is a growing consensus that ROS play a dual role, and can be either harmful or beneficial to living systems.[3] Beneficial effects of ROS occur at low/moderate concentrations and involve physiological roles in cellular responses to danger, such as immune cells defending against infectious agents. Low to moderate concentrations of ROS can serve as signals in important pathways involved in normal cell activities.

High levels of ROS can initiate harmful alterations in key biomolecules, such as lipids, proteins and DNA in a condition called oxidative stress. Oxidative stress occurs in the body when there is an overproduction of free radicals and ROS on one side, and a deficiency of antioxidants on the other (**Figure 1 A, B, C**). The efficiency of body's own antioxidant defense system reduces as we age (**Figure 1B**), while the overproduction of free radicals/ROS can take place at any point in life, and particularly in response to certain lifestyle and environmental factors (**Figure 1C**).

It is estimated that each cell in the body forms more than 20 trillion ROS per day through normal metabolism, and that each cell may be attacked by these reactive molecules 10,000 times per day[5] Over time, oxidative stress can damage cells and tissues, leaving them unable to function properly. Notably, overproduction of ROS impairs biological systems either directly – by oxidation of cellular lipids, proteins, and DNA, or indirectly – by disrupting normal physiological signaling.[6]

In a normal healthy human body, the generation of ROS and other free radicals is kept in check through antioxidant defenses. However, when the body is exposed to adverse physicochemical, environmental or pathological stressors, this delicate balance is shifted in favor of pro-oxidants, and results in oxidative stress. Oxidative stress accompanies most, if not all, pathological conditions, including cardiovascular, immunological and neurological disorders,[7, 8] diabetes[9] and male infertility.[10] Oxidative stress is also closely linked to premature aging.[11]

How Does the Antioxidant Defense System Work?

The antioxidant defense system of the body is a complex network which comprises several enzymatic and non-enzymatic antioxidants.[12] Enzymatic antioxidant defenses include superoxide dismutase, glutathione peroxidase, and catalase. There are also several non-enzymatic antioxidants, including vitamins C and E, selenium, and carotenoids such as β-carotene, lycopene, lutein, zeaxanthin and astaxanthin. Dietary intake is an important source of these non-enzymatic antioxidants. They function as chain-breaking antioxidants, working in tandem with enzyme antioxidants to temper ROS to within physiological limits. Low intake or impaired availability of dietary antioxidants weakens this important antioxidant network.[13] Protective antioxidant compounds are located in organelles, subcellular compartments and in extracellular spaces enabling maximum cellular protection to occur. The components of the antioxidant network play specific roles in different parts of the cell, depending on whether they are water-soluble or lipid-soluble. For example, water-based vitamin C and glutathione protect cytosol and/or the cytoplasmic matrix. The lipid-soluble antioxidants, including vitamin E and carotenoids like β-carotene and astaxanthin, are predominantly located within cell membranes.

In the next section, we will introduce astaxanthin and discuss some of the unique features that make it a superior antioxidant.

Where Does Astaxanthin Come From?

Natural astaxanthin belongs to a family of naturally-occurring organic pigments called carotenoids. There are over 600 known carotenoids such as lycopene, lutein, and β-carotene. They are responsible for the bright red, yellow and orange colors found in many fruits and vegetables. Natural astaxanthin is the main carotenoid in aquatic animals such as shrimp, lobster, salmon, trout, and red seabream. It contributes to the pinkish-red color of their flesh. Natural astaxanthin is also found in some birds such as the flamingo. Synthetic astaxanthin can be produced by chemical synthesis in the laboratory using petrochemicals. Natural astaxanthin is far superior to synthetic astaxanthin in regard to efficacy, safety and chemical assembly, including isomers and esterification.

Although astaxanthin has a long history of use in the human diet as a naturally occurring component of seafood, most people do not consume enough of it in their diet. For instance, the United States population consumes only 2-3 pounds of wild and farmed salmon per year, with an estimated astaxanthin intake of 0.029 mg/day.[14] This is about 200 times less astaxanthin than the documented dose for health benefits, which ranges from 2 mg to 12 mg.[15-21] The microalgae *Haematococcus pluvialis*

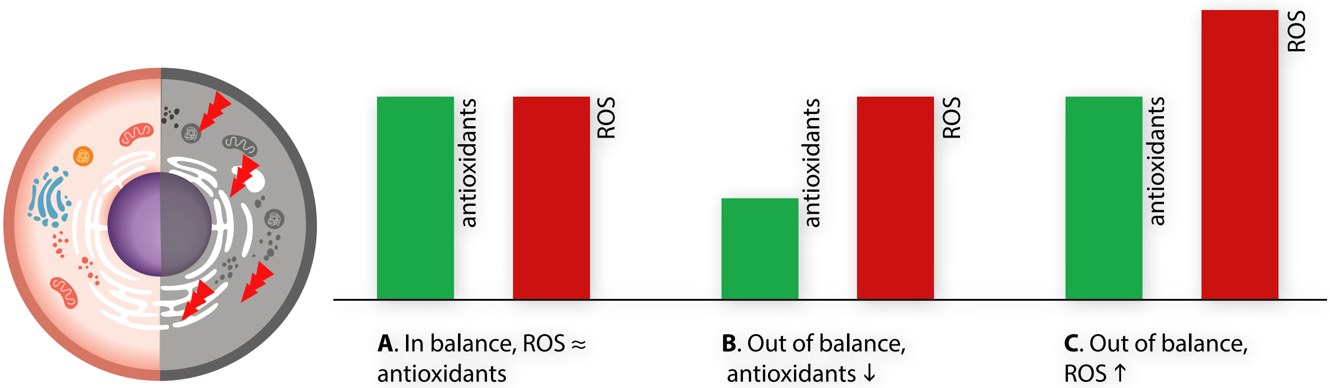

Figure 1*. Schematic overview with the regulation of oxidative balance.* **A***. Healthy oxidative balance;* **B***. Activity of antioxidant defense reduces as we age, resulting in depletion of antioxidants;* **C***. The overproduction of ROS that takes place in response to endogenous or exogenous factors in any time of life.*

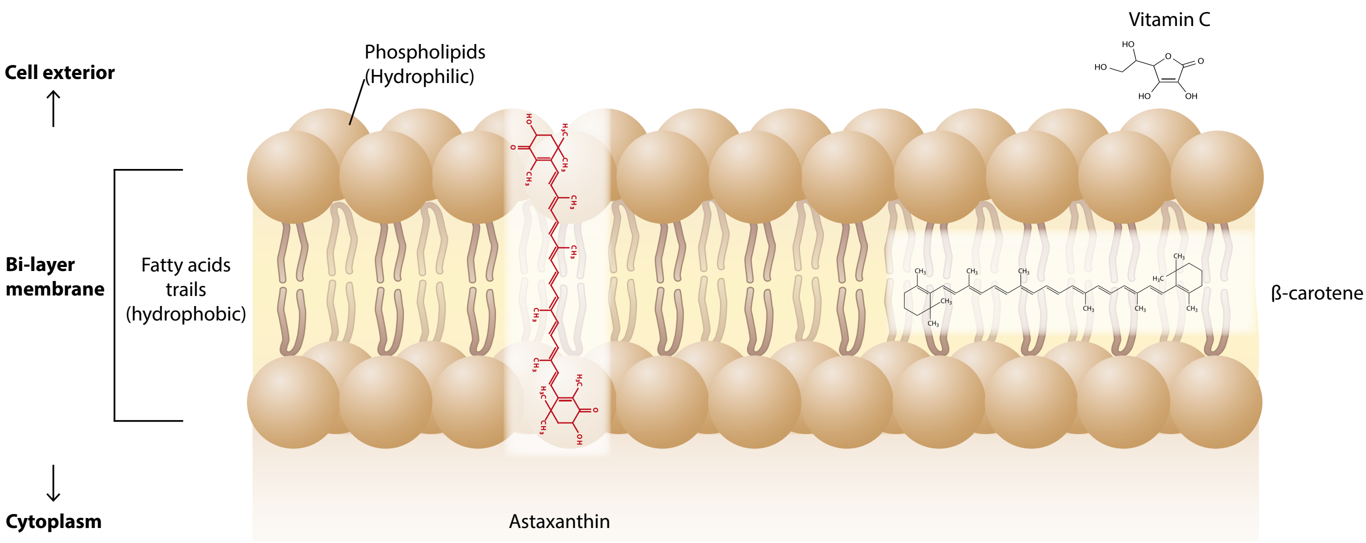

***Figure 2**. Astaxanthin orients into optimal hydrophilic and hydrophobic position within cell membrane and acts as a chain-breaking antioxidant. Since astaxanthin spans the cell membrane bilayer, it can effectively scavenge ROS at the membrane surface as well as in the interior of the membrane.*

synthesizes the highest amount of natural astaxanthin in nature, which makes it an optimal choice for commercial production of natural astaxanthin. Dry meal of *Haematococcus pluvialis* has been marketed as dietary supplements in the United States since at least 1999.[22] There is sufficient scientific evidence, including human and animal data, to support the safety of natural astaxanthin.[23-26]

How is Astaxanthin Superior?

Natural astaxanthin is considered as a "superior antioxidant" because of its unique chemical properties based on the molecular structure and localization within the cell membrane.

While structurally similar to the carotenoid β-carotene, astaxanthin has thirteen conjugated double bonds, whereas β-carotene has eleven. In the cyclohexene structure, it has oxo groups in the fourth and fourth prime positions. The antioxidant activity of carotenoids depends on the length of the electron rich, conjugated, double bond system. An extension of the conjugated double bond system increases the potency of astaxanthin compared to β-carotene and vitamin E.[27] Additionally, astaxanthin has hydroxyl groups at the third and third prime position, making the molecule somewhat polar.

The antioxidant properties of various antioxidants *in vivo* are strongly influenced by how they inte act with the membrane bilayer, their orientation, and location within the membrane. Nonpolar carotenoids (i.e.: β-carotene and lycopene) are located between membrane bilayers and therefore may disrupt the intermolecular packing of the phospholipid molecules.[28, 29] By contrast, polar astaxanthin spans the membrane, with its polar end groups extending toward the head group regions of the membrane bilayer. Astaxanthin position does not modify the structure of constituent membrane lipids[28-30] (**Figure 2**). As a result, astaxanthin acts as a chain- breaking antioxidant by stopping free radical chain reactions and scavenging lipid peroxyl radicals. Furthermore, since astaxanthin spans the cell membrane bilayer, its terminal rings can effectively scavenge ROS on the membrane surface, while its polyene chain is responsible for trapping ROS in the interior of the membrane.[30]

Astaxanthin can use different methods to prevent oxidative stress. Astaxanthin counteracts potentially harmful free radicals/ROS by trapping energy (quenching) and the transfer of electrons, or through hydrogen abstraction (scavenging).[27, 31-34] Energy from the high-energy ROS compounds can be transferred to astaxanthin by direct contact, and that energy is converted to heat.[27] In this process of quenching, astaxanthin remains intact so that it can undergo further cycles of singlet oxygen quenching. Singlet molecular oxygen is a strong pro-oxidant that displays substantial reactivity towards DNA, proteins, and lipids.[35]

Comparative studies have shown that natural astaxanthin is 6,000 times more powerful than vitamin C, 100 times more powerful than vitamin E, and five times more powerful than β-carotene in its ability to trap energy from singlet oxygen[33] (**Figure 3**). Furthermore, astaxanthin reacts as a strong antioxidant without any pro-oxidative nature.[36, 37] Consequently, astaxanthin is gentle on the body's cells as it effectively neutralizes harmful ROS.

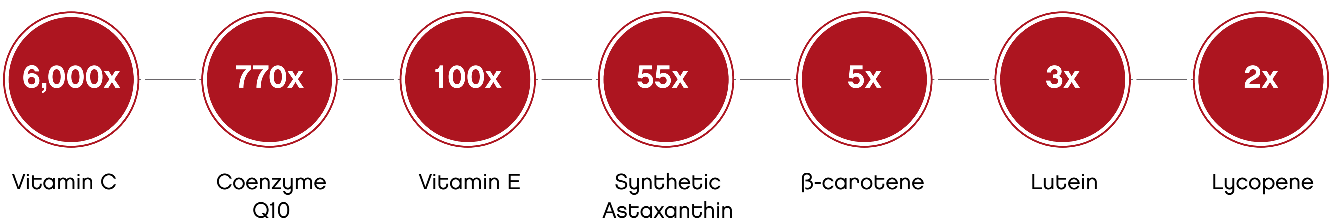

***Figure 3.** Natural astaxanthin in comparison to other antioxidants. Natural astaxanthin is more powerful than other antioxidants in trapping energy from singlet oxygen.[33, 37]*

Conclusion

Antioxidants are important nutrients that help combat oxidative stress by removing ROS and promoting a healthy oxidative balance. Through the antioxidant defense system, ROS-triggered oxidative damage to biomolecules is controlled, allowing the restrained ROS to do their useful work in physiological cellular responses.

Astaxanthin stands apart from other antioxidants because of its unique chemical properties. A growing body of clinically-validated evidence indicates the benefits of natural astaxanthin for a range of target groups – from young, highly-trained athletes with increased ROS production, to healthy middle-aged and senior subjects with weakened antioxidant defense activity. Astaxanthin is a valuable functional ingredient that supports normal immunity, heart, eye, joint, and skin health and expands our healthy aging options.

Avoiding an excess of ROS, adopting a healthy lifestyle, and introducing astaxanthin into the diet, can help prevent oxidative stress. Dietary supplements and functional foods are good sources for increasing daily intake of astaxanthin. It is a promising strategy to maintain good health and wellbeing and offers exciting opportunities for the nutraceutical industry.

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