

## Astaxanthin protective barrier and its ability to improve the health in patients with COVID-19

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Received: January 2021, Accepted: May 2021

### ABSTRACT

Inflammation acts like a double-edged sword and can be harmful if not appropriately controlled. COVID-19 is created through a novel species of coronavirus SARS-CoV-2 (2019-nCoV). Elevated levels of inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), etc. lead to Acute Respiratory Distress Syndrome (ARDS) and severe complications of infection in the lungs of coronavirus-infected patients. Astaxanthin is a natural and potent carotenoid with powerful antioxidant activity as well as an anti-inflammatory agent that supports good health. The effects of astaxanthin on the regulation of cyclooxygenase-2 (COX-2) pathways and the reduction and suppression of cytokines and other inflammatory agents such as IL-6 and TNF- $\alpha$  have already been identified. Therefore, these unique features can make this natural compound an excellent option to minimize inflammation and its consequences.

**Keywords:** COVID-19; Interleukin-6; Tumor necrosis factor-alpha; Respiratory distress syndrome; Astaxanthin; Anti-inflammatory agent

### INTRODUCTION

The new pandemic SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2), began in late 2019 in Wuhan, China, as a COVID-19 spread around the globe (1). Infection with the new coronavirus SARS-CoV-2 is initially associated with nonspecific and general symptoms such as nausea, fatigue, and body aches, fever, and dry cough. Patients may suffer symptoms of nausea and diarrhea shortly before the fever. A small number of patients may also have headaches or vomiting of blood and may even be relatively asymptomatic. In severe cases, the suf-

ferer shows severe symptoms, which include pneumonia and shortness of breath. In cases where the patient's condition is deteriorating, respiratory distress, infectious shock, and failure are present in other body organs (2). A lot of pro-inflammatory cytokines and chemokines such as IL-6, IL1B, IFN $\gamma$ , IP10, and MCP1 IL2, IL7, IL10, GCSF, MIP1A, and TNF- $\alpha$  have been observed in patients infected with SARS-CoV-2 (3, 4). The main factor in the development of cytokine release syndrome (CRS) is IL-6. The uncontrolled increase in IL-6 causes an over-immune response and a cytokine storm in the body (5). Chemical signals (cytokines) cause inflammation, and if

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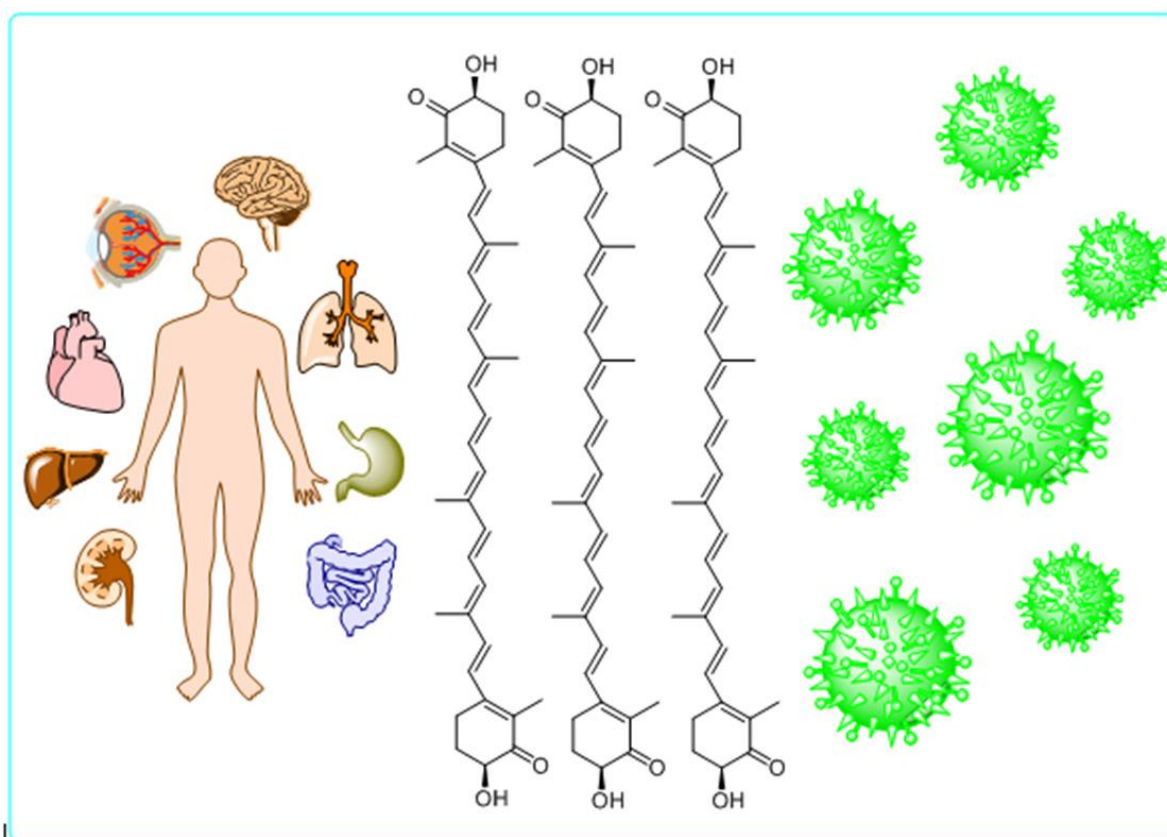
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the immune system is unable to balance, over-inflammation and, consequently, the immune system overreaction can exacerbate the disease. Laboratory studies confirm that the angiotensin-converting enzyme 2 (ACE2) expressed at the cellular level acts as a gateway for 2-CoV-SARS to enter the cell (6). But in addition to the respiratory system, other organs in which the ACE2 is expressed, such as endothelial vascular cells of the heart, brain stem, kidneys, liver, intestines, and testicles, etc., are also prone to infection and damage caused by coronavirus (7).

Astaxanthin is an antioxidant and anti-inflammatory compound extraordinary. This bright orange compound has a significant impact on human health, including strengthening the immune system and preventing cardiovascular disease, various cancers, diabetes, liver disease, stomach, obesity problems, and the aging process of cells (8). Astaxanthin balances and boosts the immune system and ameliorates the body's ability to fight inflammation (9). In some studies, anti-inflammatory therapies have been used to control acute respiratory syndrome (10). Astaxanthin prevents cytokine storms by inhibiting nuclear fac-

tor- $\kappa$ B (NF- $\kappa$ B) signaling cascade as well as inflammatory cytokines. It thus has the potential to prevent acute respiratory syndrome due to coronavirus infection (11-13). To reduce and also counteract the severe effects of the virus and the resulting disease, it is necessary to use methods and treatments that reduce anti-inflammatory agents and cytokines. The immune system needs to be strengthened to prevent chronic inflammation and severe complications from respiratory SARS-CoV-2. Using natural astaxanthin, an extremely potent and highly effective antioxidant, can be a great option with high potential to protect the immune system and other organs. The purpose of this paper is to review the properties of astaxanthin as a powerful natural anti-inflammatory that has the ability to protect, strengthen and balance the immune system. Therefore, it may have a beneficial and positive effect on reducing the complications of the SARS-CoV-2 disease and acts as a barrier against coronavirus (Fig. 1).

**Coronavirus pathogenesis and human immune system.** Human coronaviruses, as important patho-



**Fig. 1.** Astaxanthin as a barrier against Coronavirus

gens, have always caused infections of varying severity in the respiratory tract and intestines and have been associated with a variety of complications. High-pathogenic coronaviruses SARS-CoV (SARS), MERS-CoV (MERS) and more recently SARS-CoV-2 can cause severe respiratory illness by infecting the lower respiratory tract (14). The new coronavirus uses spike glycoprotein (S) to bind to ACE2 cell surface receptors and enter the cell, as well as SARS-CoV, while MERS-CoV utilizes dipeptidyl peptidase 4 (DPP4) for the binding process (2, 6, 15). The crucial role of this binding in tissue proliferation as well as in the multidrug infection of the SARS-CoV-2 is related to the pervasive expression of ACE2 in cells, such as alveolar type II (ATII) cells, the upper esophagus, epithelial cells, the vascular endothelial cells of the heart, kidney, liver, testis and absorptive enterocytes of the ileum and colon (16). Examination of C-reactive protein (CRP) levels is a reliable indicator for measuring the rate of hazardous silent inflammation in many diseases, such as atherosclerosis, Alzheimer, colon cancer, diabetes, and heart disease (17). An increase in neutrophils and a decrease in lymphocytes have been associated with disease severity and mortality. It has been demonstrated that during the disease, neutrophils, serum IL-6, and other cytokines, and CRP increased, and against lymphocytes showed a decrease (18). The leading reason for death in patients with COVID-19 is ARDS caused by cytokine storms (19). Elevated IL-6 in patients infected with the coronavirus has been reported to be a major cause of inflammation and pneumonia (20). The assumed SARS-CoV-2 receptor, ACE2, is mainly expressed in a small subset of cells in the lungs called ATII (21). To start the antiviral immune response, it is necessary first to identify the intrinsic immune cells of the virus, which often happens with Pathogen-associated molecular patterns (PAMPs). The involvement of innate immune receptors in the process of virus detection leads to the secretion of various types of cytokines, interferon type I, and other inflammatory mediators. Detection of the virus leads to cascading signaling events downstream of the cell. For example, identification is associated with a change in the state of NF- $\kappa$ B and IRF3 in the host cell nucleus. In the cell nucleus, the activity of transcription factors and changes in the macrophage polarization to the M1 phenotype of pro-inflammatory cause the expression of IFN-I and other pro-inflammatory cytokines such

as TNF- $\alpha$ , IL-6, MCP-1. As a result of the increase in these factors, the host's first line of defense against the virus at the site of virus entry, the penetration of mast cells, neutrophils, and macrophages into lung immune cells increased, which in turn increased the risk of inflammation, infection, and defects in lung function (5, 22). Preliminary studies have shown that people with underlying conditions and chronic diseases such as cardiovascular or cerebrovascular, liver, malignant tumors as well as such as diabetes and chronic kidney disease (CKD) are at higher risk for complications and death from SARS-CoV-2 infection (1, 23, 24). This infectious disease has various clinical complications, in addition to ARDS which is its most important complication, it also causes damage to myocardial cells, liver, and kidneys, immune system, thrombotic disease, circulatory failure as well as multiple organ dysfunction syndromes (MODS) and pneumothorax (16, 24-26). The kidneys are one of the target organs of the SARS-CoV-2. Some studies have shown that patients with COVID-19 have acute kidney damage with no history of kidney failure (27). In addition to the increased risk of COVID-19 disease in heart patients, coronavirus can also cause heart problems with myocardial injury, vascular inflammation, cardiac arrhythmias, and chronic damage to the cardiovascular system in healthy people (28). The harmful effects of coronavirus on the nervous system have been approved. In some cases, coronavirus has been found in the brain and cerebrospinal fluid. According to some reports causes nerve damage by invading the central nervous system (CNS) (29). A study has shown that if cancer patients become infected with the coronavirus, the severity of the disease and its complications will be higher (30). Secondary side effects of COVID-19 include type 2 diabetes and high blood pressure. Inflammation from metabolic problems raises the level of fat, blood pressure, and glucose in patients. In addition to cardiovascular problems, diabetes, and high blood pressure can endanger the immune system and disrupts the healing process (31).

**Astaxanthin.** Astaxanthin is a potent carotenoid with powerful antioxidant and anti-inflammatory activity that produced by *Phaffia rhodozyma*, *Agrobacterium aurantiacum*, and *Haematococcus pluvialis* (32). The most important major sources of natural astaxanthin are *H. pluvialis* and *Phaffia yeast*, which many scientists have extracted astaxanthin

from these compounds and increased the amount of astaxanthin in these sources in diverse ways (33-37). Years of laboratory and clinical researches that lead to commercial production have proven that natural astaxanthin has no side effects or toxicity (38). Astaxanthin safety has been confirmed by extensive experiments, including acute toxicity, mutagenesis, transgenicity, fetal toxicity, and reproductive toxicity (33, 39). In addition to balancing the immune system, astaxanthin can inhibit unnecessary inflammation by suppressing overactive immune responses (40). Astaxanthin increases the body's immune response by increasing the number and activity of lymphocytes and natural killer cells (41). Natural astaxanthin has clinically shown excellent and unique benefits in immunity, inflammatory diseases, and neurological problems. Evidence has shown that astaxanthin, with its protective properties, has beneficial effects in the treatment and prevents various diseases such as cancer, cardiovascular disease, chronic inflammatory diseases, diabetes, and liver disease. Astaxanthin protects the heart, lungs, eyes, skin, immune system, liver, nervous system, and other organs and cells of the body against inflammation, oxidative stress, and other irritants (42-44).

**Astaxanthin protective effect on the body.** Given the tremendous impact of astaxanthin on the prevention and even cure of diseases caused by oxidative stress, inflammation, and other chronic diseases of the nervous system, many researchers have focused on investigating the effect of this natural product on neurological disorders and diseases (45). In addition to its antioxidant, anti-inflammatory, and anti-apoptotic activity, the special chemical structure of astaxanthin allows it to cross the blood-brain barrier (BBB), thereby exerting its protective effect on the brain (46). Astaxanthin has an antihypertensive efficacy and brings down the danger of stroke. It has likewise experienced a positive impact on improving the cardiovascular system (47). The use of astaxanthin in the diet has significantly reduced the risk of autoimmune diseases caused by abnormal T cells (48). The outcomes of the survey indicate a positive impact of astaxanthin in restoring humoral immune responses, which has reduced due to aging (49). Due to its high antioxidant power, astaxanthin supplementation reduces arterial stiffness, oxidative stress, and inflammation in kidney transplant patients that thereby reducing cardiovascular complications in

these patients (50). Numerous studies have examined the ability of astaxanthin to prevent atherosclerosis. Natural astaxanthin can be utilized as a prophylactic compound against atherosclerotic cardiovascular disease (CVD) (51).

**Astaxanthin protective effect on the immune system and reduction inflammation.** One of the important roles of astaxanthin is to reduce inflammation. Astaxanthin exerts its anti-inflammatory effects through various mechanisms and pathways. This natural compound reduces the amount of these inflammatory markers by affecting various inflammatory factors such as IL-6, IL-1B, TNF- $\alpha$ , the NF- $\kappa$ B, COX 1 & 2 enzymes, NO, IFN- $\gamma$ , IL-8, and prostaglandin E-2 (PGE-2) (17, 52, 53). Natural astaxanthin, with acting on inflammatory markers, can eliminate or reduce inflammation without side effects. Compared to some anti-inflammatory and analgesic drugs, astaxanthin has had a much more positive effect. In various surveys, many consumers with various inflammatory problems such as back pain, joint pain, muscle and tendon pain, carpal tunnel syndrome, rheumatoid arthritis, asthma, and prostate cancer reported complete improvement or improvement in symptoms after using this supplement (17, 54). Various studies have confirmed the significant effect of astaxanthin on inhibitory and anti-inflammatory activity against a wide range of internal and external inflammatory factors such as mast cells, UV rays, and cytokines (55). *In vitro* and *ex-vivo* studies have shown that astaxanthin could suppress not only inflammatory markers of NO, PGE-2, and TNF- $\alpha$  but also other inflammatory agents such as IL-1B, COX-2, and NF- $\kappa$ B as well. Astaxanthin *via* inactivating the NF- $\kappa$ B prevents the release of inflammatory cytokines and protects cells from oxidative stress (52, 56). Macedo et al. perused the therapeutic effect of astaxanthin on phagocytic and microbial capacity, cytokine secretion, and ROS production in human neutrophils. They have concluded that in the presence of astaxanthin, the phagocytic and microbial capacity increased and in contrast to the production of superoxide anion and hydrogen peroxide was reduced without any affecting the capacity of neutrophils as well as cytokines (IL-6 and TNF- $\alpha$ ) (57). Research has shown that astaxanthin exerts its protective effect on the acute pulmonary inflammatory disease by inhibiting the MAPK / NF- $\kappa$ B signaling pathway which leads to a decrease in the production of TNF- $\alpha$



and IL-6 inflammatory cytokines (58). Regulation of IL-6 production is important for maintaining brain homeostasis and preventing many neurological disorders. Kim and his colleagues first concluded in a study that astaxanthin inhibits IL-6 expression and NF- $\kappa$ B transcriptional activation in active microglial cells (59). After treating with astaxanthin was observed improvement and reduction of cognitive impairment due to hyperglycemia in diabetic encephalopathy (DE). Astaxanthin inhibits the expression of TNF- $\alpha$  expression in the hippocampus and retina by inhibiting the NF- $\kappa$ B nuclear transfer factor, thus protecting the neurons against inflammatory damage (60). According to the mechanism of action of astaxanthin, this natural compound inhibits the cytokine storm by inhibiting the NF- $\kappa$ B signaling cascade and inhibiting inflammatory cytokines. It thus has the potential to prevent acute respiratory syndrome due to coronavirus infection. Due to the many benefits of natural astaxanthin, clinical trials have been conducted in various fields (61). Recent clinical trial reports on the protective effect of natural astaxanthin on the immune system are presented in Table 1.

## CONCLUSION

The outbreak of a new coronavirus, called SARS-CoV-2 by the World Health Organization (WHO) has led to the global disease COVID-19, the control and treatment of which is a worldwide concern. The leading solution in the current situation is to avoid contamination and care to prevent its spread. In the case of illness, it is a priority to reduce its complications such as secondary infections or organ failure. The virus invades the body, causing a cytokine storm and an overgrowth of IL-6 and other inflammatory factors, leading to complications such as acute lung syndrome. Controlling and preventing the onset of cytokine storms and reducing inflammatory factors is essential in the cure and prophylaxis of COVID-19. The use of compounds with high antioxidant power in the treatment of COVID-19 is a viable and effective suggestion. Protecting the immune system with antioxidants plays a vital role in health and longevity. A healthy immune system is one indicator of health, and by examining the immune system, lifespan can be predicted. Most medications prescribed for the remedy of diseases, especially chronic diseases, have serious side effects. The ACE2 has a positive

**Table 1.** Clinical trial studies investigating the protective effect of natural astaxanthin on the immune system

Tested Parameters	Study design	dosage	Duration of study	Effects of astaxanthin	Ref
salivary IgA (sIgA) and oxidative stress status in plasma, along with changes in biochemical parameters and total/differential white cell counts	Randomized double-blind and Placebo controlled	4 mg daily	12 weeks	improves salivary IgA response and attenuates muscle damage	(54)
Immune response and tuberculin test performed	randomized double-blind, placebo-controlled	8 mg daily	8 weeks	Decreased DNA damage biomarkers, without affecting lipid peroxidation, decreased C-reactive protein concentration, increased cytotoxic activity of natural killer cells and increased total sub-T and B population due to mitogen-induced I lymphoproliferation, increased IFN- $\gamma$ and IL-6	(62)
Inflammatory markers (IL-4, IL-6, IL-8, IL-10, interferon- $\gamma$ , CD4, CD8, CD14, CD19, CD25 and CD30)	Randomized, placebo controlled	Not informed	40 mg	a significant decrease in gastric inflammation in <i>H. pylori</i> -positive patients, no significant changes in the density of <i>H. pylori</i>	(63)

impact on the body's defenses and, unfortunately, has destructive effects owing to its role as a receptor for the coronavirus. Through pretreatment with astaxanthin, the protective role of ACE2 can be used to manage and balance its expression. Hence, the use of natural anti-inflammatory compounds without side effects can be a good option in preventing inflammation and thus controlling cytokine storms. Side effects of Covid-19 diseases, such as metabolic inflammation, reduce the body's ability to fight coronavirus infection. Natural astaxanthin is a robust anti-inflammatory compound that executes a protective effect on the body by controlling metabolism, balancing the immune system, and preventing the formation of cytokine storms. IL-6 plays a crucial role in various inflammatory diseases such as infections, cancer, cardiovascular disease, and autoimmune disorders and becomes an inflammatory agent with an excessive increase from one anti-inflammatory agent. Multitudinous studies and clinical trials confirm this well that astaxanthin can play a vital role in the control and prevention of inflammatory diseases. In particular, it can balance the immune system and control the release of inflammatory agents.

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