

Carotenoids: Therapeutic Strategy in the Battle against Viral Emerging Diseases, COVID-19: An Overview

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Abstract

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INTRODUCTION

The world continues to face a pandemic crisis caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a highly pathogenic infectious virus that has infected over 178 million and lead to the death of ~4 million people worldwide as of June 2021 ([Dong et al., 2020](#)). SARS-CoV-2 is a single-stranded RNA virus that belongs to the genus *Betacoronavirus*, one of four genera of Coronaviridae. At the nucleic acid level, SARS-CoV-2 shows 78% similarity with SARS-CoV and 50% with the Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 is transmitted via aerosolized droplets via direct contact and oral-fecal, and generally has an incubation period of 5 to 14 days, reaching 24 days in certain cases. At the onset COVID-19, the main symptoms are fever, cough, fatigue, and muscle pain and, in severe cases, many patients show signs of dyspnea, acute respiratory distress syndrome (ARDS), cardiac injury, multi-organ failure, and shock ([Zhong et al., 2020](#)). The risk of serious COVID-19 infection increases with age, male gender, and underlying health problems, such as cardiovascular diseases, obesity, diabetes, chronic obstructive pulmonary disease (COPD), and asthma ([Goyal et al., 2020](#)). Accumulated data suggest that COVID-19 is characterized by a hyperinflammatory state in which pro-inflammatory cytokines that underlie the pathology of COVID-19 infection, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-2, IL-17, granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1- α (MIP-1 α), C-reactive proteins (CRP), and interferon (IFN)- γ inducible protein 10 (IP-10), are prominent ([Xu et al., 2020](#)). Patients with COVID-19 show immune system perturbation with profound alterations of various components, such as decreases in peripheral T lymphocytes, natural killer (NK) cells and CD8⁺ T cells, loss of major histocompatibility class (MHC) class II molecules, and increases in chemokine production from monocytes ([Huang et al., 2020a](#)). Since no active medication is yet available and limited amounts of vaccines are used worldwide, strengthening immune systems thorough diet may be central in the combat against the virus and its related symptoms. Indeed, phytochemicals and selected foods, such as garlic, ginger, basil, drumstick, and liquorice/licorice, may inhibit several viruses including SAR-CoV by directly inhibiting either viral entry or replication, and by immunomodulation ([Anand et al., 2021](#); [Fasogbon et al., 2021](#)). Furthermore, phytochemical-containing foods, such as cashew nuts and ginger, have been described to exhibit many health benefits for inflammatory processes and oxidative stress, which are the key factors in developing several chronic diseases such as diabetes mellitus and metabolic syndromes ([Darvish Damavandi et al., 2019](#); [Morvaridzadeh et al., 2020](#)). In this regard, natural phytochemicals compounds such as carotenoids and polyphenols appear to have a role in this viral battle due to their acknowledged biological and pharmaceuticals effects in preventing several human diseases and maintaining good health. Some primarily contribute to vitamin A dietary, which has a potent role in COVID-19 treatment ([Li et al., 2020](#)). High plasma and serum concentrations of carotenoids have been associated with a lower incidence of acute respiratory infections and immune response

improvement in elderly people, resulting in a decreased risk of infectious diseases and improved pulmonary function (van der [Horst-Graat et al., 2004](#); [Semba et al., 2012](#)). [Herold et al. \(2020\)](#) showed that CRP and IL-6 levels are elevated (IL-6: >35 pg/mL at presentation and maximal value >80 pg/mL; CRP: >32.5 mg/L at presentation and maximal value >97 mg/L) in COVID-19 patients, which is associated with risk of respiratory failure and a need for mechanical ventilation. Thus, IL-6 or CRP could be used to guide treatment acceleration in patients with COVID-19-related hyper-inflammatory syndrome. An inverse correlation between CRP, a marker of inflammation, and β -carotene have been reported in infants with acute infections. In addition, the association of lower CRP with higher carotenoid intake likely reflects carotenoid antioxidant and immunomodulatory properties in preterm infants ([Cser et al., 2004](#); [Rubin et al., 2012](#)). According to the World Health Organization, maintaining a strong immune system with a nutritious diet rich in fruit and vegetables, and low in sugar and calories is important against COVID-19. Thus, diets containing carotenoids and polyphenols may be important for combating the emergence of COVID-19 and its related symptoms. This review summarizes and highlights the available up-to-date facts related to the potential role of the major carotenoids studied from natural sources in human immunity boosting, via their beneficial properties in the combat against COVID-19 and related symptoms. In addition, this review aimed to gather the literature on each carotenoid compound, to be used as a potential tool to further the antiviral pharmaceutical industry.

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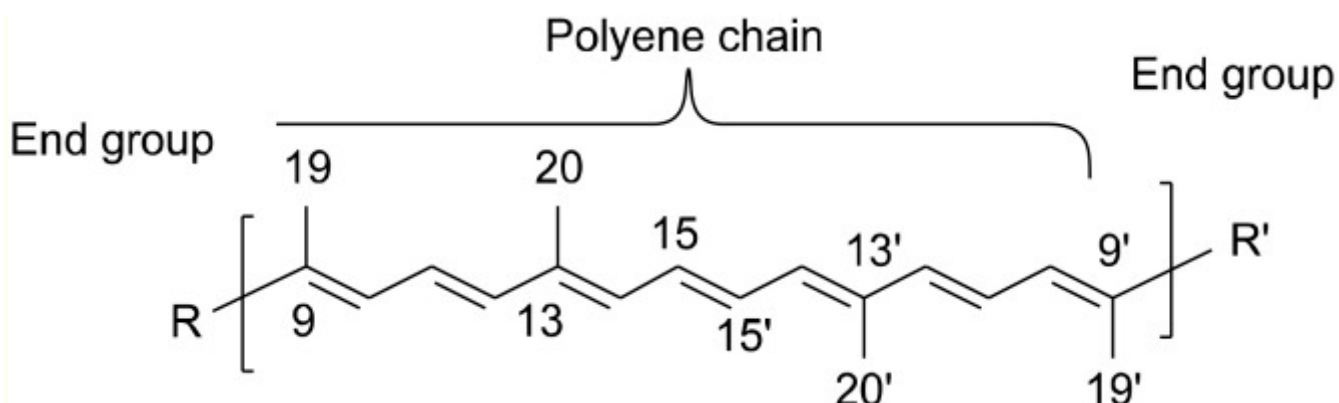
RESEARCH STRATEGY

The medical websites PubMed and Medline, and Science direct and Cochrane Library were searched for the carotenoids included in this review and were archived by the number of studies found on these sites. The initial electronic database yielded approximately 2,070 records. For each individual carotenoid compound, a detailed search was conducted with the following keywords: inflammation, immunity, immune, asthma, influenza, common cold, flu, lung, lung disease, pulmonary, fibrosis, ARDS, COPD, viral, anti-viral, virus, SARS, MERS, and COVID-19, for each section of this review was followed. After evaluation of the titles and abstracts, and removal of duplicates, the full texts of 477 studies were examined and reviewed by the authors. Finally, ~200 articles containing outcomes on human health, published until March 2021, were included in this review. This included *in vitro* and *in vivo* to epidemiological studies. The most relevant papers, which elucidate the foremost role of each studied carotenoids as anti-inflammatory, immunity supporting, and anti-viral agents, were discussed and papers showing similar results were gathered or excluded from the reference list. Our strategy was based mainly on the beneficial role of carotenoids from natural sources that make up the human diet, and the relevant molecular pathways, particularly those involved in the combat against emerging diseases, such as COVID-19 and related symptoms.

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CAROTENOIDS: STRUCTURE, CLASSIFICATION, SOURCES, AND BIOLOGICAL ACTIVITIES

Carotenoids, a large group of organic compounds that are biosynthesized by plants, bacteria, and fungi but not humans ([Ruiz-Sola and Rodríguez-Concepción, 2012](#); [Kiokias et al., 2016](#); [Maoka, 2020](#)), have a common backbone structure called polyene chain, which is a system of conjugated double bonds and two end groups ([Maoka, 2020](#)) ([Fig. 1](#)).



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Fig. 1

Shared backbone structure of the majority of carotenoids.

In general, carotenoids are tetraterpenoids containing eight isoprenoid building blocks (e.g., isoprene in [Fig. 2](#)). Four isoprenoids are present in the polyene backbone and four are present in the two end groups ([Kiokias et al., 2016](#); [Meléndez-Martínez et al., 2019](#)).

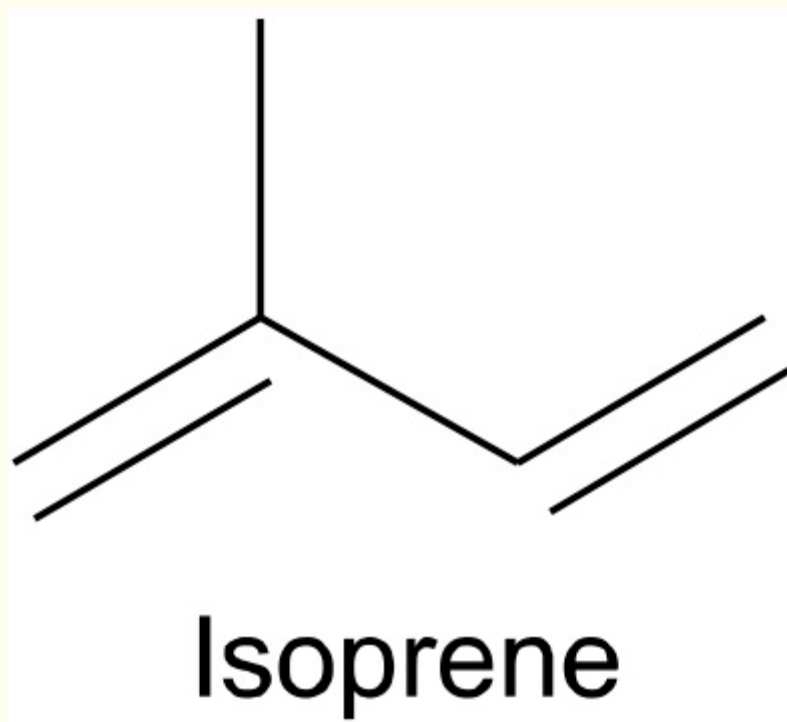


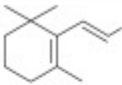
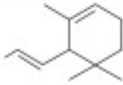
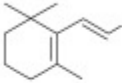
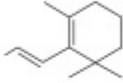
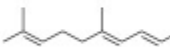
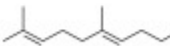
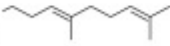
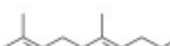
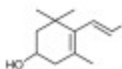
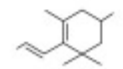
Fig. 2

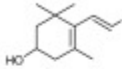
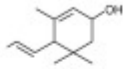
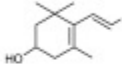
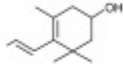
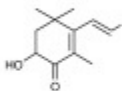
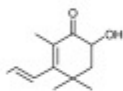
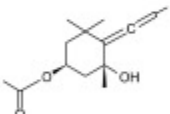
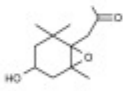
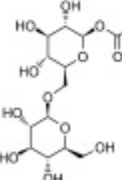
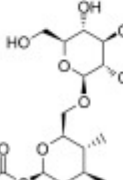
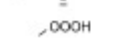
Isoprene containing five carbon atoms is an example of an isoprenoid.

Carotenoids can be grouped in different classes chemically or by activity, and usually contain 40 atoms of carbon ([Table 1](#)). Carotenoids may be described as carotenes that have cyclized or acyclized hydrocarbon end groups, or as xanthophyll, which has oxygenated end groups (hydroxyl, epoxy, carbonyl, etc.). Furthermore, many carotenoid groups contain provitamin A and can be enzymatically converted in the intestinal mucosa to yield retinol (vitamin A) ([Sayahi and Shirali, 2017](#)).

Table 1

Chemical composition, classification, natural sources, and biopharmaceutical activities of studied carotenoids

End groups		Name Color Chemical formula Molar mass (g/mol)	Classification		Pharmacology/ biological activities/ recommended dose for healthy humans
R	R'		Nature of end groups Provitamin or non Carotenes/ xanthophyll's	Natural sources	
		α -Carotene Orange-yellow $C_{40}H_{56}$ MW: 536.873	β -Ionone and α -ionone Provitamin Carotenes	Carrots, pumpkin, winter squash, Swiss chard, broccoli, cantaloupe, green beans, green peas, grape leaves, chili, red and yellow pepper, turnip greens, collards, leaf lettuce, avocado, tangerines, napa cabbage, and bananas	Antioxidant, anti-carcinogenic, immune function enhancing, and lower risk of cardiovascular disease
		β -Carotene Orange $C_{40}H_{56}$ MW: 536.873	β -Ionone Provitamin Carotenes	Sweet potatoes, carrot, pumpkin, spinach, beet, lettuce, onions, muskmelon, apricot, butternut squash, broccoli, mangoes, oranges, podded peas, kale, papayas, cantaloupe, dark leafy greens, orange root vegetables, chili, sage, coriander, paprika, parsley, cayenne, cilantro, and marjoram	Lower occurrences of certain cancers (lung cancer) Enhance the immune function, antioxidant, and anti-inflammatory 5–15 mg/d
		Lycopene Red $C_{40}H_{56}$ MW: 536.873	Acyclic Non-provitamin Carotenes	Tomatoes and tomato products (ketchup, tomato juice, paste, sauce and soup) and other red-pink fruits and vegetables such as watermelons, red oranges, carrots, red bell peppers, red cabbage, persimmon, gac, wolfberry, pink grapefruits, apricots, rosehips, papaya, and guavas also lycopene found in egg yolk	Enhance immunity, antioxidant, anti-proliferative, anti-cancer, anti-inflammatory, cognition enhancer, neuroprotective, hepatoprotective, bone protective anti-obesity, anti-diabetes, and against dermatologic diseases 3–7 mg/d
		Phytoene ¹¹ Colorless $C_{35}H_{54}$ MW: 544.952	Acyclic Non-provitamin Carotenes	Tomato, and tomato products, watermelon, apricot, avocado, banana, caja, cantaloupe, carrot, clementine and clementine juice, grapefruit, papaya, and peach, pepper and vegetable soup and juice	Antioxidant, anti-inflammatory, enhance immunity, protect against skin, leukemia, breast, and prostate cancer
		Phytofluene ²¹ Pale yellow $C_{40}H_{58}$ MW: 542.936			
		β -Cryptoxanthin $C_{40}H_{56}O$ MW: 552.871	β -Ionone, hydroxyl Provitamin Xanthophyll's	Papaya, peaches, paprika, oranges and orange juice, tangerines and citrus tangerines, yellow and orange maize, squash, persimmons, peppers, chili powder, rose hips, sweet pickles, carrots, and kumquats	Antioxidant anti-obesity, anti-inflammatory, anti-osteoporosis, and anti-cancer

End groups		Name Color Chemical formula Molar mass (g/mol)	Classification		Pharmacology/ biological activities/ recommended dose for healthy humans
R	R'		Nature of end groups Provitamin or non Carotenes/ xanthophyll's	Natural sources	
		Lutein $C_{40}H_{56}O_2$ MW: 568.871	Hydroxyl Non-provitamin Xanthophyll's	Chard, chicory greens, kale, paprika, green, and red pepper, spinach, turnip greens, celery, basil, parsley, leek, peas, beans, lettuce, broccoli, carrot, pumpkin, asparagus, pistachio, corn, and egg yolks	Antioxidant, anti-inflammatory, neuroprotective, autophagy, photo protection, hepatoprotective, immunomodulation, anti-carcinogenic, and also to improve skin pliability 20 mg/d, 53 mg/d
		Zeaxanthin $C_{40}H_{56}O_2$ MW: 568.871			
		Astaxanthin Red-pink $C_{40}H_{52}O_4$ MW: 596.84	Hydroxy carbonyl Non-provitamin Xanthophyll's	Seafood and algae such as salmonids, shrimp, krill and krill oil, crayfish, and crustacean	Immunomodulatory, anti-fibrotic, anti-cancer, anti-diabetic, anti-inflammatory, anti-oxidant, neuro-, cardiovascular, optical, and skin-protective 3 mg/d
		Fucoxanthin Orange $C_{40}H_{56}O_2$ MW: 568.871	Hydroxy epoxy carbonyl Non-provitamin Xanthophyll's	Brown algae (class <i>Phaeophyceae</i> , such as Kombu (<i>Laminaria japonica</i>) and Wakame (<i>Undariapinnatifida</i>) which are used in macrobiotic diet (especially, Japan and Korea), and diatoms (<i>Bacillariophyceae</i>)	Antioxidant, anti-inflammatory, anti-cancer, anti-obesity, anti-diabetes, hepatoprotective, cardiovascular cerebrovascular protective, hepatoprotective, antiangiogenic anti-malaria, and anti-bacterial
		Crocin $C_{44}H_{54}O_{24}$ MW: 976.972	Hydroxy carbonyl Non-provitamin Xanthophyll's	Saffron (<i>Crocus sativus</i> L. from <i>Iridaceae</i>) and Gardenia (<i>Gardenia jasminoides</i>) flowers	Antioxidant, anti-inflammatory, anti-ischemia, anti-viral, anti-cancer, neuroprotective, antihypertensive, anti-hyperlipidemia, anti-atherosclerotic, cardioprotective, anti-depressant memory improvement, antidote, and anti-arthritis Genoprotective
		Crocetin $C_{42}H_{54}O_{22}$ MW: 954.952			

¹)Simple bond between C11-C12 and C11'-C12'.

²)Simple bond between C11-C12.

Carotenoids ([Table 1](#)) have a wide variety of health benefits due to their protective and medical properties, ability to strengthen the immune system, and their antioxidant, anticancer, anti-inflammatory, antidiabetic and antiobesity/hypolipidemic activities ([Krinsky and Johnson, 2005](#); [Rao and Rao, 2007](#); [Burrows et al., 2015](#)).

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CAROTENOIDS ALLEVIATE INFLAMMATORY RESPONSES THAT LEAD TO ACUTE LUNG INJURY DURING COVID-19 INFECTION

Inflammation is a preserved biological procedure characterized by activation of immune and non-immune cells that protect the host from invading pathogens (bacteria, viruses, and toxins) that may cause organ injury by eliminating, and promote tissue repair and recovery. Inflammation is mainly divided into two phases: an acute inflammatory response (typically occurring at the time of infection) and a systematic chronic inflammatory response (arising over the time of infection, and causing tissue and organ damage). Consequently, inflammation increases the risk of developing non-communicable diseases over time. The acute inflammatory response is typically characterized by temporally controlled up-regulation of inflammatory activity against pathogens. Switching the inflammatory response from short-to long-term inverses the acute inflammatory response into a chronic inflammatory response, which interrupts immune tolerance and leads to major modifications in all organs and tissues. These alterations increase the risk of impaired immune function, leading to infection vulnerability, and a poor vaccine response ([Furman et al., 2019](#)). Subsequently, inflammation is a key factor in the pathogenesis of many conditions, including chronic non-communicable disease (such as neurodegenerative diseases, arthritis, and diabetes mellitus) and infectious communicable diseases (e.g., the emerging infectious disease COVID-19). There is a strong correlation between inflammatory cascade severity, pathological progression, and organ damages in patients with COVID-19 ([Huang et al., 2020b](#)). Cytokine storms are a manifestation in the host immune response, characterized by overproduction of pro-inflammatory cytokines and chemokines including IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , chemokine (C-X-C motif) ligand (CXCL) 10, CXCL8, CXCL9, chemokine ligand (CCL) 2, CCL3, and CCL5 ([Coperchini et al., 2020](#)). This results in a reduction in the upsurge of the inflammatory storm during SARS-CoV-2 infection making it a major target for developing future drugs. Therefore, a favorable anti-inflammatory candidate targeting diverse mechanisms related to the cytokine storm should be taken into consideration. IL-6 plays a major role in inflammatory responses and is significantly augmented in COVID-19 patients, and could be considered a target for the treatment of COVID-19. In general, antagonizing inflammatory ILs, such as IL-6, and IL-1 α , IFN- γ , TNF- α receptors, toll-like receptors (TLRs), and Janus kinase-signal transducers and activators of transcription-3 (JAK/STAT) and nuclear factor- κ B (NF- κ B) pathways could be of potential importance for reducing SARS-CoV-2 complications and suppressing COVID-19 ([Coperchini et al., 2020](#); [Yarmohammadi et al., 2021](#)).

Lung tissue with the epithelial cells of the bronchial and alveolar are constantly exposed to air irritants and pathogens and produce a number of inflammatory mediators in response to injury. These tissues produce an immune response against the progress of the pathogen that involves several cell types critical for viral clearance and establishing antiviral immune memory. During infection with extremely pathogenic viruses, such as SARS-CoV-2 or influenza viruses (i.e., certain H1N1 and H5N1 influenza virus strains), failure to promptly clear these infections can lead to excessive uncontrolled inflammation, initiating lung tissue damage. However, vascular angiogenesis distinguishes the lung pathobiology of COVID-19 from that of equally severe

influenza viral infections ([Ackermann et al., 2020](#); [Alon et al., 2021](#)). ARDS is characterized by acute lung injury (ALI) and increased-permeability, lung edema and severe hypoxemia due to injury to the alveolar capillary barrier in lung tissues. ARDS is common cause of hospital admissions and death in patients with SARS-CoV-2 infection ([Ware, 2020](#)). ARDS is accompanied by deadly cytokine release (cytokine storm), in which IL-6 and neutrophils play a critical role in the development cytokines leading to hyperinflammation, resulting in ALI and, in some cases, irreversible lung tissue degradation ([Alharthy et al., 2020](#); [Korkmaz et al., 2020](#)). Indeed, the cytokine storm that occurs during COVID-19 infection is characterized by an increase in intra-alveolar fibrin that stimulates production of both profibrotic growth factors and profibrotic cytokine transcripts, such as transforming growth factor- β (TGF- β), connective tissue growth factor (cellular communication network factor 2), and platelet-derived growth factor. In addition, decreases in lung surfactant proteins leading to alveoli failure and altering lung compliance may provoke an ultimate environment for fibroblast adherence and growth, resulting in collagen deposition and development of lung fibrosis, which may eventually induce lung cancer ([Fernandez and Eickelberg, 2012](#); [Gallelli et al., 2020](#)). There is increasing evidence that COPD prevalence and smoking may be associated with substantial severity and mortality rates from COVID-19 compared with those who are former smokers or those who never smoked ([Alqahtani et al., 2020](#)). This could be related to poor underlying lung reserves or increased expression of angiotensin-converting enzyme 2 receptors in small airways ([Leung et al., 2020](#)).

In this context, we reported the most important and relevant studies on the role of each carotenoid in inflammatory processes, chiefly inflammatory responses resulting from viral and airway infection.

β -Carotene

After absorption, β -carotene can be enzymatically converted into vitamin A by oxidative cleavage of provitamin A via the intestinal enzyme β -carotene 15-15'-oxygenase ([Harrison, 2012](#)). Epidemiological studies demonstrated that high serum β -carotene levels are associated with lower occurrences of certain cancers, especially lung cancer, which might be due to the fact that β -carotene enhances immune function or through the antioxidant capacity of β -carotene ([Bendich, 1991](#); [Wawrzyniak et al., 2013](#)). Indeed, β -carotene has strong antioxidant properties. β -Carotene scavenges free radicals and other oxidants involved in the pathogenesis of several chronic diseases processes, mainly reactive oxygen species (ROS) types, such as the superoxide anion radical ($O_2^{\cdot-}$), the hydroxyl radical ($HO^{\cdot}$), hydrogen peroxide (H_2O_2), and singlet oxygen (1O_2) ([Liebler and McClure, 1996](#); [Fiedor and Burda, 2014](#)). The strong antioxidant activity of β -carotene attributes to its anti-inflammatory propriety by preventing the oxidative inflammatory disorder, which is associated with tissue damage ([Stahl and Sies, 2003](#)). β -Carotene suppresses ROS-mediated inflammatory signaling pathways, such as mitogen-activated protein kinases (MAPKs), redox-sensitive transcription factors [such as NF- κ B and activator protein 1 (AP-1)] and reduces pro-inflammatory cytokines, such as IL-8, inducible nitric oxide (NO) synthase (iNOS), and cyclooxygenase-2 (COX-2) in human gastric tissues infected by *Helicobacter pylori* ([Kang and Kim, 2017](#)). Moreover, β -carotene inhibits expression of pro-inflammatory mediators, such as NO, prostaglandin E2 (PGE2), inducible iNOS, COX-2, TNF- α , and IL-1 β , by functioning as an inhibitor of NF- κ B activation ([Bai et al., 2005](#)).

Synergistic effects have been described for bioactive lipid compounds from three algal red seaweeds (*Porphyra dioica*, *Palmaria palmata*, and *Chondrus crispus*) and one microalga (*Pavlova lutheri*). These compounds contain 34~ 42% polyunsaturated fatty acids (n-3) and 5~7% pigments, including chlorophyll A, β -carotene, and fucoxanthin, and effectively inhibit pro-inflammatory signaling pathways mediated by TLRs (e.g., TLR1, TLR2, TLR4, and TLR8), chemokines (e.g., IL-6 and IL-8), and NF- κ B signaling molecules in lipopolysaccharide (LPS)-stimulated human THP-1 macrophages ([Robertson et al., 2015](#)). An earlier study demonstrated

that β -carotene decreases phytohaemagglutinin (PHA)-stimulated proliferation of human peripheral blood mononuclear 6 times more than theophylline and sodium cromoglycate. The study suggested use of β -carotene as an anti-inflammatory agent for bronchial asthma in clinical practice. Similarly, another study conducted on mice suggested that β -carotene is a promising drug for preventing and treating influenza as it decreases symptoms ([Sukhinin et al., 1999](#), [Landells et al., 2000](#)).

β -Carotene, quercetin, and luteolin are the major compounds extracted from Qi-Wei-Du-Qi-Wan (QWDQW), a Chinese traditional medicine that is used to treat chest tightness, coughs, shortness of breath, night sweats, and asthma. QWDQW reduces overproduction of inflammatory mediators, such as IL-12, IFN- γ , IL-13, IL-4, regulated upon activation, normal T cell expressed and secreted (RANTES), eotaxin, and MCP-1, in the lungs of chronic asthmatic mice. In addition, QWDQW inhibits mast cell degranulation in RBL-2H3 cells and acts as an anti-asthmatic during treatment with each extract compounds ([Lin et al., 2020](#)).

Accelerated declines in lung function are observed over 8 years in heavy smokers who have low levels of antioxidants, which increases the risk of developing COPD. β -Carotene and vitamin E may have protection effects against this decline in lung function by reducing oxidative stress and excessive airway smooth muscle contractility and/or proliferation by neutralizing $O_2^{\cdot -}$ associated with COPD pathogenesis. Additionally, β -carotene, alongside other carotenoids is associated with improved pulmonary function in patients with COPD (average total carotenoid intake: 9 ± 7 mg/d) ([Guénégou et al., 2006](#); [Jun and Root, 2020](#)). Furthermore, in animal models, orally administering β -carotene (1 mL or 15 mg/kg) before exposure to cigarette smoke was protective against development of chronic bronchitis induced, by increasing production of NO, clearing oxidative free radicals, and improving chronic inflammation ([Pang et al., 2003](#)).

α -Carotene

The risk of childhood asthma is increased by lower levels of serum vitamin C and α -carotene. Asthmatic children have lower serum concentrations of α -carotene compared with healthy controls (2.97 mg/dL vs. 3.42 mg/dL). Similarly, total carotenoids, including α -carotene, in whole blood are significantly lower in asthmatic individuals (5.69 mg/d) than controls (8.44 mg/d) ([Schock et al., 2003](#); [Harik-Khan et al., 2004](#); [Wood et al., 2005](#)). An earlier study established that serum levels α -carotene are significantly associated with decreased risk of cervical dysplasia due to human papillomavirus (HPV) infection [odds ratio=0.16; 95% confidence interval, 0.04~0.62 (highest vs. lowest tertiles)] ([Nagata et al., 1999](#)). Moreover, a study on older dwelling-women aged 65 years and older showed that higher serum α -carotene (257 μ mol/L) and β -carotene (195 μ mol/L) concentrations (which reflect higher intakes of orange and dark green leafy fruits and vegetables) were independently associated with improved pulmonary function. In addition, α -carotene, β -carotene, and lycopene were associated with improved lung function in Dutch elderly individuals aged 65 to 85 years ([Grievink et al., 2000](#); [Semba et al., 2012](#)).

β -Cryptoxanthin

A study conducted on ferrets indicated that β -cryptoxanthin at 104 μ g/d [~ 1.5 μ g/kg body weight (bw) per day in a 70 kg person] is beneficial against cigarette smoke-induced inflammation, oxidative DNA damage, and squamous lung metaplasia. Indeed, β -cryptoxanthin reduced TNF- α levels in alveolar, bronchial, bronchiolar, bronchial serous/mucous gland epithelial cells, and in lung macrophages. In addition, β -cryptoxanthin decreased smoke-induced activation of NF- κ B and AP-1, and levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG)-induced oxidative DNA damage in lung tissue ([Liu et al., 2011](#)).

Lutein/zeaxanthin

Lutein/zeaxanthin and their isomer meso-zeaxanthin are pigments in the central region of the retina of the eye that forms the macular pigment (MP), which protects the retina from blue light cytotoxicity and ROS. MP could be utilized against development of age-related macular degeneration by increasing the intake of foods that are rich in lutein/zeaxanthin or by supplementation with lutein/zeaxanthin ([Krinsky et al., 2003](#)). Lutein/zeaxanthin have several beneficial properties, e.g., antioxidant, anti-inflammatory, neuroprotective, autophagy, photo protection, hepatoprotective, immunomodulation, and anti-carcinogenic properties, and improving skin pliability ([Woodside et al., 2015](#); [Cho et al., 2018a](#)). A randomized study demonstrated that supplementation with lutein 20 mg/d for 3 months increased serum lutein levels and decreased serum inflammatory cytokines, such as IL-6 and MCP-1, serum triglyceride (TG), and low-density lipoprotein (LDL)-cholesterol. These results suggest that protective roles of lutein in atherosclerosis are a result of its anti-inflammatory effects and ability to maintain endothelial function by inhibiting attraction of macrophages ([Xu et al., 2013](#)).

In a study of LPS-stimulated macrophages, lutein inhibited LPS-induced NF- κ B-regulated inflammatory genes (e.g., iNOS, TNF- α , IL-1 β , and COX-2), and decreased intracellular H₂O₂ accumulation by scavenging superoxide and H₂O₂ ([Kim et al., 2008](#)). Likewise, in a study of UV-irradiated keratinocytes, lutein (up to 30 μ M) reduced IL-6 from LPS-treated macrophages, COX-2 from IFN- γ /TNF- α -treated immortalized human keratinocytes and matrix metalloproteinase (MMP)-9 levels. The study suggested that lutein-mediated AP-1 suppression and anti-inflammatory activity results from its strong anti-oxidative and p38/c-Jun N-terminal kinase (JNK) inhibitory activities ([Oh et al., 2013](#)). An earlier study indicated that of the 51 carotenoids, β -cryptoxanthin, lutein, and lactucaxanthin show the strongest inhibitory activities against the Epstein-Barr virus activation in Raji cells ([Tsushima et al., 1995](#)). Additionally, lutein suppresses Th2 lymphocyte-mediated airway inflammation in a murine model of asthma. However, the literature suggests a potential positive association between lutein and respiratory health ([Song et al., 2012](#); [Melo van Lent et al., 2016](#)).

In addition, a positive connection between β -cryptoxanthin and lutein/zeaxanthin with pulmonary function was observed in individuals diagnosed with asthma or COPD ([Ochs-Balcom et al., 2006](#)). A recent study in rats demonstrated that lutein (at 12.5, 25.0, and 50.0 mg/kg bw for 28 days) improved oxidative damage markers, such as methane dicarboxylic aldehyde, superoxide dismutase (SOD), NOS, and 8-OHdG, in lung tissues. In addition, lutein reduced inflammatory injury caused by particulate matter (2.5 μ m) from the air and mediated pro-inflammatory cytokines such as IL-6, IL-8, and TNF- α ([Chen et al., 2020b](#)).

Lycopene

Lycopene attenuated LPS-induced neuro-inflammation and depression-like behaviors in animal models ([Zhang et al., 2016](#)). Lycopene (25 or 50 mg/kg) enhanced recovery of neurological function in rats following spinal cord ischemia/reperfusion injury through COX-2 suppression ([Hua et al., 2019](#)). The antioxidant and anti-inflammatory properties of lycopene (25 or 50 mg/kg/d) are critical for significantly decreasing ROS, leukocytes, lipid peroxidation, and DNA damage produced by cigarettes smoke in mice lungs, and for attenuating pro-inflammatory cytokines, such as TNF- α and INF- γ ([Campos et al., 2017](#)).

A decreased risk of chronic lung lesions in COPD induced by smoking is associated with a high intake of lycopene (6.6 mg/kg bw/d) ([Mustra Rakic et al., 2020](#)). Likewise, lycopene (~30 and ~90 mg/d) in human inhibits smoke-induced COPD by decreasing neoplastic lesions and protecting against reverse cholesterol transport-mediated cholesterol accumulation in lungs ([Mustra Rakic et al., 2019](#)). A combination of lycopene (100 mg/kg) and matrine (an alkaloid isolated from the traditional Chinese medicine Sophora; 25 mg/kg) for 7 days was protective

against LPS-induced acute lung injury in mouse ([Li et al., 2019](#)). Similarly, adequate intake of lycopene and vitamin A rich foods could be beneficial for asthmatic subjects. In a previous study, treatment with tomato juice and extract reduced airway neutrophil influx. In addition, lycopene reduced allergic inflammation in lungs by decreasing Th2 cytokine (IL-4 and IL-5) responses, indicating its potential as a therapeutic intervention ([Riccioni et al., 2007](#); [Wood et al., 2008](#); [Hazlewood et al., 2011](#)). Moreover, an immunopharmacological role of lycopene (8 or 16 mg/kg/d) was accompanied by significant inhibition of inflammatory immunocyte infiltration into the bronchoalveolar, decreases in MMP-9 activity, attenuation of eosinophil peroxidase expression, and reduction in increased levels of GATA binding protein 3 (GATA-3) mRNA and IL-4 expressions in an ovalbumin (OVA)-induced murine asthma model ([Lee et al., 2008](#)).

Rhinovirus infection, the origin of asthma and the common cold, increases inflammation and inflammatory mediators from airway epithelial cells. Rhinovirus infection was reduced by lycopene treatment [2.5 µg/mL; two times higher than circulating plasma lycopene levels in healthy people (0.8~1.34 µg/mL)]. Furthermore, lycopene decreased IL-6 and IP-10 levels following exposure of airway epithelial cells to LPS ([Saedisomeolia et al., 2009](#)).

Astaxanthin

Various *in vitro* and *in vivo* studies demonstrated the robust anti-oxidant ability of astaxanthin to suppress NF-κB activity and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, and PGE2) and restores physiological levels of Src homology 2 domain-containing protein tyrosine phosphatase 1, a protein tyrosine phosphatase that acts as a negative regulator of inflammatory cytokine signaling. In addition, astaxanthin reduces release of ROS and inflammatory cytokines via the MAPK pathway ([Kishimoto et al., 2016](#)). Astaxanthin has potential to alleviate the risk of cytokine storm in patients with COVID-19 through different mechanisms, acting via its strong anti-inflammatory and antioxidant properties ([Lin et al., 2015](#); [Talukdar et al., 2020](#)). Moreover, astaxanthin stopped *in vitro* and *in vivo* pulmonary fibrosis by promoting myofibroblast apoptosis (their numbers correlating with progressive physiological deterioration and injury as well as shortened survival in lungs) by activating dynamin-related protein-1-mediated mitochondrial fission pathway. In addition, astaxanthin inhibits apoptosis in alveolar epithelial cells type II cells by blocking H₂O₂-induced ROS formation and prompting cytoprotective gene expression [e.g., caspase-9, caspase-3, and nuclear factor erythroid 2-related factor 2 (Nrf-2)].

Furthermore, a recent study revealed that long non-coding RNA regulated host gene *Itgb11* during pulmonary fibrogenesis (lncITPF) promotes lncRNA (subclass of ncRNA that regulates various essential biological processes and contributes to pathogenesis and development) in lung fibrosis and is blocked by astaxanthin. Therefore, astaxanthin blocks activated fibroblast proliferation and migration through lncITPF and mitochondria-mediated signaling pathways, and alleviates pulmonary fibrogenesis. These data strongly suggest that astaxanthin may be a potential drug candidate for lung fibrosis ([Wang et al., 2013](#); [Song et al., 2014](#); [Zhang et al., 2015b](#); [Chen et al., 2020a](#)). Astaxanthin treatment (60 mg/kg/d), has a protective influence against ALI in mice by inhibiting the inflammatory response mediated by NF-κB p65, oxidative/nitrative stress mediated by iNOS and nitro tyrosine, and pulmonary apoptosis by decreasing cecal ligation and puncture-induced mortality ([Bi et al., 2017](#)). In addition, the inhibitory effect of astaxanthin on airway inflammation in a mouse model of OVA-induced asthma revealed that astaxanthin (5, 10, and 50 mg/kg) suppressed total IL-4, and IL-5 (Th2), mediated inflammatory cytokines in bronchoalveolar lavage fluid (BALF) and airway hyperresponsiveness, and increased IFN-γ (Th1) levels in BALF. In addition, in OVA-induced asthmatic mice, astaxanthin suppressed infiltration of inflammatory cells in the lung, production of mucus, lung fibrosis, and expression of caspase-1/caspase-3, suggesting that astaxanthin has potential for treating asthma ([Hwang et al., 2017](#)).

Astaxanthin has therapeutic potential in the airway inflammatory response associated with COPD. In LPS-stimulated RAW264.7 cells, astaxanthin inhibited NO levels, pro-inflammatory mediators and iNOS. Furthermore, in mice exposed to cigarette smoke and LPS, astaxanthin suppressed release of pro-inflammatory cytokines and decreased ROS levels. In addition, in animal models of LPS-induced sepsis and acute lung injury, astaxanthin significantly enhanced survival, protected lungs from injury via inhibiting activation of the MAPK/NF- κ B pathway, and attenuated LPS-increased inflammatory factors, such as IL-6 and TNF- α , *in vitro*. Furthermore, astaxanthin reduced the inflammatory response mediated by IL-1 β , IL-6, and TNF- α , as well as oxidative damage mediated by malondialdehyde and total SOD in ochratoxin A-induced lung injury in mice by regulating Nrf-2 (antioxidant activity) and NF- κ B (pro-inflammatory activity) pathways. Similarly, astaxanthin directly activates the Nrf-2 pathway, which has preventive effect against cigarette smoke-induced emphysema and COPD in mice. Moreover, astaxanthin reduced lung damage caused by inflammation and hyperoxia by its anti-inflammatory, antioxidant, and anti-apoptotic properties, and protected the pulmonary from severe damage.

These data and other published data show an advantageous role of astaxanthin in protecting against numerous lung diseases by regulating several nuclear factors in NF- κ B and MAPK signaling pathways, JAK/STAT signaling pathways, Nrf-2/heme oxygenase-1 (HO-1) signaling pathway, the phosphoinositide 3-kinase/Akt (PI3K/Akt) signaling pathway, and modulates the immune response ([Cai et al., 2019](#); [Kubo et al., 2019](#); [Nian et al., 2019](#); [Xu et al., 2019](#); [Akduman et al., 2021](#); [Cheng and Eroglu, 2021](#)).

Crocin and crocetin

Several studies demonstrated that crocin and crocetin encompass numerous pharmacological activities, including antioxidant, anti-inflammatory, anti-ischemia, anti-viral, anti-cancer, neuroprotective, antihypertensive, anti-hyperlipidemia, anti-atherosclerotic, cardioprotective, anti-depressant, memory improvement, antidote, anti-arthritis, and genoprotective activities ([Mohamadpour et al., 2013](#); [Soleymani et al., 2018](#); [Luo et al., 2019](#)). Indeed, several *in vitro* and *in vivo* studies indicated that crocin alleviates inflammation and pain in various organs, such as lung, heart, brain, and kidney, mainly through inhibiting NF- κ B, NF- κ B p65, PI3K/Akt, and nucleotide-binding oligomerization domain-, leucine rich repeat-, and pyrin domain-containing protein 3 inflammatory pathways ([Hashemzai et al., 2020](#)). Furthermore, crocin (50 mg/kg) pretreatment significantly alleviated and protected against severe lung injury by inhibiting TNF- α and IL-1 β production in mice with ALI induced by LPS (1 mg/kg). Wet/dry lung weight ratios, an index of lung edema, and myeloperoxidase (MPO) activities were also reduced by crocin, and the expression of iNOS was significantly suppressed by crocin pretreatment ([Wang et al., 2015a](#)). Moreover, crocin (50 mg/kg) ameliorated COPD induced by cigarette smoke in mice, by suppressing PI3K/ Akt mediated inflammatory pathways. Crocin treatment diminished inflammatory cells, such as macrophages, neutrophils, and lymphocytes, concealed infiltration of peribronchial inflammatory cells, and reduced the concentration of proinflammatory cytokines, including IL-6, TNF- α , and IL-1 β , in BALF and lung tissue. Furthermore, insulin like growth factor 1, a PI3K activator, revoked the effect of crocin against cigarette smoke-induced activation of the NF- κ B pathway ([Xie et al., 2019](#)). In *in vitro* studies, crocin reduced inflammation of human bronchial epithelial cells induced by *Aspergillus fumigatus* infection by suppressing NF- κ B signal pathways and inhibiting pro-inflammatory cytokines, such as TNF- α , IL-8, IL-6, and IL-1 β ([Du et al., 2018](#)).

Crocin improved *in vitro* and *in vivo* LPS-induced ARDS by protecting against glycocalyx damage in ARDS and by suppressing NF- κ B and MAPK inflammatory signaling pathways. Indeed, crocin effectively enhanced vascular pulmonary edema by maintaining the integrity of glycocalyx in LPS-induced ARDS mice, which affords a pharmacological role of crocin in ARDS treatment ([Zhang et al., 2020a](#)). Moreover, a previous study demonstrated that crocin

might be a candidate for treatment of asthma by suppressing airway inflammation and hyper-reactivity in a murine model by acting on MAPK signaling pathways. In this study, crocin significantly suppressed airway inflammation and hyper-reactivity, reduced levels of interleukins (IL-4, IL-5, and IL-13) and tryptase in BALF, eosinophil peroxidase in the lung and IgE in serum, and inhibited expression of eotaxin, p-extracellular signal-regulated kinase, p-JNK, and p-p38 in lung ([Xiong et al., 2015](#)). Similarly, crocin showed a significant protective effect against allergic asthma progression. Crocin alleviated OVA-induced allergic asthma-associated alterations in inflammatory and oxidative stress biomarkers by enhancing antioxidant defenses, reducing the incidence of oxidative stress, and restored pro-inflammatory cytokines (e.g., TNF- α) to normal levels, and modulating IL-4/IL-13 pathways, which enhances Th2-mediated immune reactions ([Yosri et al., 2017](#)). In addition, saffron with its major compounds crocin and safranal decrease airway hyper-responsiveness and airway cellular infiltration to the lungs as well as reduced iNOS production, bronchial epithelial cell apoptosis, and Th2 type cytokine production in inflamed lungs of mice, which attenuates asthma ([Bukhari et al., 2015](#)). Crocetin alleviates OVA-induced asthma in mice by increasing forkhead box P3 (Foxp3, a protein involved in immune system responses and a crucial regulator of regulatory T cells) and the number of Treg cells in the lung. Crocetin is protective against LPS-induced ALI by reducing NF- κ B activity, and decreasing LPS-induced mRNA and protein expression of IL-6, MCP-1, and TNF- α in lung tissue ([Yang et al., 2012](#); [Ding et al., 2015](#)). Furthermore, an *in vitro* study demonstrated that crocin and picrocrocin from saffron could be promising anti-herpes simplex virus type 1 (HSV-1) and anti-human immunodeficiency virus (HIV) agents against viral infections ([Soleymani et al., 2018](#)).

Phytoene and phytofluene

Phytoene and phytofluene have not been associated with health benefits in epidemiological studies as they are not included in food databases. However, several *in vitro* and *in vivo* studies as well as human studies have demonstrated their health benefits (e.g., antioxidant, anti-inflammatory properties, and their roles in decreasing DNA damage in lymphocytes and protecting skin against leukemia, and breast and prostate cancers). Phytoene and phytofluene are predominantly found in human plasma, milk, and other tissues such as skin ([Meléndez-Martínez et al., 2015](#); [Havas et al., 2018](#)). These carotenoids strongly enhance antioxidant activity of coenzyme Q10 (CoQ10) in human dermal fibroblast cell cultures and protect CoQ10 from degradation by ROS and hypochlorite. Moreover, phytoene and phytofluene enhance inhibition of Q10 against three inflammatory mediators, PGE-2, IL-6, and MMP-1 ([Fuller et al., 2006](#)).

An algal preparation containing phytoene and phytofluene isolated from *Dunaliella bardawil* demonstrated inhibition of LDL oxidation *in vitro*. Thus, phytoene and phytofluene may be part of the defense system against oxidative stress ([Shaish et al., 2008](#)). Despite the several benefits of these carotenoids, which traditionally coexist with lycopene in food, they are often ignored from studies due to lower bioavailability vs. other carotenoids and the safe use of phytoene and phytofluene-rich products in current applications ([Mapelli-Brahm et al., 2017](#); [Havas et al., 2018](#)). Therefore, it is rare to find an *in vitro*, *in vivo*, or human study that describes the roles of these colorless carotenoids and their mechanisms of action.

Fucoxanthin

Fucoxanthin has a unique structure involving an unstable allenic bond and nine conjugated double bonds, and exhibits strong antioxidant activity. Fucoxanthin shows several biological and pharmaceutical properties, including anti-inflammatory, anti-cancer, anti-obesity, anti-diabetes, hepatoprotective, cardiovascular and cerebrovascular protective, hepatoprotective, antiangiogenic, anti-malaria, and anti-bacterial properties ([Zhang et al., 2015a](#); [Karpinski et al., 2019](#)). Previous studies have demonstrated the ability of fucoxanthin to inhibit transcription

factor pathways, including NF- β B and MAPK pathways, and reduce levels of pro-inflammatory mediators, such as NO, PGE2, IL-1 β , TNF- α , IL-6, iNOS, and COX-2 ([Peng et al., 2011](#); [Zhang et al., 2015a](#)). A recent study revealed that fucoxanthin, isolated for the first time from *Conticribra weissflogii* ND-8, has strong anti-inflammatory effects on mouse models of sepsis. Fucoxanthin (0.1~1.0 mL/kg) reduces pro-inflammatory cytokines, such as IL-6, IL-1 β , and TNF- α , in a prophylactic manner in sepsis induced by LPS (20 mg/kg). Furthermore, the 50% inhibitory concentration (IC₅₀) inhibitory effect of fucoxanthin on NF- β B was about 11 μ M, and the IC₅₀ inhibitory effect on pro-inflammatory IL-6 production was about 2 μ M in macrophage cells ([Su et al., 2019](#)). Fucoxanthin (50 mg/kg) showed significant protective activity against OVA-induced asthma in mice by efficiently decreasing intracellular secretion of ROS and increasing antioxidant enzyme activities. In addition, fucoxanthin decreased pro-inflammatory cytokines in BALF, suggesting that fucoxanthin may be a potential anti-asthma drug in human ([Yang et al., 2019](#)).

A previous study showed that fucoxanthin is effective against pulmonary fibrosis. Fucoxanthin inhibited TGF- β 1-induced expression of alpha-smooth muscle actin (α -SMA), type 1 collagen, fibronectin, and IL-6 in human pulmonary fibroblasts (HPFs), and inhibited TGF- β 1-induced phosphorylation of p-38 MAPK, PI3K/Akt, and Smad2/Smad3. Furthermore, fucoxanthin significantly reduced collagen contraction. In addition, intraperitoneal injection of fucoxanthin (10 mg/kg) inhibited bleomycin-induced pulmonary fibrosis and type I collagen protein expression in mice ([Ma et al., 2017](#)). A more recent study demonstrated that fucoxanthin markedly increased nuclear translocation of Nrf-2 in LPS-treated macrophages, which significantly attenuated LPS-induced ROS accumulation and expression of pro-inflammatory cytokine (including IL-6, IL-1 β , and TNF- α) ([Kim et al., 2021](#)).

[Go to:](#)

CAROTENOIDS ENHANCE IMMUNITY FACING COVID-19 AND RELATED SYMPTOMS

The primary host immune response to SARS-CoV-2 infection and the obliteration of lung tissue damage is characterized by macrophage/monocyte and neutrophil recruitment, cytokine (i.e., IL-2, IL-6, granulocyte-colony-stimulating factor, IFN- γ , IP-10, MCP-1, MCP-3, MIP-1 α , and TNF- α) release, adaptive immune response stimulation, and adaptive T (CD4⁺ and CD8⁺ T cells) and B cells. In general, innate and adaptive immune processes eradicate COVID-19 disease. However, when the immune system cannot appropriately function (such as due to individual responses to viral loads during primary SARS-CoV-2 infection), dysfunctional immune responses can lead to cytokine overproduction. This can result in increased viral replication and lung tissue damage, functional lung injury, reduced lung capability, and even systemic pathology and multi-organ failure (including of the heart, kidney, and gastrointestinal tract) ([Catanzaro et al., 2020](#); [Perico et al., 2021](#)). In clinically severe cases of COVID-19, individuals experience noticeable decreases in total numbers of CD4⁺ cells, CD8⁺ cells, B cells, and NK cells, and decreases in monocytes, eosinophils, and basophils ([Catanzaro et al., 2020](#); [Tay et al., 2020](#)). CD8⁺ cells are important for attacking and killing viral infections, whereas CD4⁺ cells are vital for both CD8⁺ T cells and B cells. CD4⁺ T cells are also responsible for cytokine production to drive immune cell recruitment. Both CD4⁺ and CD8⁺ cells signified strong predictive values for severity and mortality of hospitalized COVID-19 patients ([Catanzaro et al., 2020](#)). In addition, it has been reported that SARS-CoV-2 inhibits components of host immunity, such as increased levels of exhausted CD8⁺ T cells and loss of CD4⁺ T cell function, sloping towards Th17 in the peripheral blood ([Tay et al., 2020](#)). In the early stage of infection, SARS-CoV-2 impairs and even suppresses the immune system, and damages tight junctions in lung tissues, whereas the severe stage might involve activated immune responses, which leads to a cytokine storm and multi-organ damage. Therefore, enhancing the balanced host immune response against

pathogens, in particular SARS-CoV-2, by adaptive and innate immune responses is vital for controlling and eradicating infections ([Tian et al., 2020](#)).

Incidentally, carotenoids have shown several worthy immune roles. Herein, we report the most well-known carotenoids as immune promoters in several studies found in relevant literature.

β-Carotene

β-Carotene (20, 40, and 60 mg/kg bw orally for 30 days) decreases liver tissue damage and improves the immune function of hepatocellular carcinoma (HCC) rats by inhibiting tumor growth ([Cui et al., 2012](#)). β-Carotene (5 μM or 10 μM for 2 h) exhibits anti-inflammatory effects by inhibiting pro-inflammatory adipokines regulated by NF-κB, AP-1, and signal transducer and activator of transcription-3 pathways, such as MCP-1, normal T cell expressed, and presumably secreted chemokines (RANTES or CCL5). Thus, β-carotene enhanced adiponectin in adipocytes by ceasing oxidative stress-induced inflammation, which is related to adipokine dysfunction ([Cho et al., 2018b](#)). A pilot study indicated that β-carotene increased CD4⁺ cell population in patients with acquired immunodeficiency syndrome, which enhances immunological function. Similarly, β-carotene treatment (60 mg/d for 25~36 months) significantly increased blood CD4⁺ and CD8⁺ lymphocytes and reduced other HIV symptoms in patients with HIV ([Fryburg et al., 1995](#); [Milani et al., 2017](#)). Low serum concentrations of β-carotene, retinol and vitamin E have been reported in children with HIV in Brazil, Argentina, and Mexico. Another study indicated that β-carotene modulates certain immune markers in HIV-infected subjects. In addition, an observational study in Kenyan women concluded that low serum β-carotene concentrations reflect more active HIV-1 infections ([Garewal et al., 1992](#); [Baeten et al., 2007](#); [Monteiro et al., 2009](#)). Moreover, anti-inflammatory activities of β-carotene against have been demonstrated against the human herpes simplex virus due to its ability to inhibit pro-inflammatory mediators, such as NO, IL-1β, IL-6, and MCP-1, and suppress the sub-units p50 and p65 of NF-κB ([Lin et al., 2012](#)).

α-Carotene

α-Carotene has antioxidant and possible anti-carcinogenic and immune enhancing properties. Some epidemiological studies noted that a higher α-carotene intake is associated with lower risk of cardiovascular disease (CVD) and cancer ([Tanumihardjo, 2013](#)). In addition, a nutritional survival study demonstrated that serum α-carotene concentrations are inversely associated with the risk of death from all causes, including CVD and cancer ([Li et al., 2011](#)). In the human neuroblastoma cell line GOTO, α-carotene inhibits proliferation 10 times more than β-carotene, acting via reducing mRNA levels of the proto-oncogene protein N-myc ([Murakoshi et al., 1989](#)). α-Carotene, but not β-carotene, can reduce lung tumor numbers, and α-carotene has a stronger effect than β-carotene on suppressing the activity of 12-O-tetradecanoylphorbol-13-acetate on skin carcinogenesis in a mouse model. In addition, α-carotene alongside lycopene is inversely associated with risk of prostate cancer (although not at the advanced stage), suggesting that α-carotene plays an important role in cancer prevention ([Murakoshi et al., 1992](#); [Wang et al., 2015b](#)). Additionally, α-carotene shows anti-metastatic activity in Lewis lung carcinoma *in vitro* by inhibiting invasion, migration, activities of MMP-2, MMP-9, urokinase plasminogen activator, and integrin b1-mediated phosphorylation of focal adhesion kinase, which decreases phosphorylation of the MAPK pathway. This study also indicated that α-carotene in combination with taxol has a strong effect on lung metastasis and effectively inhibits Lewis lung carcinoma, suggesting that α-carotene could be used as an anti-metastatic agent or as an adjuvant for anti-cancer drugs ([Liu et al., 2015](#)).

A longitudinal study indicated that serum α-carotene concentrations are inversely associated with all measures of body composition (e.g., body mass indices, fat mass, and lean mass) in a group

of women aged 19~50 years, showing a clear association between α -carotene and body fatness of the studied group, and which appears to go beyond simply fat-soluble properties ([Nuss et al., 2017](#)). Furthermore, another cohort studying patients during the year following hip fractures indicated that higher baseline and time-varying α -carotene and time-varying lutein concentrations are associated with lower pro-inflammatory mediators, such as soluble TNF- α receptor 1 and IL-16, at post-fracture visits ([D'Adamo et al., 2012](#)).

β -Cryptoxanthin

β -Cryptoxanthin is an important precursor of vitamin A, and has several functions important for human growth, vision, development, and immune function. β -cryptoxanthin is readily absorbed from its major food sources at a rate probably greater than that of other common carotenoids, and may provide a generous amount of vitamin A, equivalent to the amount of vitamin A from β -carotene ([Burri, 2015](#); [Burri et al., 2016](#)). β -Cryptoxanthin has demonstrated various beneficial activities, such as antioxidant, anti-obesity, anti-inflammatory, anti-osteoporosis, and anti-cancer activities ([Burri et al., 2016](#); [Jiao et al., 2019](#)). Furthermore, β -cryptoxanthin prevents nonalcoholic steatohepatitis (NASH) in mice by reducing expression of M1 and M2 macrophages, T helper cells and cytotoxic T cells, suppresses expression of LPS-inducible and/or TNF- α -inducible genes in NASH, and decreases thiobarbituric acid reactive substances, markers of oxidative stress, which is considered a major mechanism of inflammation in liver. Thus, β -cryptoxanthin is effective in inhibiting inflammatory gene expressions in NASH. Moreover, β -cryptoxanthin reverses steatosis, inflammation, and fibrosis through an M2-dominant shift in macrophages/Kupffer cells in the liver of NASH mice ([Kobori et al., 2014](#); [Ni et al., 2015](#)). β -Cryptoxanthin (2.5 mg/kg bw for 12 weeks) reduces cardio-metabolic and inflammatory markers in high-fat diet rats by down-regulating NF- κ B and TNF- α and up-regulating Nrf-2, HO-1, and peroxisome proliferator-activated receptor (PPAR) α pathways ([Sahin et al., 2017](#)). Several epidemiological studies have shown inverse associations between serum β -cryptoxanthin and the risks for atherosclerosis, insulin resistance, liver dysfunction, metabolic syndrome, low bone mineral density, and oxidative stress ([Sugiura, 2015](#)). *In vitro*, protective effects of lutein and β -cryptoxanthin against human chondrocyte dysfunction were demonstrated by scavenging ROS required for NF- κ B activation and inhibiting pro-inflammatory responses induced by 10 μ g of IL-1 β ([Di Filippo et al., 2012](#)). In both *in vitro* and *in vivo* studies, β -cryptoxanthin demonstrated a potentially beneficial effect on health and on preventing immunity of related diseases by increasing CD4⁺ lymphocytes and serum IgG, IgM, and IgA levels in mammals ([Di Filippo et al., 2012](#); [Ghodratizadeh et al., 2014](#)). Indeed, a study demonstrated that ingestion of a few kumquats, which mainly contain a cyclic monoterpene (R-limonene) and β -cryptoxanthin, on a daily basis could help combat stress and enhance NK cell activity, which plays an important role in innate immunity by eliminating cancer cells and cells infected with viruses ([Terao et al., 2019](#)).

Lutein

Lutein increases the percentage of CD4⁺, CD21⁺, CD5⁺, and CD8⁺ lymphocytes, MHC II molecules, and plasma IgG and IgM, inducing the immuno-modulatory action of lutein in domestic animals (Kim et al., 2020a; Kim et al., 2020b). Moreover, lutein is the major carotenoid in yellow cocoons of *Bombyx mori* silkworms, exhibiting *in vivo* immune enhancement activities by increasing NK cell activity, CD3⁺, CD4⁺, and CD3⁺ cell populations, and IL-2 and IFN- γ production. This suggests that lutein treatment plays an important role in reinforcing immunity ([Promphet et al., 2014](#)).

Lycopene

Several studies have indicated that lycopene and consumption of lycopene in diet could affect susceptibility to cancer, cardiovascular disease and diabetic complications through enhancing antioxidant enzyme activities and immunity function ([Neyestani et al., 2007](#); [Story et al., 2010](#); [Luo and Wu, 2011](#)). Moreover, lycopene 10 mm has immunopharmacology effects in inhibiting dendritic cells maturation induced by LPS in murine bone marrow through inhibiting MAPK and NF- κ B p65 translocation pathways ([Kim et al., 2004](#)). Indeed, treatment with lycopene 10 mg/kg, 20 mg/kg, and 40 mg/kg for 28 days improves the immune status of diabetic rats by decreasing neutrophil count, low neutrophil-lymphocyte ratios, and platelet counts, and by stabilizing albumin-globulin levels ([Eze et al., 2019](#)).

Another study demonstrated protective roles of lycopene at 10 mg/kg for 10 days in rat intestinal injury induced by methotrexate, acting by reducing the elevated oxidative stress and pro-inflammatory cytokine (IL-1 β) levels ([Yucel et al., 2016](#)). Furthermore, tomato lycopene extract inhibits intestinal inflammation induced by LPS-induced proinflammatory gene expression by blocking NF- κ B signaling ([Joo et al., 2009](#)). In addition, lycopene at 0.3% mixed into a high-fat and high-fructose western diet 10 weeks induces cognitive impairments in a mouse model by improving insulin resistance, lipid metabolism dysfunction, and inflammatory responses in the gut-liver-brain axis, suggesting that lycopene may be a nutritional strategy for Western diet-induced dysfunction of the central nervous system ([Wang et al., 2019a](#)). Moreover, lycopene at 50 mg/kg bw/d for 40 days ameliorates dextran sulfate sodium-induced gut barrier damage and inflammatory responses in mice by mediating the microbe-gut-brain axis balance ([Zhao et al., 2020](#)).

In addition, lycopene at 10 mM exerts potential beneficial effects on skeletal muscle metabolism by its effects on the activities of metabolic enzymes in muscle fibers, which promotes expression of slow-twitch fibers and enhances mitochondrial respiratory capacity ([Liu et al., 2021](#)).

Astaxanthin

A randomized double-blinded, placebo-controlled study concluded that dietary astaxanthin at 2 and 8 mg for 4 or 8 weeks decreases DNA damage biomarkers and acute phase proteins, and enhances immune responses in young healthy females approximately 21.5 years of age. Furthermore, astaxanthin decreases plasma CRP concentrations. In addition, dietary astaxanthin stimulates mitogen-induced lymph proliferation, increases NK cell cytotoxic activity, and increases total T and B cell subpopulations ([Park et al., 2010](#)). Similarly, astaxanthin reveals antioxidant and anti-inflammatory activities, and boosts immune responses in humans. Indeed, supplementation of healthy adult females with 2 and 8 mg/d of astaxanthin for 8 weeks diminished levels of oxidative damage biomarkers and inflammation, and enhanced immune responses ([Kishimoto et al., 2016](#)).

In primary cultured lymphocytes, astaxanthin demonstrates immunomodulatory effects both *in vitro* and *ex vivo* by increasing production of INF- γ and IL-2 cytokines without inducing cytotoxicity. Furthermore, astaxanthin enhances immune responses in mice by increasing INF- γ , IL-2, and IL-10 in response to *Helicobacter pylori* infection ([Lin et al., 2015](#); [Davinelli et al., 2019](#)). In a previous study, astaxanthin administered daily at two doses (20 mg/kg and 40 mg/kg) for 14 days reduced serum liver enzymes and pathological damage in mice treated with concanavalin A-induced 25 mg/kg murine autoimmune hepatitis. Astaxanthin acted by reducing release of inflammatory factors such as NF- κ B p65, IL-6, IL-1 β , and IFN- γ through reducing JNK/p-JNK-mediated apoptosis and autophagy by blocking interactions between TNF- α and TNF receptor-associated factor 2. In addition, astaxanthin demonstrates an anti-apoptotic effect by decreasing phosphorylation of B-cell lymphoma 2 through down-regulating the JNK/p-JNK pathway, suggesting that astaxanthin may be a promising potential therapeutic agent against autoimmune diseases ([Li et al., 2015](#)).

In rats, astaxanthin significantly reduces pro-inflammatory mediators, including IL-1 β , IL-6, NF- κ B p65, and I β Ba, and increases levels of IL-2, IgM, and IgG, suggesting that astaxanthin ameliorates oxidative stress and improves immune impairment ([Chen et al., 2020c](#)). Zhang and colleagues recently demonstrated that administration of astaxanthin (60 and 120 mg/kg/bw) in cyclophosphamide-induced immunodeficient mice effectively prohibited intestinal mucosa damage, by reducing oxidative stress levels, increasing intestinal morphological structural integrity, stimulating goblet cells growth and mucous secretion, decreasing development of Paneth cells and expression levels of antimicrobial peptides, increasing IgA secretion, and ameliorating main gut flora (especially total bacteria, *Lactobacillus* and *Enterobacteriaceae* spp.) and its metabolites (acetic acid, propionic acid, and butyric acid). In addition, astaxanthin enhanced intestinal mucosal barriers, which is of a role of great significance in maintaining immune function in the body ([Zhang et al., 2020b](#)).

In bleomycin-induced pulmonary fibrosis, astaxanthin at 2 mg/kg has anti-fibrotic effects, both *in vitro* and *in vivo*. Indeed, *in vivo*, astaxanthin significantly enhances the structure of alveoli, alleviates collagen deposition, and reduces levels of α -SMA, vimentin (intermediate filament expressed in a variety of cells, including lymphocytes and neutrophils), hydroxyproline (a major component of the protein collagen), and B cell lymphoma/leukemia-2. In addition, astaxanthin may increase E-cadherin and cellular tumor antigen p53 protein expression *in vitro* and *in vivo* ([Zhang et al., 2015b](#)).

Crocin and crocetin

Saffron is used in traditional medicine for treatment of various conditions, including coughs, stomach disorders, amenorrhea, asthma, and cardiovascular disorders ([Mokhtari-Zaer et al., 2015](#)). Most of the pharmacological activities of saffron are related to the presence of carotenoids (crocin and crocetin). Saffron inhibits serum levels of NF- κ B p65 unit, and pro-inflammatory mediators, including TNF- α , IFN- γ , IL-1 β , IL-6, IL-12, and IL-17A, and is an agonist of PPAR-g, which has inhibitory effect on NF- κ B. Furthermore, saffron reduces key pro-inflammatory enzymes, such as MPO, COX-2, iNOS, phospholipase A2, prostanoids (a subclass of eicosanoids), and adhesion molecules including intercellular adhesion molecule, vascular cell adhesion molecule, and E-selectin. In addition, saffron modulates MAPK and NF- κ B pathways. Therefore, saffron and its components could have a promising role in treatment of immune disorders ([Zeinali et al., 2019](#)).

Fucoxanthin

Fucoxanthin has an immunoregulatory role as an anti-inflammatory agent. *In vivo*, suppression of antigen-induced aggregation of the high affinity IgE receptor (FceRI) and FceRI-mediate degranulation signals of mast cells. Fucoxanthin inhibits degranulation of mast cells by suppressing aggregation of FceRI ([Sakai et al., 2009](#); [Zhang et al., 2015a](#)). A methanol extract of *Undaria pinnatifida*, which contains a bioactive amount of fucoxanthin, demonstrates anti-edema, and anti-erythema effects with relative inhibition ratios of 85% and 78%, respectively, against mouse ear edema and erythema induced by phorbolmyristate acetate. In addition, the extract demonstrates antipyretic effects in yeast-induced hyperthermic mice ([Peng et al., 2011](#)).

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CAROTENOIDS AS POTENTIAL ANTIVIRAL AGENTS

Microalgae extracts traditionally used as food are rich in carotenoids source, such as *Haematococcus pluvialis* (source of astaxanthin 0.2~2.0%/dry weight) and *Dunaliella salina* (β -carotene 400 mg/m² from cultivated area) show anti-viral activity *in vitro* (African green monkey kidney cell) against HSV-1 at different stages of viral infection. However, this

study and other similar studies suggest that the anti-viral activity of microalgae extracts may related to its polysaccharide compounds ([Santoyo et al., 2012](#)). A recent study demonstrated that *Haloarchaea*, such as *Natrialba* sp., are good candidates for carotenoid production (such as astaxanthin, lutein, canthaxanthin, bacterioruberin, and salinixanthin). Indeed, *in vitro*, the extracted pigment exhibited significantly stronger ability to eliminate hepatitis C virus (HCV) and hepatitis B virus (HBV) in infected human blood mononuclear cells than currently used drugs. The pigment inhibits both polymerase-dependent HCV and HBV replication ([Hegazy et al., 2020](#)).

Carotenoids, such as lutein, zeaxanthin, and carotene, in plasma also have potential antiviral roles ([Iddir et al., 2020](#)). Lutein demonstrates *in vitro* antiviral activity against HBV infection. Lutein inhibits the activity of the HBV full-length promoter through inhibiting the HBV transcription cycle. This mechanism of action is supported by a docking study that demonstrated a promising role of lutein a future anti-viral drug against the nonstructural protein 3 of the HCV helicase that is essential for viral replications ([Pang et al., 2010](#); [Fatima et al., 2014](#)).

Crocetin improves host responses to dengue virus (DENV)-induced liver injury. In the liver of DENV-infected mice, crocetin reduces DENV-induced oxidative stress, pro-inflammatory responses and NF- κ B (both NF- κ B p65 and NF- κ B p50) translocation. However, crocetin does not inhibit DENV replication but improves host responses that reduce liver injury. In addition, crocetin, ergosterol peroxide, and κ -carrageenan have demonstrated strong bonding to both HPV-16 and HPV-18 (strains 16 and 18 of HPV are the most common) in mucosal epithelium. Thus, these compounds could represent further anti-viral drugs ([Sreekanth et al., 2020](#); [Meza-Menchaca et al., 2021](#)).

Crocin and picrocrocin (a derivative from zeaxanthin that is responsible for the taste of saffron) are the major components of saffron extract, indicate significant anti-HSV-1 and anti-HIV-1 activities *in vitro*. Crocin inhibits HSV replication before and after entry into Vero cells. Indeed, crocin suppresses HSV penetration into target cells and disturbs viral replication after entry into cells. Picrocrocin is also effective at inhibiting viral entry and replication, suggesting that crocin and picrocrocin could be promising anti-HSV and anti-HIV herbal therapy agents against viral infections ([Soleymani et al., 2018](#)).

In addition, a molecular docking study demonstrated that crocin, digitoxigenin, and β -eudesmol were three of 67 compounds found in medicinal plants from Morocco that effectively inhibit the main protease of SARS-CoV-2, determined by the energy of the interactions between these molecules and the studied protein of the COVID-19 receptor. The *in vitro* and *in vivo* activity demonstrated in this study suggests that these molecules could target the major SARS-Cov-2 protease ([Aanouz et al., 2021](#)). Moreover, astaxanthin can reduce binding of HPV to cell membranes of human sperm *in vitro* by about 50% through inhibiting HPV-late protein 1 (L1, involves in structural component of viral capsid), expressed during initial stages of infection to binding to membranes ([Donà et al., 2018](#)).

Recent network pharmacology and molecular docking analyses was conducted on the traditional Chinese herb Lianhua Qingwen capsule (LQC), which is composed of 13 components. LQC is usually used to prevent and treat viral influenza (e.g., H1N1) in China and has shown some effectiveness for COVID-19 treatment, both in clinical surveillance and in randomized controlled trials. After molecular docking, 6 molecules directly interact with Akt1, including β -carotene, kaempferol, luteolin, naringenin, quercetin, and wogonin. Akt1, a serine/threonine protein kinase (Akt kinase), plays a vigorous role in easing viral infections (including SARS-CoV-2) and could be an ideal therapeutic agent with a wide range of antiviral effects, with its overexpression shown to promote viral protein synthesis. Thus, these six compounds, including β -carotene, could be potential agents for COVID-19 treatment by inhibiting Akt1 pathways. Furthermore, the study suggested synergistic effects of these molecules ([Xia et al., 2020](#)).

Similarly, a molecular docking study was conducted on buriti oil (*Mauritia flexuosa* L.), a natural product extracted from the fruit of the palm in Brazil. Carotenoids are the main constituents of buriti oil, and include β -carotene (and β -carotene derivatives such as 13-cis- β -carotene 9-cis- β -carotene), α -carotene, phytofluene, and zeaxanthin. One study focused on the main peptidase of SARS-CoV (PDB ID: 2GTB), which is similar (96%) to the main SARS-CoV-2 peptidase that caused the COVID-19 pandemic. 2GTB has an important role in the viral life cycle. Results of molecular docking analysis revealed promising interaction energies in formation of complexes between 2GTB with 13-cis- β -carotene ligands ($\Delta_{\text{Gbind}} = -10.23$ kcal/mol), 9-cis- β -carotene ($\Delta_{\text{Gbind}} = -9.82$ kcal/mol), and α -carotene ($\Delta_{\text{Gbind}} = -8.34$ kcal/mol). The study demonstrated substantial interactions of these ligands, with an emphasis on α -carotene, and suggested possible *in vitro* and *in vivo* experiments for detecting new drugs with inhibitory enzymatic action against COVID-19 ([Costa et al., 2021](#)).

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CONCLUSIONS AND PERSPECTIVES

Carotenoids are a group of naturally occurring pigments that possess several health benefits. Carotenoids have advantageous pharmacological and biological effects and may be directly implicated in several cellular and molecular pathways related to inflammatory processes, which likely reflect their favorable protective nature against inflammation and oxidative damage as well as their immune modulation capability. Despite the fact that carotenoids are one of the major groups of phytochemicals in human diets and are diverse in nature, data about their effects against human viral diseases are still erratic and mixed compared to their counterparts, such as polyphenolic compounds, which are intensively studied ([Khalil and Tazeddinova, 2020](#)). Most studies reported that consumption of carotenoids from their natural sources is safe and efficacious. However, others reported a risk of β -carotene supplementation with some lung cancers, particularly in smokers. Nevertheless, a meta-analysis revealed that both dietary intake and circulating levels of β -carotene are inversely associated with the risk of all-cause mortality, mainly dietary β -carotene, and that it has a protective effect on preventing non-communicable chronic diseases ([Furman et al., 2019](#)). Carotenoids could be utilized as potential drugs for combating against COVID-19 by targeting the inflammatory storm resulting from viral infections. In addition, diets rich in carotenoids may protect against progression of inflammation related to the acute phase of COVID-19, preventing disease progression, principally among elderly individuals. Previous studies have shown that older individuals have higher circulating levels of cytokines, chemokines, and acute phase proteins, and higher expression of genes involved in inflammation ([Zhao et al., 2016](#)), which may partly explain why elderly individuals have the highest risk of COVID-19 infection. Carotenoids also play an imperative role in boosting body immunity, mainly through their effects on several antioxidant and anti-inflammatory pathways and on components of the immune response. Thus, carotenoids may have roles as immune-enhancers against COVID-19 and other emerging diseases and related syndromes ([Fig. 3](#)). Alternative therapeutic strategies based on available foods and plants have been shown to alleviate similar infections ([Fasogbon et al., 2021](#)). Therefore, carotenoids from natural resources or supplements may be future therapeutic strategies against these viral diseases. However, further research and clinical trials must be conducted before conclusions can be drawn.

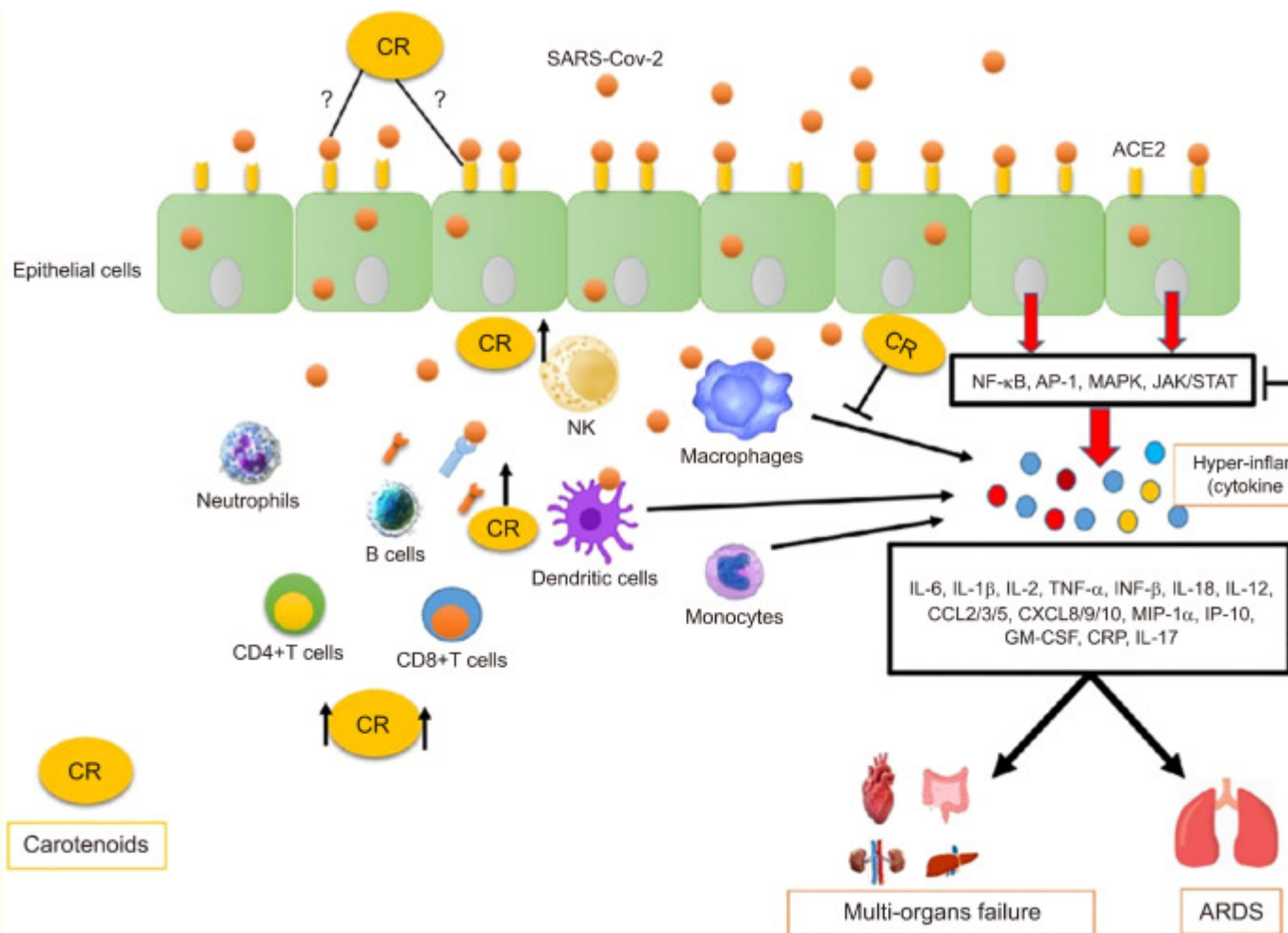


Fig. 3

Proposed protective mechanisms of carotenoids (CR) during COVID-19 and related symptoms. When the SARS-CoV-2 invades the host, the virus activates NF-κB and MAPK signaling pathways either in the infected cells or in the immune responsive cells such as dendritic cells and macrophages, which results in an excessive inflammatory response mediated by an extra production of pro-inflammatory cytokines and hyperinflammation (cytokine storm). This accumulation plays a substantial role in the COVID-19 pathogenesis and can lead to acute respiratory distress (ARDS) and multi-organs failure. CR could inhibit these main signaling pathways as well as the overproduction of inflammatory cytokines. Followed by the SARS-CoV-2 infection, which contributes to immune system perturbations such as exhaustion and a decrease number of the total number of CD4⁺ T cells, CD8⁺ T cells, IgE, IgM, and natural killer (NK) cells. CR increase the total number of these immune cells and enhance the immune system. CR could have anti-viral properties, which has to be elucidate in experimental.

This review suggests that the first and the most promising carotenoid candidate for treatment of COVID-19 is astaxanthin due to its countless proprieties and antioxidant activities against several symptoms of viral infections, such as inflammation. In addition, astaxanthin is a multi-target agent that exhibits potential anti-inflammatory effects via several mechanisms of action and an acceptable safety profile when administrated at doses of 2 to 24 mg/d ([Fakhri et al., 2020](#)). Similarly, lycopene, crocin, and crocetin exhibit anti-viral roles, owing to their effects on several pathways implicated in asthmatic and airway inflammation.

However, carotenoids, which are natural compounds derived from the Plant kingdom, require more intensive research to better understand their potential independent roles in human disease prevention, particularly in the context of newly emerging diseases. Therefore, future research

should isolate and characterize the pharmacology of each compound both *in vitro* and *in vivo* to define their activities and to determine the optimal doses of each compound, accounting for toxicity and possible side effects. However, before carotenoids can be utilized medically, their bioavailability, which varies depending on dietary factors and genetic variants ([Desmarchelier and Borel, 2017](#)), must be considered and thoroughly evaluated through extensive *in vitro* and *in vivo* studies.

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Footnotes

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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