Biomedicine & Pharmacotherapy 154 (2022) 113625

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

The landscape of potential health benefits of carotenoids as natural supportive therapeutics in protecting against Coronavirus infection

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ARTICLE INFO

Keywords:
Carotenoids
COVID-19
SARS-CoV-2
Anti-inflammation
Immunity
Natural supportive therapeutics

ABSTRACT

The Coronavirus Disease-2019 (COVID-19) pandemic urges researching possibilities for prevention and management of the effects of the virus. Carotenoids are natural phytochemicals of anti-oxidant, anti-inflammatory and immunomodulatory properties and may exert potential in aiding in combatting the pandemic. This review presents the direct and indirect evidence of the health benefits of carotenoids and derivatives based on in vitro and in vivo studies, human clinical trials and epidemiological studies and proposes possible mechanisms of action via which carotenoids may have the capacity to protect against COVID-19 effects. The current evidence provides a rationale for considering carotenoids as natural supportive nutrients via antioxidant activities, including scavenging lipid-soluble radicals, reducing hypoxia-associated superoxide by activating antioxidant enzymes, or suppressing enzymes that produce reactive oxygen species (ROS). Carotenoids may regulate COVID-19 induced over-production of pro-inflammatory cytokines, chemokines, pro-inflammatory enzymes and adhesion molecules by nuclear factor kappa B (NF-κB), renin-angiotensin-aldosterone system (RAS) and interleukins-6- Janus kinase-signal transducer and activator of transcription (IL-6-JAK/STAT) pathways and suppress the polarization of pro-inflammatory M1 macrophage. Moreover, carotenoids may modulate the peroxisome proliferator-activated receptors γ by acting as agonists to alleviate COVID-19 symptoms. They also may potentially block the cellular receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human angiotensin-converting enzyme 2 (ACE2). These activities may reduce the severity of COVID-19 and flu-like diseases. Thus, carotenoid supplementation may aid in combatting the pandemic, as well as seasonal flu. However, further in vitro, in vivo and in particular long-term clinical trials in COVID-19 patients are needed to evaluate this hypothesis.

1. Introduction

Since the start of the 21st century, the world has been hit by three coronavirus outbreaks: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003–2004, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020. As of 21 January 2022, SARS-CoV-2, which causes Coronavirus Disease-2019 (COVID-19) [262], is associated with 5.6 million death and 340.5 million reported infection cases.

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https://doi.org/10.1016/j.biopha.2022.113625
Received 8 July 2022; Received in revised form 28 August 2022; Accepted 29 August 2022

Abundant evidence shows that severe COVID-19 symptoms are often linked to high levels of pro-inflammatory cytokines (a.k.a. "cytokine storm syndrome"); severe local vascular dysfunction caused by the extension of widespread alveolar and interstitial inflammation to the pulmonary vasculature; and intensive oxidative stress associated conditions, such as clotting and platelet aggregation, impaired artery dilatation, and endothelial dysfunction. A higher risk of developing severe COVID-19 illness has been associated with the following underlying medical conditions: chronic obstructive pulmonary disease (COPD) [178,228], chronic kidney disease (CKD) [271,272,275], cardiovascular disease (CVD) [165,228], obesity [36,73,74,186], type 2 diabetes mellitus (T2D) [3,228,252,253], hypertension [16,50] and cancer [11].

Despite the rapid progress in vaccine and treatment options for COVID-19, the continuous emergence of new variants remains a threat to vaccine-induced immunity [227]. Besides, the symptoms and severity of COVID-19 are diverse, and medical interventions require a careful balancing of benefits and risks. Adequate intake of nutrients, such as omega-3 fatty acids, vitamins A, B6, B12, C, D, E, folate, and minerals iron, selenium, zinc, magnesium, and copper, is one of the pivotal factors that reduce the risk of a compromised immune homeostasis in COVID-19 days [33]. A potential solution to health challenges in the COVID-19 era is to enhance the general immunity of at-risk populations via dietary intervention and nutraceutical supplementation [156]. The European Food Safety Authority (EFSA) scientific panel has emphasized that a healthy immune system is associated with dietary vitamin D, C, A (including β-carotene), and B group vitamins (B6, B12 and folate) [71].

Carotenoids (Fig. 1) are pigments that are commonly present in edible plants (particularly fruits and vegetables) and marine sources, such as algae. They exhibit a range of biological activities; for example, they are well-known antioxidants, and a body of evidence suggests that carotenoids are beneficial for improving immunity [42,62,119] and reducing the risk of diseases with underlying chronic inflammation such as obesity [281], T2D [105], metabolic syndrome [23] and CVD [204]. These properties of carotenoids may ease the COVID-19 symptoms [31,149,206], however, the role of carotenoids and their possible underlying mechanisms of effect against COVID-19 have not been fully discussed [104]. This article explores and updates the potential mechanisms of the beneficial effect of carotenoids in COVID-19 illness, including attenuating oxidative stress, suppressing excessive inflammatory cytokines, modulating peroxisome proliferator-activated receptor γ (PPARγ), examines in vitro, in vivo, and human clinical evidence to determine the possible beneficial effects of carotenoids on COVID-19 illness, and identifies the gaps in current knowledge.

2. Pathogenesis of COVID-19 and severe illness

Approximately 80 % of COVID-19 cases experienced asymptomatic or exhibited mild or moderate symptoms [96]. The asymptomatic or pre-symptomatic cases experienced no significant changes in cytokines, chemokines or lymphocytes. Around 15 % of cases developed severe pneumonia, with 5 % progressing to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) when hypoxemia worsens and the illness becomes severe [291]. The progression of symptoms from mild to moderate and severe is accompanied by increased plasma concentration of inflammatory cytokines (Interleukins: IL-1β, IL-2R, IL-6; interferon: IFN-γ; tumor necrosis factor: TNF-α) and chemokines (C-C motif chemokine ligands: CCL-2, CCL-3, CCL-10) [38–41,222,271,272,275] and an increase in immune cell recruitment to the infection site result in a "cytokine storm", which leads to tissue damage [296]. The main pathological pathways putatively involved in the progression of COVID-19 are presented in Fig. 2 and Fig. 3.

SARS-CoV-2 comprises 4 structural proteins: spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins [250]. After S protein binds to the human angiotensin-converting enzyme 2 (ACE2), S protein undergoes structural change through the endosomal pathway (i.e., proteolysis) and facilitates virus-cell fusion to inject viral RNA into the host cell [20,250]. SARS-CoV-2 proteins are assembled with viral RNA into virions in the endoplasmic reticulum (ER) and released from the host cells. A novel route for SARS-CoV-2 entry is via the cluster of differentiation 147 (CD147) transmembrane protein, which is implicated in the development of tumour, entry of plasmodium and infection mediated by viruses, though with a lesser affinity towards COVID-19 virus as compared to ACE2 [20]. Dysfunction of the renin-angiotensin-aldosterone system (RAS) is involved in the progression of severe COVID-19 illness [63]. In the ACE/Ang II/ATR1 pathway, renin protease cleaves angiotensinogen and generates angiotensin (Ang) I, which is subsequently cleaved by ACE to generate Ang II. Ang II activates the nuclear factor kappa B (NF-κB), NADH/NADPH oxidase (NOX), and toll-like receptor (TLR) 4 to induce oxidative stress and exert pro-inflammatory effects by signalling the Ang II receptor type I (AT1R) and type 2 (AT2R) [65]. In a healthy person, the anti-inflammatory ACE2/Ang (1−7)/Mas pathway counteracts inflammation by antagonizing the pathway of ACE/Ang II/ATR1. ACE2 cleaves Ang II into Ang (1−7) to activate the G-protein-coupled Mas receptor. When

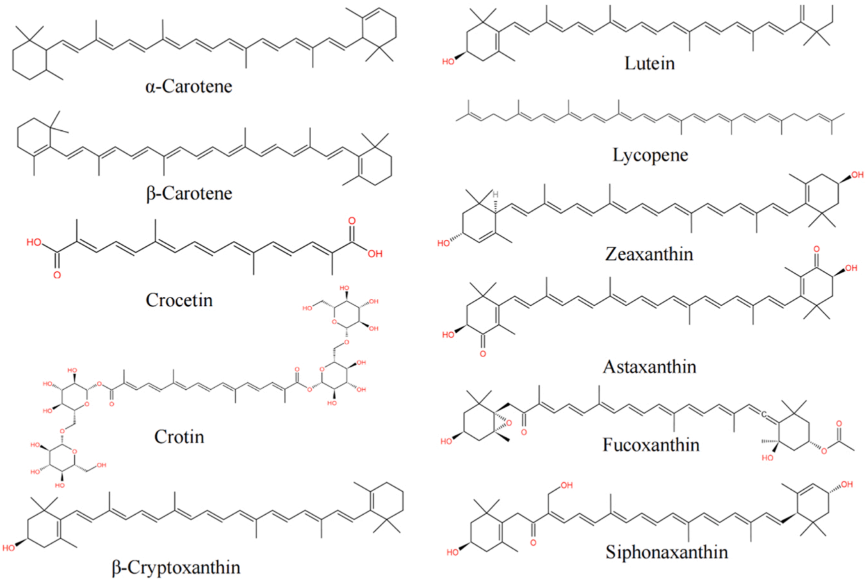

Fig. 1. Structures of common carotenoids.

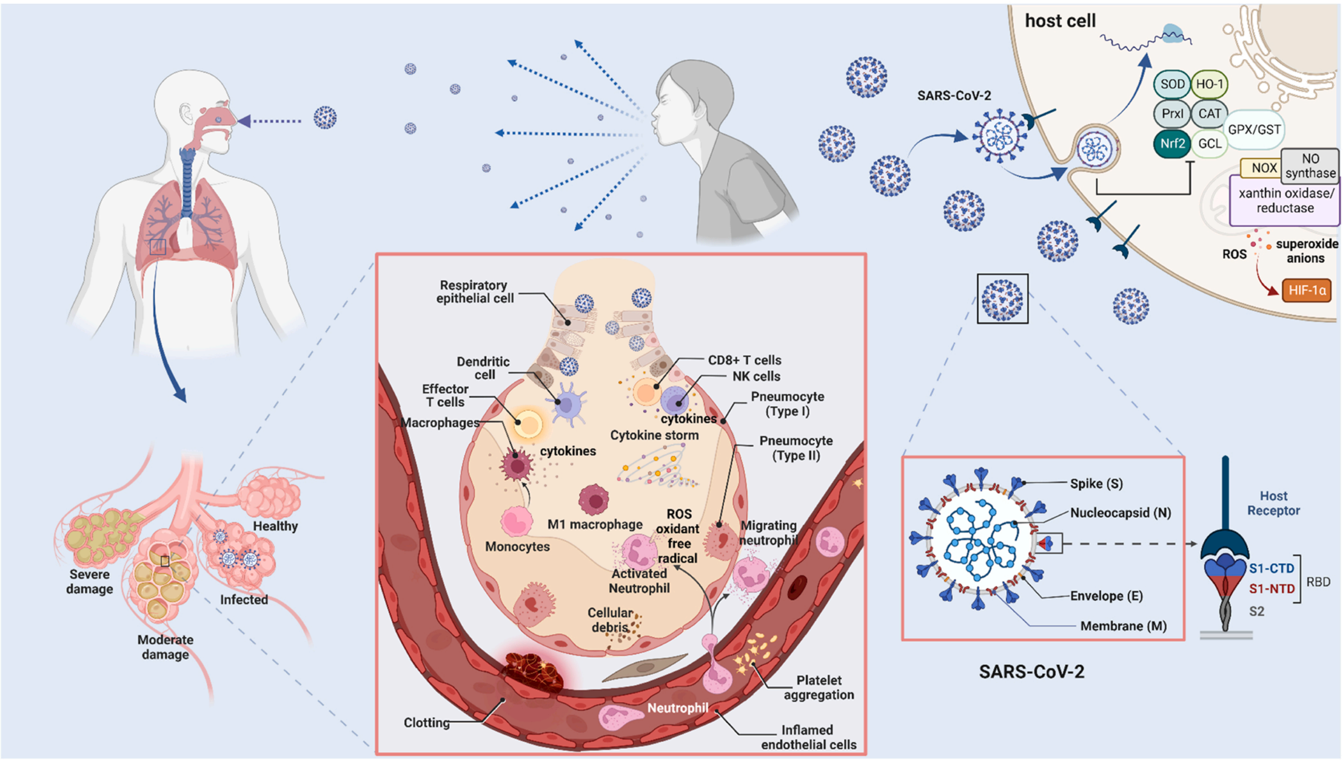

Fig. 2. Structure and pathogenesis of Coronavirus Disease-2019 (COVID-19). (Created with BioRender.com).

SARS-CoV-2 binds to ACE2, the expression of ACE2 from the host cell (e.g., alveolar epithelial cells) is downregulated. As a result, the anti-inflammatory ACE2/Ang (1–7)/Mas pathway is suppressed, and the increasing Ang II level amplifies oxidative stress and inflammatory response [63]. The infected host cells undergo necrosis and further induce high reactive oxygen species (ROS) levels and proinflammatory chemokines and cytokines. Notably, the death of infected immune cells may induce high lymphocytopenia [264,276,277,280], leading to a deprived innate immune system.

Activation of transcription factor NF-κB in various cells is also implicated in the pathogenesis of severe COVID-19 cases. Upon entry of SARS-CoV-2, the viral RNAs and pathogen-associated molecular patterns (PAMPs) are detected and recognized by pattern recognition receptors (PRRs) (e.g., TLRs, RIG-I-like receptors, NOD-like receptors, C-type lectin-like receptors and cytosolic DNA sensors) expressed by innate immune cells (i.e., macrophages, dendritic cells and neutrophils) [89]. The binding of PRRs to PAMPs activates the NF-κB pathway. NF-κB activates pro-inflammatory genes to induce the M1 polarization of macrophages. This process is characterized by increasing the production of pro-inflammatory cytokines IL-1, IL-6, IL-12, TNF-α and promoting the differentiation of inflammatory T cells (e.g. Th17 cells) to recruit immune cells (macrophages, monocytes and neutrophils) to the inflammation sites. The process also increases vascular exudation and leakage [89,194] and stimulates the generation of free radicals, including ROS, in neutrophils [131,265]. In turn, the elevation of free radicals activates the expression of pro-inflammatory cytokines (including IL-6, IL-1, TNF- α, and IFN), chemokines (monocyte chemoattractant protein-1 (MCP-1) and fractalkine (FKN)), and intercellular adhesion molecule-1 (ICAM-1) to contribute to leukocyte adhesion and penetration across the vascular wall into the organ tissue [101]. The elevation of free radicals also increases additional inflammatory mediators in the loop of innate immune response [28,150]. As a result, it is commonly seen that patients with severe COVID-19 illness display immune-mediated inflammatory injuries in multiple organs at the systemic level [265], excessive inflammatory innate responses, and a dysregulated adaptive immune defence [28,89]. Therefore, elderly and patients with metabolic syndrome with sensitized NF-κB are more susceptible to COVID-19 and complications [84].

Potential therapeutic options for COVID-19 include antivirals, anti-inflammatories, antibody-based immunotherapeutic strategies, stem cell-based therapy and nutraceutical supplementation [172]. Modulating the overproduction of inflammatory cytokines to reduce the risk of cytokine storm-related organ and systematic failure has become the focus of effective treatments for severe illness alleviation [86]. U.S. Food and Drug Administration (FDA) has authorized a number of drugs targeting cytokine storm, e.g. dexamethasone [132], tocilizumab [213], remdesivir [22], and baricitinib in combination with remdesivir [108]) and antiviral drugs (e.g., Molnupiravir [146,147], Paxlovid [146,147]). In addition, macrolide antibiotics have been used because they could also have some anti-inflammatory properties, even though no clear evidence of direct anti-viral effect has been demonstrated [185]. Furthermore, nutraceuticals have been proposed as adjunctive therapy to attenuate hyperactive immune response to decrease the risk of cytokine storms and thus the severity of COVID-19, which include vitamin C [4], vitamin D [151], vitamin E [242], magnesium [53,241], selenium [14,120], zinc [260], probiotics [238], omega-3 polyunsaturated fatty acids, and plant-derived compounds with immune-boosting potential such as β-1,3/1,6-D-glucan, inulin, fucoidans, soybean oligosaccharides, polyphenols, curcumin, etc. Basak, Gokhale [19].

3. The protective role of carotenoids in COVID-19 treatments

3.1. Overview

Carotenoids are a range of lipid-soluble pigments that display yellow, orange, red, purple and colorless optical effects [263,290,292]. In the marine and land ecosystems, carotenoids are synthesized by photosynthetic plants, algae, fungi, and bacteria. The chemical structure of these

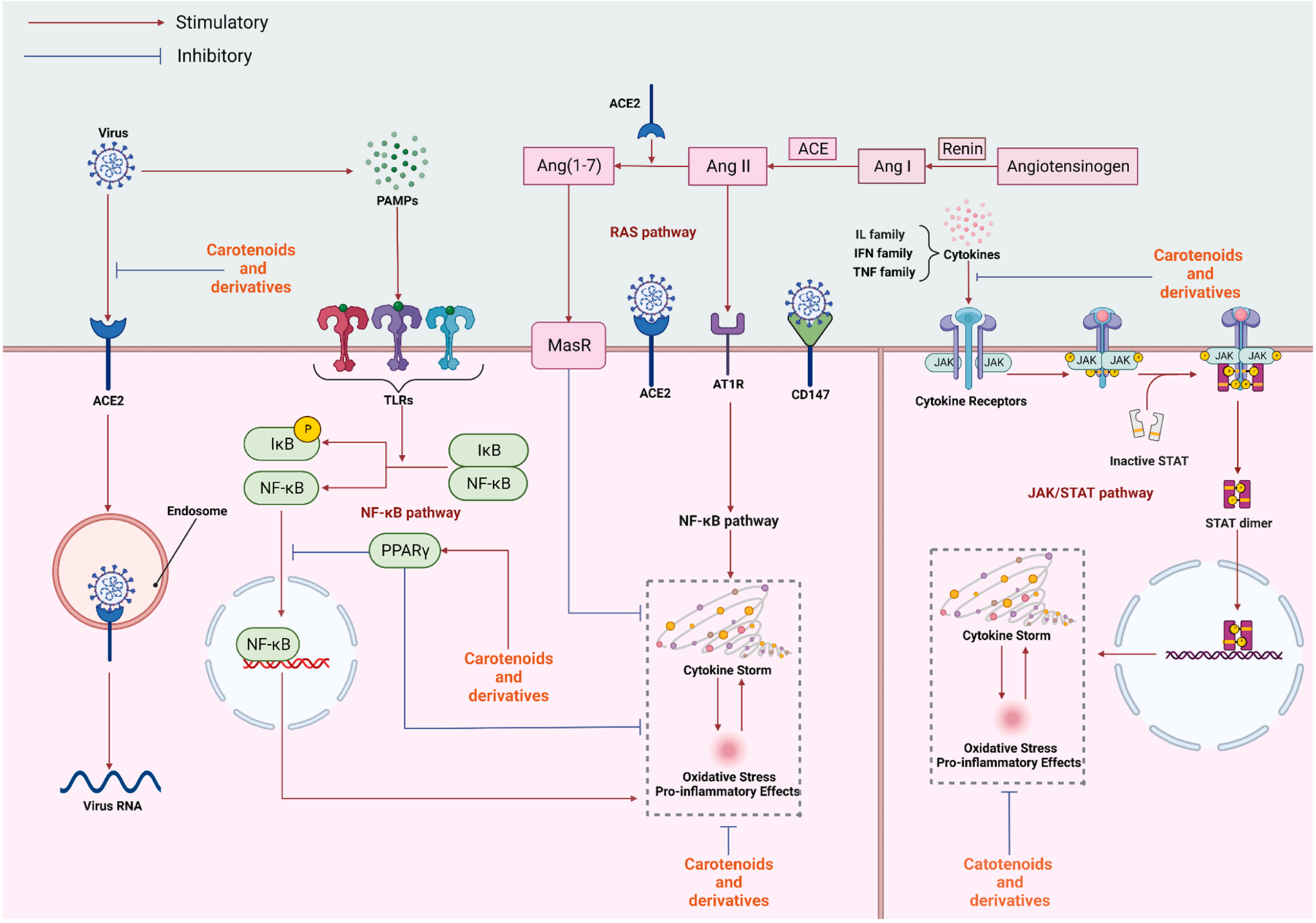

Fig. 3. Putative mechanisms contributing to increased susceptibility for severe Coronavirus Disease-2019 (COVID-19) illness and the hypothetical protective mechanisms of dietary carotenoids. We presume that following viral entry of SARS-CoV-2 into the respiratory epithelial cell and other target cells via binding the cell surface angiotensin converting enzyme 2 (ACE2), the patient experiences oxidative stress and reactive oxygen species (ROS)-mediated inflammation and dysregulated innate and adaptive immune response. The accumulation of a series of complications may lead to severe illness, multi-organ damage, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS). Carotenoids can inhibit these main signalling pathways to suppress the excess oxidative stress and overproduction of pro-inflammatory cytokines.
(Created with BioRender.com).

tetraterpene pigments comprises C40 lipophilic isoprenoids of a polyene chain with 9 conjugated double-bonds and 2 end groups (Fig. 1) [18]. Based on the presence of oxygen in the chemical structure, carotenoids can be categorized into 2 groups: carotene and xanthophyll. The typical carotenes found in nature are α-carotene, β-carotene, and lycopene, which are abundant in some vegetables, fruits, and algae. Because of the diverse presentation of xanthophylls in different forms (e.g., fatty acids, glycosides, sulfates, and protein complexes), over 800 xanthophylls have been recorded in nature until 2020 [149]. Common xanthophylls include astaxanthin, lutein, zeaxanthin, cryptoxanthin and fucoxanthin. Six carotenoids have been discovered in blood circulation following consumption, i.e. α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin [118,196].

Apocarotenoids (e.g. bixin, norbixin, crocin and crocetin from plant source) comprise a group of compounds derived from carotenoids via enzymatic [117] or non-enzymatic [67] cleavage. Dietary apocarotenoids, such as bixin from annatto, crocin from *Crocus sativus linne* (saffron) and *Gardenia jasminoides* (Common Gardenia or Cape Jasmine), are essential food colorants in Central American and Mediterranean cuisine [155].

Carotenoids and derivatives have the potential to attenuate oxidative stress caused by viral infection [117], suppress excess pro-inflammatory cytokine production to prevent cytokine storm [117], and potentially block ACE2, the entry point for SARS-CoV-2 invasion [283]. These activities may benefit COVID-19 patients; several previous studies have reported that carotenoids exhibit a potential effect on improving lung function and immunity [182] and reducing the development of T2D [105], CVD [72,130,259], obesity [281], and cancer [173,209]. These underlying comorbidities appear to positively correlate with the risk of developing severe complications in COVID-19 cases. The potential mechanisms of carotenoids and derivatives targeting different pathophysiologic pathways of COVID-19 are discussed in the following sections, which summarize the indirect evidence of the health benefits of carotenoids and derivatives based on in vitro, in vivo, human clinical trials and epidemiological studies (Table 1 and Table 2), and discuss the potential mechanism of action (Fig. 3) and conceptual application of carotenoids as coadjutant supplement in COVID-19 therapies. The proposed mechanisms include possible anti-oxidative mechanisms by evoking hypoxia-associated superoxide anion (O2•−) generation, activating ROS-generating enzymes, suppressing the expression of antioxidant enzymes, inducing neutrophil extracellular traps (NETs) to boost ROS generation; anti-inflammatory mechanisms by NF-κB pathway, RAS pathway, and JAK/STAT pathway; modulation of peroxisome proliferator-activated receptor γ (PPARγ); and, blocking ACE2 receptors.

Table 1

Pre-clinical studies investigated the effect of carotenoids on oxidative stress, inflammation, ACE2 blocker, and modulation of PPARγ.

Agent	Study design	Method	Main effect (s)	Ref
Attenuate Oxidative Stress				
β-carotene	*In vitro*	ABTS radical cation decolorization assay	↓$ABTS\bullet^{+}$	Sen Gupta, Ghosh [221]
β-carotene zeaxanthin	*In vitro*	Human erythrocytes with tBHP or by AAPH-induced lipid peroxidation; and AAPH-induced oxidation of hemoglobin	↓ROO•	Chisté et al.,[43]
β-carotene	*In vivo*	Renal ischemia/reperfusion injury in rat	↓MDA ↑GSH; SOD	Hosseini et al.,[93]
Astaxanthin	*In vitro*	Human lymphocytes induced by fatty acid mixture	↓H_2O_2; NO ↑SOD	Campoio et al.,[34]
	In vitro	AEC-II cells	↓apoptosis in AEC-II cells; ROS-dependent mitochondrial signaling pathway	Song et al.,[230]
	In vivo	Streptozotocin-induced diabetic rats	↓Lipid peroxidation; ROS; AGEs	Park et al.,[180]
	In vivo	Alloxan-induced diabetic rats	↓MDA; protein carbonyl	Sila et al.,[225]
	In vivo	Streptozotocin-induced diabetic rats	↓MDA; ↑Nrf2; SOD1	Zhu et al.,[297]
Fucoxanthin	*In vitro*	Chemiluminescence technique and ESR technique	↓HO•	Sachindra et al., [211]
	In vitro	SDS micelles and in methanol solution	↓peroxyl radicals; lipid peroxidation	Takashima et al., [240]
	In vitro	DPPH, ABTS, hydroxyl, and superoxide radical-scavenging assay	↓DPPH radical; ABTS radical; $O2\bullet^{-}$; HO•	Zhang et al.,[290, 292]
	In vitro	Monkey kidney fibroblast cells	↓H_2O_2	Heo et al.,[88]
	In vitro	Human HaCaT keratinocytes	↓H_2O_2	Zheng et al.,[293]
	In vitro	Human HaCaT keratinocytes	↑Nrf2; GCL; GSS	Zheng et al.,[294]
	In vitro	HepG2 cells incubated with 0.2 μM TBT	↓ROS; MDA	Zeng et al.,[289]
	In vitro	Human hepatic L02 cells	↓H_2O_2	Wang et al.,[257]
	In vivo	Retinol deficient rat	↓Lipid peroxidation ↑CAT; GST	Sangeetha et al., [216]
	In vivo	High-fat-diet induced obese rats	↑CAT; GSH-Px; total antioxidant capacity; mRNA expression of Nrf2/NQO1	Ha et al.,[81]
	In vivo	OVA-induced asthma mice	↓MDA	Wu et al.,[266]
Suppress excessive inflammatory cytokines				
Astaxanthin	*In vitro*	Proximal tubular epithelial cells	↓Lipid peroxidation; total RS; •O; NO•; ONOO-; NF-κB; iNOS; COX-2 ↑anti-apoptotic Bcl2 protein levels	Kim et al.,[126]
	In vitro	1. RAW 264.7 macrophages; 2. bone marrow-derived macrophages (wild-type and Nrf2-deficient mice) 3. splenocytes and peritoneal macrophages (obese mice)	↓NF-κB; ROS; NOX2; IL-6; IL-1β ↑Nrf2	Farruggia et al., [66]
	In vitro in vivo	1. LPS-stimulated RAW264.7 cells and M1 macrophages; 2. LPS-administrated mice	↓NO; NF-κB; iNOS; PGE2; TNF-α; IL-1β	Lee et al.,[134]
	In vivo	High fructose-fat diet-fed mice	↓ROS; NF-κB; ER stress markers	Bhuvaneswari et al.,[25]
	In vivo	Cecal ligation and puncture induced ALI mice	↓NF-κB; NT; iNOS	Bi et al.,[26]
	In vivo	OTA-induced lung injury mice	↓NF-κB; Keap1; TLR4 ↑Nrf2; HO-1; MnSOD	Xu et al.,[273]
	In vivo	Streptozotocin-induced diabetic rats	↓NF-κB; TNF-α; IL-1β; IL-6	Xu et al.,[270]
Fucoxanthin	*In vitro*	TGF-β1-stimulated human pulmonary fibroblasts	↓IL-6	Ma et al.,[142]
	In vitro/ *In vivo*	RAW264.7 macrophages; LPS-induced ALI mice	↓NF-κB; iNOS; COX2; IL-10; IL-6	Li et al.,[135,137]
	In vitro/ *In vivo*	human bronchial epithelial cells (BEAS-2B); asthmatic mice	↓ROS; IL-8; IL-6; MCP-1; CCL5; CCL11; CCL24; eotaxin	Wu et al.,[266]
	In vivo	LPS-induced ALI rats	↓MPO; IL-6; IL-1β; TNF-α; infiltration of inflammatory cells in BALF	Xiao et al.,[268]
	In vivo	OVA-induced asthma mice	↓ROS; inflammatory cytokine ↑antioxidant enzyme activity	Yang et al.,[279]
	In vivo	LPS-induced sepsis mice	↓NF-κB; IL-6; IL-1β; TNF-α	Su et al.,[232]
	In vivo	OVA-induced allergic rhinitis	↓NF-κB; IL-5; IL-6; IL-12; cytokine	Li et al.,[136]
β-carotene	*In vitro*	LPS-stimulated macrophages	↓NO; NF-κB; iNOS; COX-2; TNF-α; IL-1β	Bai et al.,[15]
	In vitro	LPS-stimulated macrophages	↓NF-κB; IL-6; IL-8; TLRs	Robertson et al., [205]
Lutein	*In vivo*	Streptozotocin-induced diabetic rats	↓NF-κB ↓ICAM-1; MCP-1; FKN	Yeh et al.,[282]
lycopene	*In vitro*	LPS-induced dendritic cells	↓NF-κB	Kim et al.,[122]
Modulate PPARγ				
Astaxanthin	*In vitro*	Thioglycollate-elicited peritoneal macrophage	↑expression of PPARγ target genes (CD36, liver X receptor)	Inoue et al.,[102]
Fucoxanthin	*In vitro*	3T3-L1 preadipocytes	↑PPARγ mRNA expression	Kang et al.,[111]
lycopene	*In vitro*	Bovine subcutaneous adipose tissue cells	↑PPARγ mRNA expression	García-Rojas et al., [75]
Crocin	*In vivo*	High-fructose-diet induced MetS mice	↑PPARγ mRNA expression ↓IL-6; TNF-α	Algandaby[9]
Block ACE2				

(*continued on next page*)

Table 1 (*continued*)

Agent	Study design	Method	Main effect (s)	Ref
Siphon-axanthin	*In silico/In vitro*	HEK293 cells overexpressing ACE2	Binding ACE2	Yim et al.,[283]
Lutein	*In silico*	Protein-ligand docking program (GalaxyDock)	Binding ACE2	Ahmed, Husaini[7]

Abbreviation: 1,1-diphenyl-2-picrylhydrazyl, DPPH; 2,2'-azobis (2-methylpropionamidine) dihydrochloride, AAPH; 2–2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid), ABTS; acute lung injury (ALI); Advanced glycation end products, AGEs; Alveolar epithelial cells type II, AECs-II cells; angiotensin-converting enzyme 2, ACE2; bronchoalveolar lavage fluid, BALF; catalase, CAT; cyclooxygenase 2, COX-2; electron spin resonance, ESR; endoplasmic reticulum, ER; fractalkine, FKN; Glutamate Cysteine Ligase, GCL; glutathione S-transferase, GST; glutathione synthetase, GSS; gluthathione peroxidase, GSH-Px; heme oxygenase-1, HO-1; inducible nitric oxide synthase, iNOS; intercellular adhesion molecule-1, ICAM-1; interleukin, IL; malondialdehyde, MDA; Metabolic Syndrome, MetS; monocyte chemoattractant protein-1, MCP-1;Myeloperoxidase, MPO;NAD(P)H quinone oxidoreductase1, NQO1; NADH/NADPH oxidase, NOX; nuclear factor kappa B, NF-κB; nitric oxide, NO; nitrotyrosine, NT; nuclear erythroid factor like 2, Nrf2; ovalbumin, OVA; peroxisome proliferator-activated receptors γ, PPARγ;Prostaglandin E2, PGE2; reactive oxygen species, ROS; Sodium dodecyl sulfate, SDS; Superoxide dismutase, SOD; tert-butyl hydroperoxide, tBHP; toll-like receptor, TLR; tumor necrosis factor, TNF; transforming growth factor-beta1, TGF-β1.

3.2. *Attenuation of oxidative stress in SARS-CoV-2 infection*

3.2.1. *Oxidative stress in SARS-CoV-2 infection*

A relatively low level of ROS induced by viral infection is sufficient for intracellular redox sensing to induce inflammatory reactions and eradicate phagocytosed viruses (e.g., pulmonary alveolar macrophages). However, ROS overproduction compromises the antioxidant activities of the defensive system, resulting in extensive cellular and tissue damage [131,299]. SARS-CoV-2 infection drives a significant rise in oxidative stress systemically (84, 85) through a number of possible mechanisms, including by evoking hypoxia-associated superoxide anion generation, activating ROS-generating enzymes, suppressing antioxidant enzymes expression, and inducing NETs to boost ROS generation.

3.2.1.1. Evokes hypoxia-associated superoxide anion ($O2\bullet^{-}$) generation. Hypoxia has been identified as the hallmark of severe COVID-19 illness and an independent predictor of the admission to intensive care unit (ICU) [114,187]. When lungs cannot maintain adequate oxygenation, hypoxia can lead to the generation of superoxide anions and increased ROS generation in mitochondria [12]. The oxidative stress in virally infected monocytes may cause mitochondrial dysfunction and accelerate virus replication [12]. Evoking the production of mitochondrial ROS also induces hypoxia-inducible factor-1α (HIF-1α) stabilisation and consequently promotes glycolysis [51].

3.2.1.2. Activates ROS-generating enzymes. At the cellular level, multiple isoforms of NOX (e.g. NOX2 oxidase in immune cell phagosomes that are predominantly involved in ROS production during lung infections, and NOX4 in pulmonary ROS production), xanthin oxidase/reductase, and endothelial/inducible nitric oxide synthase (iNOS) catalyse the synthesis of superoxide via one-electron reduction of oxygen [249].

3.2.1.3. Suppresses the expression of antioxidant enzymes. Superoxide dismutase (SOD) [131], heme oxygenase-1 (HO-1) [90], catalase (CAT) [154], glutathione peroxidase (GPX) [243], glutathione S-transferase (GST) [210], peroxiredoxin (PrxI) [112], and nuclear factor erythroid 2–related factor 2 (Nrf2) [55] are enzymes that mitigate oxidative stress and are implicated in the pathogenesis of COVID-19. The correlation between decreased expression of SOD3 in lungs and severity of COVID-19 has been reported in elderly patients [131].

3.2.1.4. Induces NETs to boost ROS generation. Neutrophils are among the first defensive systems to contain viral infections [131]. At the early stage of infection, neutrophils are recruited to the infection site to engulf and destroy the virus intracellularly by releasing potent oxidants and free radicals (hydrogen peroxide H_2O_2, superoxide anion, hydroxyl radicals and peroxynitrite) [109]. Neutrophils can also entrap a virus extracellularly by forming NETs (a combination of DNA and protein web structures). NETs efficiently in improve defense against viral attacks; however, excessive NETs and neutrophil infiltration into the lungs can lead to severe damage to the lungs and other organs [169,252,253].

In response to viral infection, it is vital to prevent the shift towards excessive ROS generation, including in the first line of immune defence such as the epithelial lining fluid in the lungs.

3.2.2. *Possible anti-oxidative mechanisms of carotenoids in response to SARS-CoV-2 infection*

Carotenoids have been appraised for their antioxidant functions because of their ability to quench singlet oxygen and free radicals in the lipid bilayers of the cell membrane [129]. They can also act on the production of antioxidant enzymes as well as the NF-κB pathway to mediate oxidative stress. Epidemiological studies have reported an inverse association between total plasma carotenoids and oxidative stress (ROS, non-enzymatic antioxidant activities and lipid peroxidation) and the risk of developing chronic disease [29,251]. The association seems to be more significant in people with chronic diseases than healthy participants [29], suggesting a protective effect in patients with pre-infection metabolic problems. Human studies on the antioxidant efficacy of carotenoids are largely centred on astaxanthin, thus further clinical evidence is required to support the antioxidant role of carotenoids on viral infection.

β-carotene, a pro-vitamin A carotenoid, quenches singlet oxygen without degrading and reacts with free radicals (e.g., peroxyl, hydroxyl and superoxide). *In vitro* studies have reported that β-carotene might diminish cellular oxidative damage via scavenging lipid-soluble radicals including peroxyl radical (ROO•) [43], superoxide anion radical ($O_2\bullet^{-}$) and hydroxyl radical (HO•) [247], peroxynitrite anion ($ONOO^{-}$) [179] and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) ($ABTS\bullet^{+}$) [221]. Scavenging activities of β-carotene with a dose higher than 30 mg/kg body weight were reported by in vivo studies in rats [93]. The efficacy seems to be observed under low oxygen tension (i.e., in normal physiological conditions) [121]. During the inflammatory process, a high oxygen pressure may cause the activity to shift to pro-oxidative activity [121,203]. Moreover, a high concentration of β-carotene was reported to exert a pro-oxidative effect, whilst a low concentration maintained the scavenging activities [221].

Astaxanthin is an oxycarotenoid derived mainly from microalgae, yeast and fungi [258]. Numerous in vitro and in vivo studies support the antioxidative activities of astaxanthin. Evidence from in vitro studies demonstrated the potential antioxidant property of astaxanthin in epithelial cells and macrophages. It was reported that astaxanthin might block H_2O_2 or bleomycin-induced ROS production in alveolar epithelial cells type II (AEC-II) [230] and increase total-SOD activity [126] while reducing the lipid peroxidation products in proximal tubular epithelial cells (PTECs) [126]. Furthermore, studies on macrophages demonstrated that astaxanthin could reduce the LPS-induced ROS [66,225] and suppress NF-κB and iNOS [134].

The anti-oxidative stress effect of astaxanthin supplementation was further evidenced in various animal models. It was reported that

Table 2
Randomized clinical trials investigating the effects of dietary and supplementary carotenoids on inflammation and oxidative stress.

Study design	Study Participants	Dose	Duration (week)	Main outcomes	Proposed implication	Ref
Inflammation related studies						
Astaxanthin vs. placebo	T2D patients	Study1: 6 mg/d	8	↔CRP; IL-6; TNF-α; MDA	No effect	Chan et al.,[37]
		Study2: 12 mg/d	8	↓CRP; IL-6; TNF-α; MDA	Anti-inflammation	
Astaxanthin vs. placebo	Renal transplant recipients	12 mg/d	48	↔pentraxin-3	No effect	Coombes et al.,[52]
Astaxanthin vs. placebo	Trained male soccer teenage players	4 mg/d	12	↓CRP	Anti-inflammation	Baralic et al.,[17]
Astaxanthin vs. placebo	Healthy adult female human subject	Study1: 2 mg/d Study2: 8 mg/d	8	↔CRP; IL-6; TNF-α	No effect	Park et al.,[181]
Astaxanthin vs. placebo	Healthy nonsmoking adult men	8 mg/d	12	↓CRP; IL-6	Anti-inflammation	Karppi et al.,[113]
Lutein vs. placebo	Early atherosclerosis patients	20 mg/d	12	↓IL-6; MCP-1	Anti-inflammation	Xu et al.,[274]
Lutein vs. placebo	Healthy nonsmokers	Study1: 10 mg/d	12	↔CRP; MDA	Anti-inflammation	Wang et al.,[256]
		Study2: 20 mg/d	12	↓CRP; MDA	Anti-inflammation	
Lutein + anthocyanins vs. anthocyanins	Postmenopausal women	6 mg/d lutein + 2 mg/d zeaxanthin	32	↔CRP; IL-6	No effect	Estévez-Santiago et al.,[64]
Lutein + zeaxanthin vs. placebo	Healthy adult subjects	Study1: 10 mg/d lutein + 5 mg/d zeaxanthin	8	↔CRP	No effect	Graydon et al.,[78]
Lutein, zeaxanthin and meso-zeaxanthin vs. placebo	Healthy adult subjects	13 or 27 mg/d	24	↓IL-1β	Anti-inflammation	Stringham et al.,[231]
Carrot juice fortified with β-carotene vs. normal carrot juice	T2D patient	10 mg/d	8	↔CRP; IL-6	No effect	Ramezani et al.,[195]
β-Carotene vs. placebo	Healthy adult subjects	15 mg/d	8	↔CRP	No effect	Graydon et al.,[78]
Lycopene vs. placebo	COPD patients	20 mg/d	16	↓IL-6; TNF-α	Anti-inflammation	Kırkıl et al.,[127]
Lycopene prior to running vs. placebo	Runners (crossover)	11 mg/d	4	↔CRP; IL-6	No effect	Nieman et al.,[171]
Lycopene vs. placebo	Healthy adult men	Study1: 6 mg/d	8	↔CRP	No effect	Kim et al.,[123, 124]
Lycopene vs. placebo	Healthy adult men	Study2: 15 mg/d	8	↔CRP	No effect	Kim et al.,[123, 124]
Lycopene vs. placebo	CVD Patients/healthy participants	7 mg/d	8	↔CRP; TNF-α; IL-6 in all participants	No effect in CVD/ healthy volunteers	Gajendragadkar et al.,[70]
Lycopene vs. placebo	Moderately overweight healthy middle-aged adults	10 mg/d	16	↔CRP; IL-6	No effect	Thies et al.,[244]
Lycopene vs. placebo	Patients with prehypertension	7 mg/d	4	↔CRP	No effect	Petyaev et al.,[184]
Whey protein isolates embedded into lycopene micelles vs. whey protein	Patients with prehypertension	7 mg/d	4	↔CRP	No effect	Petyaev et al.,[184]
Lycopene Tomato extract capsules vs. placebo	Healthy smokers and nonsmokers	14.64 mg/d	2	↔TNF-α in smokers and non-smokers ↓IL-4 in smokers	Reduction of IL-4 in smokers	Briviba et al.,[32]
β-cryptoxanthin vs. placebo	Patients with NAFLD	6 mg/d	12	↓CRP ↔IL-6	Anti-inflammation	Haidari et al.,[82]
Crocin vs. placebo	Osteoarthritis Patients	15 mg/d	16	↓CRP	Anti-inflammation	Poursamimi et al.,[188]
Crocin vs. placebo	Patients under MMT	30 mg/d	8	↓CRP; MDA	Anti-inflammation	Ghaderi et al.,[76]
Crocin vs. placebo	Patients with multiple sclerosis	30 mg/d	8	↓TNF-α	Anti-inflammation	Ghiasian et al.,[77]
Oxidative stress related studies						
Astaxanthin	heavy smokers and non-smokers;	Study1: 5 mg/d Study2: 20 mg/d Study3: 40 mg/d	3	↓MDA; F2-isoPs; ↑SOD; TAC	Reduce oxidative stress in smokers	Kim et al.,[123, 124]
Astaxanthin vs. placebo	Healthy subjects in mid-40 s (crossover)	3 mg/d	4	↓PLOOH	Reduce oxidative stress	Imai et al.,[100]
Astaxanthin vs. placebo	healthy middle-aged and senior subjects	Study1: 6 mg/d Study2: 12 mg/d	12	↓PLOOH	Reduce oxidative stress	Nakagawa et al.,[166]
Astaxanthin high dose vs. low dose	middle-aged and senior healthy subjects	Study1: 1 mg/d	4	↑Serum carotenoids concentration	Potential to reduce oxidative stress	Miyazawa et al.,[161]
		Study2: 3 mg/d	12			
Astaxanthin vs. placebo	T2D patients	8 mg/d	8	↓MDA; IL-6	Reduce oxidative stress	Shokri-Mashhadi et al.,[224]
Astaxanthin high dose vs. low dose	overweight or obese adults	Study1: 5 mg/d Study2: 20 mg/d	3	↓MDA; isoprostane ↑SOD; TAC	Reduce oxidative stress	Choi et al.,[45]
Lutein vs. placebo	healthy senior subjects	22.9 mg /day	8	↓PLOOH	Reduce oxidative stress	Miyazawa et al.,[162]
β-carotene vs. placebo	nonsmokers and smokers	20 mg/d	4	↓lipid peroxidation marker BPO in smokers		Allard et al.,[10]

(continued on next page)

Table 2 (*continued*)

Study design	Study Participants	Dose	Duration (week)	Main outcomes	Proposed implication	Ref
				received β-carotene; ↔ BPO in nonsmokers received β-carotene	Reduce oxidative stress, improve lung function	

Abbreviation: breath-pentane output, BPO; cardiovascular disease, CVD; Chronic obstructive pulmonary disease, COPD; C-Reactive Protein, CRP; malondialdehyde, MDA; methadone maintenance treatment, MMT; Monocyte chemoattractant protein-1, MCP-1; Nonalcoholic fatty liver disease, NAFLD; phospholipid hydroperoxides, PLOOH; Superoxide dismutase, SOD; total antioxidant capacity, TAC; type 2 diabetes, T2D.

astaxanthin had the potential to protect organs from oxidative damage and inflammation through the Nrf2/NF-κB pathway in the ochratoxin (OTA)-induced lung injury mouse model [273]. OTA exposure has been found to induce immunotoxicity of the TLR4/MyD88 pathway by stimulating the overproduction of ROS and inflammatory markers IL-1β, IL-6 and TNF-α [273]. Similarly, astaxanthin-mediated scavenging action was observed in mice with ALI induced by cecal ligation and puncture (CLP) [26]. Previous studies have also shown that astaxanthin supplementation could mitigate oxidative stress in mouse models with metabolic disorders [25,180,297].

Fucoxanthin, an oxycarotenoid predominantly sourced from microalgae and brown algae, has a distinctive structure with an allenic bond, a 5,6-monoepoxide, and 9 conjugated double bonds system that can quench singlet oxygen ($^1O_2$) by transferring the excess energy of singlet oxygen to the conjugated polyene structure. Owing to its electron-rich status, fucoxanthin has a high capability of reacting with free radicals [160]. *In vitro* studies demonstrate that fucoxanthin could scavenge a wide range of free radicals, including hydroxyls and superoxide [211, 290,292], peroxyl radicals and lipid peroxides [240]. The antioxidant activities of fucoxanthin against H_2O_2-mediated cell damage has been reported in monkey kidney fibroblast cells [88], human hepatic L02 cells [257], and human HaCaT keratinocytes [293,294]. Increased antioxidative activities resulting in deceased ROS and malondialdehyde (MDA) in HepG2 cells also have been reported [289].

Evidence from animal studies further supports the antioxidant properties of fucoxanthin. Fucoxanthin decreased serum oxidative stress biomarker MDA, one of the final products of polyunsaturated fatty acid peroxidation, in male BALB/c mice with ovalbumin (OVA)-induced allergic rhinitis [136]. A recent study of OVA-sensitized asthmatic mice demonstrated that intraperitoneal injections of fucoxanthin significantly decreased the MDA concentrations in the lungs and attenuated the oxidative stress in inflammatory tracheal epithelial cells [266]. Ha and colleagues [81] found fucoxanthin significantly improved the plasma total antioxidant capacity in rats fed with a high-fat diet [81]. It has also been suggested that fucoxanthin upregulates the antioxidant enzymes CAT and GST, which intensify the free-radical-scavenging activities in retinol deficient rats [216]. The accumulating evidence further strengthens the potential use of carotenoids in reducing oxidative stress in viral infections.

3.2.3. *Clinical trials evidence of antioxidant effect of carotenoids*

The beneficial effect ascribed to carotenoid supplementation on reducing oxidative stress has been observed in randomized controlled trials (RCTs) of participants suffering from chronic oxidative stress such as smokers. A 4-week clinical trial of 20 mg/d β-carotene supplementation showed a significant reduction in lipid peroxides in smokers [10]. Astaxanthin at daily doses of 5, 20, or 40 mg led to a dose-dependent decrease of plasma level of F2-isopoprostane (F2-isoPs), a lipid biomarker of oxidative stress, over a 3-week period in an intervention study of smokers [123,124].

In healthy subjects, clinical trials have confirmed the potential of carotenoid supplementation, particularly astaxanthin, to decrease lipid peroxidation and protect against cellular damage. A 4-week RCT with healthy participants aged in their mid-40 s supplied with daily 6 mg astaxanthin (consumed with 10 mg sesamin) demonstrated significantly reduced plasma levels of phosphatidyl–hydroperoxide (PLOOH) compared to placebo [100]. Astaxanthin supplementation (1 mg/d for 4 weeks or 3 mg/d for 12 weeks) significantly increased plasma carotenoid concentrations in middle-aged and senior subjects compared to baseline, although biomarkers of oxidative stress were not evaluated [161]. The effective dose of astaxanthin supplementation was investigated by Nakagawa 2011 [166]. Various dosages of astaxanthin (at 0, 6 or 12 mg/d for 12 weeks) were administered to healthy subjects in the study. Results found that a higher dose of astaxanthin more strongly reduced erythrocyte PLOOH concentration (up to 50 %) and plasma peroxides levels [166].

The antioxidant effect of astaxanthin was reported in subjects with chronic conditions. Over an 8-week period, supplementation of astaxanthin (8 mg/day) reduced plasma concentration of MDA and IL-6 in patients with T2D [224]. A 3-week RCT in overweight and obese participants also revealed the antioxidant effect of both high (30 mg/day) and low (5 mg/day) dose of astaxanthin, suggesting the efficacy of this carotenoid in suppressing lipid peroxidation and stimulating the activity of the antioxidant defense [45].

Limited evidence is available from human studies on the antioxidant efficacy of other carotenoids besides astaxanthin. In a 2-month RCT in senior participants, compared to placebo, chlorella algae (8 g chlorella/day; with 22.9 mg lutein/day) supplementation showed a reduction of PLOOH [162]. This observation underpins the potential application of carotenoid supplementation in reducing oxidative stress. However, there is as yet no evidence from human trials to support a beneficial effect of carotenoid supplements for oxidative stress in viral infection.

3.3. *Suppression of excessive inflammatory cytokines in SARS-CoV-2 infection*

3.3.1. *Cytokine storm in SARS-CoV-2 infection*

After SARS-CoV-2 enters respiratory epithelial cells, infected cells are phagocytosed and presented by the dendritic cells. The cytotoxic CD8$^+$ T cells synthesize and release pro-inflammatory cytokines to induce apoptosis of infected cells, whilst the effector T cells kill the infected cells directly [276,277,280]. Natural killer cells (NK cells) can also eliminate infected cells by producing and releasing cytotoxic granules, cytokines and chemokines [167]. The pulmonary macrophages derived from inflammatory monocytes are activated to induce pro-inflammatory cytokine release, M1 macrophage polarization, and cytotoxic effector cell recruitment [128].

The adequate clearance of SARS-CoV-2 requires an effective and efficient immune response. However, the exacerbation of cytokine production and excessive immune cell recruitment to the infection site can cause cytokine storms mainly through the following pathways.

3.3.1.1. NF-κB pathway. This pathway was briefly discussed in the previous section (Section 2). NF-κB is a family of transcription factors that encompasses five homo and heterodimer proteins, including NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), c-Rel and Rel B [35]. NF-kB is ubiquitously expressed and impacts an extensive assortment of cellular processes, including proliferation, immunity, inflammation, and apoptosis. In unstimulated cells, it resides in the cytoplasm complexed to the inhibitor of NF-κB (IκB). The canonical pathway of NF-κB activation involves phosphorylation of IκB by IκB kinase with the concomitant release of NF-κB, which is then able to translocate from the cytoplasm to the nucleus and bind to target gene promoters. NF-κB regulates the transcription of pro-inflammatory cytokines, such as TNF-α [139,140,141], promotes upregulation of the production of pro-inflammatory enzymes (e.g., iNOS, cyclooxygenase COX) and increases the production of pro-inflammatory mediator nitric oxide (NO) [140]. Therefore, activation of NF-κB results in overproduction of pro-inflammatory cytokines and eventually leads to dysregulated immune function.

3.3.1.2. RAS pathway. This pathway was briefly discussed in the previous section (Section 2). Without redox balance (i.e., controlled intracellular ROS generation), RAS activates the excessive production of pro-inflammatory cytokines to induce a hyperactive and uncontrolled immune response [140]. Eventually, the cascade leads to an excessive inflammatory innate response and a dysregulated adaptive immune defense [28,89].

3.3.1.3. Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway. At the early stage of infection, IFNs (e.g., IFN-α, IFN-γ) are involved in signal transduction through activation of the Janus tyrosine kinase and signal transducer and activator of transcription families (JAK/STAT) signaling pathway that leads to the upregulation of genes that kill the infected cells [99]. IL-6 is a pro-inflammatory cytokine released by B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes and other non-lymphocytes during inflammation. At the early stage of infection, the TNF-α and TLRs are the main two factors that activate the production and function of IL-6. A high level of IL-6 is observed in severe COVID-19 illness caused by cytokine storm [145]. The complex of IL-6 to α-IL-6 receptor (α-IL-6R) induces IL-6 signal transduction to activate the dimerization of β-receptor gp13. Dimerization, in turn, activates JAK/STAT kinase signaling pathway to initiate the signal transduction. The JAK/STAT signaling kinase pathway activation can allow the transcription of genes such as STAT1 which inhibits immune cell division and stimulates inflammation [46].

Adjunctive therapeutic supplementation, which ameliorates the effects of COVID-19 on the abovementioned pathways, could play a critical role in supporting the management of inflammatory conditions in the COVID-19 era.

3.3.2. Possible mechanisms of carotenoids suppressing inflammatory cytokines

The anti-inflammatory functions of carotenoids have been examined in in vitro and in vivo studies, with much of the evidence centered on astaxanthin, fucoxanthin, and β-carotene. The main possible mechanism is the suppression of cytokine storm and pro-inflammatory effects via the NF-κB and JAK/STAT signalling pathways. Clinical evidence pointed out that astaxanthin exhibits the most promising anti-inflammatory efficacy. However, inconsistent results were obtained from human intervention studies on the anti-inflammatory effect of the reported carotenoids.

Astaxanthin suppresses pro-inflammatory cytokines by blocking the NF-κB signaling pathway and reduceing inflammatory mediators in alveolar macrophages [66,134], PTECs [126] and lymphocytes [34]. A study conducted using a CLP induced ALI mouse model showed that astaxanthin could downregulate the expression of pro-inflammatory enzymes iNOS and NF-κB/p65 in lung tissue and reduce the inflammation infiltration in bronchoalveolar lavage fluid [26]. Studies of rat models with metabolic disorders also support the anti-inflammatory activity from astaxanthin [25,270]. Supplementation of astaxanthin in streptozotocin-induced diabetic mice was demonstrated to reduce the activities of NF-κB/p65, TNF-α, IL-1β and IL-6 [270]. Bhuvaneswari and colleagues [25] revealed that the astaxanthin supplementation of rats consuming a high fructose–fat diet could inhibit nuclear translocation of pro-inflammatory enzymes NF-κB/p65 and phosphorylation of IκB kinase β (i.e., IKKβ, a catalytic subunit of IKK which is the main activator of NF-κB) to suppress the expression of inflammatory mediators [25].

In addition to astaxanthin, fucoxanthin and its metabolites were also suggested to be promising agents to support immune functions. Evidence from in vitro studies showed that fucoxanthin and the metabolite fucoxanthinol reduced the mRNA levels of TNF-α, iNOS and COX-2 in RAW264.7 macrophage-like cells [135,137]; decreased IL-6 level in transforming growth factor-beta1 (TGF-β1)-stimulated human pulmonary fibroblasts [142]; and lowered IL-6 and IL-8 levels in inflammatory human tracheal epithelial BEAS-2B cells [266]. Consistent with in vitro studies, fucoxanthin could manifest immune-boosting properties in animal studies. Yang et al. [279] reported that fucoxanthin could significantly reduce IL-6 and IL-10 in the OVA-induced asthma mouse model [279]. A similar anti-inflammatory effect of fucoxanthin was reported in LPS-induced ALI mice [135,137,268] and male BALB/c mice with OVA-induced allergic rhinitis [136]. A recent study on the LPS-induced sepsis mouse model showed fucoxanthin reduced IL-6, IL-1β and TNF-α levels and the NF-κB signaling pathway was inhibited [232].

The anti-inflammatory property of lutein and zeaxanthin against dysregulated immune response has been investigated. Yeh et al. (2018) reported that lutein administration could significantly inhibit NF-κB activity and suppress the downstream inflammatory molecules (ICAM-1, MCP-1 and FKN) in ocular tissues of diabetic rats [282]. Lutein has also been reported to protect against retinal neural damage caused by inflammation in an endotoxin-induced uveitis murine model [217]. Combined with zeaxanthin, lutein reduced the photooxidative damage to retinal pigment epithelial cells and oxidation-induced changes in the expression of inflammation-related genes (MCP-1, IL-8, and CFH) by inhibiting the NF-κB signaling pathway [27]. Qiao et al. [193] reported the protective effect of lutein against monosodium iodoacetate-induced osteoarthritis in primary chondrocyte cells via downregulation of inflammatory proteins (NF-κB, COX-2) and pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) as well as a reduction in MIA-induced apoptosis [193].

Evidence of the immune functions of β-carotene was identified primarily in in vitro studies. It was reported that β-carotene inhibited the NF-κB pathway and reduced the expression of pro-inflammatory mediators (NO, prostaglandin E2, TNF-α, IL-1β) and enzymes (iNOS, COX-2) in LPS-stimulated RAW264.7 cells and M1 macrophages in a dose-dependent fashion [15]. In a study of human gastric tissues infected by Helicobacter pylori, β-carotene supplementation suppressed the ROS-mediated NF-κB/MAPK (mitogen-activated protein kinases) signaling pathway and reduced IL-8 and pro-inflammatory enzyme (NO, iNOS, and COX-2) concentrations [110]. Combining three bioactive red seaweed lipid compounds, β-carotene, chlorophyll A and fucoxanthin inhibited IL-6, IL-8, and NF-κB production in LPS-stimulated human THP-1 macrophages [205].

Furthermore, carotenoids have been reported to reduce neutrophil accumulation. A combination of three carotenoids, β-carotene, lutein and lycopene, decreased neutrophil accumulation induced by transient receptor potential ankyrin 1 (TRPA1; a major player involved in various pain conditions) activation in cutaneous neurogenic inflammation on the mouse ear [91].

3.3.3. Clinical trial evidence of anti-inflammatory effects of carotenoids

Inflammation is commonly observed in COVID-19 patients, represented by a significant increase of C-reactive protein (CRP) (between 20 and 50 mg/L) and the release of pro-inflammatory cytokine IL-6 from activated macrophages and T cells [38,39,40,41,73,74]. The co-existing high serum concentrations of IL-6 and CRP appears related to the ability of IL-6 to upregulate the hepatic production of CRP [57]. In COVID-19 cases, the elevated IL-6 concentration was reported to correlate to the severity of the illness, possibly via the JAK/STAT pathway. Therefore, IL-6 blockers have been suggested as a potential therapy to mitigate cytokine storm [38–41,139,141,222].

Carotenoids have been shown to have overall beneficial effects on reducing the serum concentration of CRP and IL-6 compared to control groups in RCTs; however, the evidence suggests the efficacy is dependent on carotenoid species and doses. Amongst the available carotenoid supplements, astaxanthin exhibits the most promising anti-inflammatory efficacy in humans. A high dose of astaxanthin (12 mg per day) significantly reduced IL-6, CRP and TNF-α levels in older (> 50 years old) participants with T2D after 8 weeks [37]. In another human study, a moderate dose of astaxanthin (8 mg per day) was administrated for a longer period (12 weeks), and a significant reduction in IL-6 and CRP was observed in healthy middle-aged non-smoking males [113]. Further to support the anti-inflammatory property of astaxanthin, a study on trained teenage soccer players showed that supplementation of a moderate dose of astaxanthin (4 mg/d) for 12 weeks resulted in a reduction of CRP [17].

However, evidence of the efficacy of astaxanthin supplementation on reducing inflammation is inconsistent. A study that investigated low or moderate doses (2 or 8 mg per day) of astaxanthin did not show any protective effect against IL-6 and TNF-α accumulation in healthy young females after 8 weeks [181]. The absence of an anti-inflammatory effect in this study could be partly due to the low levels of IL-6 and TNF-α in healthy young subjects thus intervention to modulate these parameters might require a higher dose and a more extended period. Another human study on renal transplant patients suggested that a high dose of astaxanthin (12 mg/day) supplementation for 48 weeks did not significantly improve inflammatory markers such as plasma pentraxin-3 [52]. Current evidence on astaxanthin in human studies suggests that a moderate to high dose (4–12 mg per day) over a longer duration (over 12 weeks) could be considered for subjects with no or mild medical conditions as the most effective in anti-inflammation. However, direct clinical evidence is required to corroborate the view further. For those with severe medical conditions, more human studies are required to determine whether or not astaxanthin supplementation has clinical relevance.

Lutein and lycopene are common dietary carotenoids found in fruits and vegetables. Evidence of their ability to reduce inflammatory marker concentrations is mixed. A high dose of lutein supplement (> 20 mg/d, approximately 5–10-fold higher than regular dietary intake) administered daily for 12–24 weeks was found to significantly reduce plasma IL-6 and MCP-1 [274], CRP [256], and IL-1β [231] levels, whilst no significant change in CRP and IL-6 was observed in studies of lutein doses equal to or lower than 10 mg per day [64,78]. Similarly, a high dose (20 mg/day) of lycopene supplementation significantly reduced IL-6 and TNF-α levels in patients with COPD after 16 weeks [127]. However, the RCTs exploring the effects of a moderate dose (6–15 mg/day)of lycopene supplements reported no significant effect on reducing IL-6 and CRP in healthy participants [123,124,171] or in patients with CVD [70] after 8 weeks, in overweight middle-aged adults after 16 weeks [244], or in patients with prehypertension [184]. The RCT by Briviba et al. [32] reported that the lycopene tomato extract supplementation of 14.64 mg per day did not reduce the TNF-α in healthy smokers and non-smokers but significantly reduced IL-4 in healthy smokers [32].

Evidence regarding the anti-inflammatory effects of β-cryptoxanthin and crocin supplementation are also be reported. One recent RCT reported the protective effect of β-cryptoxanthin supplementation (6 mg/d) on reducing serum CRP in 46 NAFLD (non-alcoholic fatty liver disease) patients after a 12-week intervention [82]. Crocin treatment of 30 mg/d for 8 weeks was reported to significantly decrease serum CRP in osteoarthritis patients [188], and treatment of 15 mg/d for 16 weeks was observed to decrease serum CRP and MDA concentrations in patients under methadone maintenance treatment (MMT) programs [76] and TNF-α levels in patients with multiple sclerosis [77].

Human RCTs exploring the anti-inflammatory effects of β-carotene gave inconsistent conclusions despite abundant previous observational evidence supporting its protective anti-inflammatory effects [195]. Carrot juice fortified with 10 mg/day β-carotene administered over 8 weeks in patients with T2D did not significantly affect either serum CRP or IL-6 and, similarly, no significant change in CRP was observed after 8 weeks of 15 mg/d β-carotene supplementation in healthy adults [78]. Further clinical evidence is required to determine the anti-inflammatory effects of β-carotene in humans under differing conditions.

The inconsistent results observed in some human studies could be explained, at least partially, by differences in the bioaccessibility (i.e., the amount of an ingested nutrient that is available for absorption in gut) and bioavailability (i.e., the amount of an ingested nutrient that reaches the systemic circulation and the sites where it exerts the biological function) of carotenoids. After ingestion, carotenoids from the diet are dissolved in the fat phase and emulsified into lipid droplets in the stomach and duodenum [199]. The hydrolyzation of most xanthophyll esters follows this process by lipase or esterase to release free xanthophyll before absorption [30], whilst the remaining xanthophyll esters enter the enterocytes and are hydrolyzed or cleaved at the brush border [59]. The absorbed carotenoids are incorporated into major lipoproteins (i.e. very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)) and other lipids (i.e. phospholipids and cholesterols) into chylomicrons to be transported to the liver and other tissues (particularly in the brain, eyes, and the surface of skin and subcutaneous tissue) through blood circulation [198]. Because the absorption of carotenoids significantly depends on the binding vehicles (i.e. chylomicrons or mixed micelles), the bioaccessibility of dietary carotenoids is highly variable among the various types of carotenoids. An in vitro study demonstrated a limited bioaccessibility of β-carotene (between 4 % and 14 % in different forms of carrot) and lycopene (0.1–1.5 % in different forms of tomato) [200] but a higher bioaccessibility of xanthophyll (e.g. astaxanthin: >80 % recovery) [44]. It is hypothesized that the presence of hydroxylated group(s) in xanthophylls increases the solubility into the micellar binding vehicles and, thus, result in a higher bioaccessibility than carotenes [183,199]. This could be the potential reason that the clinical results of the association between dietary carotenoids and the oxidative stress remain inconsistent despite the accumulation of in vitro and in vivo, evidence demonstrating the efficacy of carotenoids in preventing and ameliorating inflammation. Because of the high heterogeneity of study design quality, characteristics of participants, and the nature of the intervention (e.g., dosage and delivery system), the efficacy of the carotenoids on anti-inflammatory function is not as yet established.

3.4. *Modulation of peroxisome proliferator-activated receptor γ (PPARγ)*

PPARγ is involved in immune cell proliferation and differentiation and inflammatory responses regulation [47,159], and regulation of the transcription of various genes in lipid and glucose metabolism via activating glucose transporter 4 (GLUT4) transcription [144,174]. As PPARγ expression has been reported in pulmonary cell types, such as inflammatory, mesenchymal, alveolar macrophages and airway epithelial cells [226], suppression of PPARγ expression could be associated with modulating the pulmonary inflammatory response [148]. The expression of PPARγ regulates oxidative stress and inflammation through its interaction with the NF-κB family in endothelial and vascular smooth muscle cells and macrophage-foam cells in human lungs [47]. Also, PPARγ reduces ROS and inhibits M1 macrophage polarization by inducing the expression of a range of antioxidants [47]. PPARγ agonists have been associated with reducing COPD and ARDS [208]. It has been postulated that enhancing PPARγ production could aid severe COVID-19 treatment by reducing oxidative-stress mediated hypercytokinemia and preventing organ injury [49]. Abdel-Massih et al. (2021) suggested using PPARγ agonists as adjunctive therapy to the COVID-19 vaccine throughout the pandemic [2]. PPARγ agonists, such as Thiazolidinediones (TZDs), and the natural form of PPARγ ligands, such as curcumin, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), have been proposed to ameliorate acute hypercytokinemia-associated lung injury in viral infection [49]. A possible mechanism of carotenoids in reducing the oxidative stress and inflammatory response is via acting as the agonists of PPARγ to increase the expression of PPARγ target gene to increase the interaction with the NF-κB family and inhibiting M1 macrophage polarization through inducing antioxidants expression.

Carotenoids and derivatives are among the reported agonists of PPARγ supported by in vitro studies [102]. Astaxanthin acted as an agonist of PPARγ by inducing the expression of PPARγ target genes, such as CD36 mRNA and liver X receptor (LXR) in thioglycollate-elicited peritoneal macrophages [102]. Astaxanthin inhibited the IL-8 expression and mitochondria dysfunction in *H. pylori*-infected gastric epithelial cells via the same mechanism [125]. Similarly, fucoxanthin and its metabolite fucoxanthinol have promoted the differentiation of adipocytes at the initial stage of treatment (days 0–2) by activating the expression of PPARγ [111]. Lutein was also reported to induce mRNA expression of PPARγ in bovine adipocytes [75]. Bixin and norbixin were reported to induce the expression of PPARγ by luciferase reporter assay using GAL4–PPAR chimera proteins in 3T3-L1 adipocytes [239].

In vivo studies also report that carotenoids can reduce inflammation via activating PPARγ. Crocin supplementation significantly ameliorated insulin sensitivity and serum glycemic profile in diabetic animals with modified lipid profiles by enhancing serum concentration of PPARγ and AMPK while inhibiting IL-6 and TNF-α [9]. Bixin and norbixin have also been shown to activate PPARγ in STZ-induced diabetic rats [207].

The available evidence from in vitro and in vivo studies demonstrates the therapeutic benefits of carotenoids as potential adjutants in regulating inflammation and preventing hypercytokinemia, possibly via modulating PPAR-γ expression.

3.5. *Blocking ACE2*

ACE2, which is responsible for modulating alveolar permeability, reducing acute lung injuries, and inhibiting lung fibrogenesis, is predominantly localized in alveolar epithelial and endothelial cells [170, 214]. ACE2 is also the entry point for SARS-CoV-2 invasion. The viral infection dysregulates the protective effect of the ACE2/MAD/G protein pathway and leads to further lung injuries [214]. Furthermore, ACE2 is expressed in various tissues in the human body: the upper respiratory system, type I and II alveolar epithelial cells in the lungs, the heart, endothelial cells, kidney tubular epithelium, enterocytes, and the pancreas, making these organs susceptible to infections [60,139,141, 250,295]. A possible mechanism of carotenoids is contributed by its ability to block the ACE2 via interacting with SARS-CoV-2 chimeric receptor-binding domain (RBD) to reduce the viral invasion and upregulate the protective function of the ACE2/MAD/G protein pathway to reduce the severity of the injuries following infection.

Current treatment for patients with COVID-19 includes ACE inhibitors (ACEIs) and Angiotensin II type-I receptor blockers (ARBs) to upregulate ACE2 levels [68]. Previous studies have also suggested that small molecules that can engage ACE2 through RBD may show promising therapeutic value in inhibiting the entry of respiratory syncytial virus by binding at the hydrophobic pocket of fusion glycoprotein [5, 189]. Ganai and Husaini (2021) screened the bioactive compounds in saffron for their anti-viral activities, including β-carotene, lycopene, lutein, crocin, picrocrocin and safranal (degradation product of carotenoid zeaxanthin) and observed *in silico* interaction of picrocrocin and lutein with surface receptor ACE2 to block the interaction between ACE2 and RBD [7]. A study of the antiviral activity from two marine polar xanthophylls, fucoxanthin and siphonaxanthin, also indicated that siphonaxanthin fits into the ACE2 binding region of SARS-CoV-2 chimeric RBD and demonstrated significant antiviral activity with an IC50 of 87.4 μM against SARS-CoV-2 entry [283]. The preliminary findings support the potential role of fucoxanthin and siphonaxanthin as candidates for COVID-19 treatments.

4. The role of carotenoids in prevention and reduction of comorbidities of COVID-19 patients

The initial correlation between coexisting comorbidities and poorer clinical outcomes in COVID-19 cases, including metabolic disorders (e.g., diabetes, obesity and hypertension) and CVD, was reported in a nationwide analysis of multiple small hospital-based cohorts in China [79,271,272,275]. Meta-analysis of co-morbidities in patients with underlying health conditions [228,284] has also confirmed a higher risk of severe COVID-19-related complications is associated with COPD and other co-morbidities including T2D, CVD, CKD, and cancer [85,178,271, 272,275].

4.1. *Protecting lung function*

ALI and ARDS are the most severe forms of COVID-19 complications. In addition to the direct damage to the alveolar epithelium, indirect damage is made to the intercellular junctions in the alveolar-capillary endothelium leading to the infiltration of immune cells (e.g. leukocytes, platelets, and plasma proteins) into the alveolar airspace to initiate diffuse alveolar damage [152,291]. The infiltration and migration of immune cells interact with resident macrophages to form edema [237]. The accumulation of cell debris, cytokines, and other proteins forms hyaline membrane deposition on the alveolar wall (i.e., characterized as patchy ground-glass densities) and eventually impedes air exchange in severe COVID-19 cases [175,291,298]. In addition to the potent anti-inflammatory and antiviral therapy, treatment protecting lung function should also be prioritized.

Several observational studies suggest that increased circulating carotenoids may support the prevention of inflammation- and age-related lung function decline (Table 3) [80,106,245]. Cross-sectional studies reported a positive correlation between lung function and circulating carotenoids [80,219] and carotenoid intake [95,220]. Total intake of dietary carotenoids is negatively associated with inflammation-related COPD in an observational study of approximately 4000 individuals (45 –64 years old) in the U.S. Jun, Root [106]. The 20-year follow-up Coronary Artery Risk Development in Young Adults (CARDIA) Study reported positive associations between higher serum carotenoids (e.g. β-carotene and β-cryptoxanthin) concentrations at baseline and lung function, measured as the maximum forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), after adjusting for age, race, height, study centre, amount of physical activity, smoking status, and BMI [245]. Higher circulating β-carotene, lutein/zeaxanthin, lycopene, and β-cryptoxanthin concentrations observed after 15 years of follow-up were associated with a significantly slower rate of decline from maximum observed lung function (i.e., a slower decline from the maximum FEV_1 and FVC) [245]. A recent epidemiology study examining the association between carotenoid intake and pulmonary function in approximately 15,000 participants aged 45–64 years observed a significant positive correlation between α-carotene, β-carotene, and β-cryptoxanthin and the FEV_1/FVC ratio [106].

Intervention studies also demonstrate the protective effect of carotenoids on lung function, although the studies were mainly on β-carotene (Table 4). One RCT of β-carotene and retinyl palmitate supplementation improved lung function (an approximately 70 ml increase in FVC ($p < 0.05$) in current and former smokers in an asbestos-exposed cohort [48]. Another RCT found that 6-months of treatment with β-carotene (1 mg/kg/day (maximum 50 mg/day) for 3 months + 10 mg/day for a further 3 months) in patients with cystic fibrosis effectively stabilized the plasma concentration of β-carotene but did not improve FEV_1 [201]. In a 2001 study by Samet et al. Samet et al., [215], the daily intake of a combination of ascorbate (250 mg), α-tocopherol (50 IU) and carrot and tomato juice (12 oz) significantly reduced the O^3-induced reductions in FEV_1 and FVC (by 30 % and 24 %, respectively).

Table 3
Epidemiological studies of the association between circulating carotenoids or dietary intake of carotenoids and lung function, risk of T2D and CVD in adults.

Exposure	Study design	Cohort	Outcome assessment	Association	Ref
Association with lung function					
Total carotenoid intake (α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin)	cross-sectional	ARIC Study, 1987–89	Pulmonary function: FEV$_1$ and FVC	α-carotene, β-carotene, β-cryptoxanthin had a significant association with FEV$_1$/FVC ratio	Jun, Root[106]
Dietary total carotene and serum β-carotene	cross-sectional	NHANES III, 1988–1994	Pulmonary function: FEV$_1$	An increase in serum β-carotene and dietary carotene was associated with an increase in FEV$_1$.	Hu, Cassano [95]
Dietary β-cryptoxanthin, lutein/ zeaxanthin, β-carotene, and retinol	cross-sectional	Erie and Niagara Counties, New York	Pulmonary function: FVC and FEV$_1$	Dietary lutein/zeaxanthin statistical significantly related to FVC % in never and current smokers	Schünemann et al.,[220]
Serum carotenoids	Prospective cohort	CARDIA, at year 0 (1985–1986) and at follow-up in years 2, 5, 10, and 20	Pulmonary function: FEV$_1$ and FVC	Baseline carotenoid concentrations and the 15-y increase in carotenoid concentrations were inversely associated with a decline from maximum observed lung function	Thyagarajan et al.,[245]
Serum β-cryptoxanthin, lutein/ zeaxanthin, β-carotene, and retinol	cross-sectional	Erie and Niagara Counties, New York	Pulmonary function: FEV$_1$ and FVC	Significant association of β-cryptoxanthin, lutein/zeaxanthin, β-carotene, and retinol with FEV$_1$ %	Schünemann et al.,[219]
Serum β-carotene	Prospective cohort	ECRHS, 8-year follow up	Pulmonary function: FEV$_1$	An increase in serum β-carotene was associated with a slower decline in FEV$_1$ over 10years	Guénégou et al., [80]
Association with glycemic control and T2D					
Serum β-carotene	Case-control	Multiple sites, Finland (1966 –1972)	T2D patients vs. control	Serum β-carotene concentration was inversely associated with risk of T2D	Reunanen et al., [202]
Serum concentrations of β-carotene and retinol, α-carotene.	Case-control	T2D patients, Saudi Arabia	T2D patients vs. control	Serum β-carotene concentration was significantly higher in control participants than those with diabetes.	Abahusain et al.,[1]
Serum β-carotene, lycopene, all carotenoids	cross-sectional	Phase I of the Third NHANES, USA (1988–1991)	glucose tolerance, or newly diagnosed diabetes	Serum β-carotene and lycopene was inversely associated with insulin resistance. All serum carotenoids were inversely associated with fasting insulin.	Ford et al.,[69]
Dietary intake of α-carotene, β-carotene, lycopene. Plasma concentration of α-carotene, β-carotene, lycopene.	cross-sectional	Botnia Dietary Study cohort, Finland (1994–1997)	OGTT; IVGTT; Insulin resistance	In men, dietary carotenoids were inversely associated with fasting plasma glucose, plasma β-carotene concentration was inversely associated with insulin resistance. In women, plasma β-carotene concentration was associated with fasting plasma glucose.	Ylönen et al., [285]
Dietary intake of α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, total carotenoids.	Prospective cohort	Finnish Mobile Clinic Health Examination Survey (1967–1972)	Risk of T2D	Dietary intake of β-cryptoxanthin was significantly associated with a reduced risk of T2D.	Montonen et al., [164]
Serum α- carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, lycopene, and total carotenoids	cross-sectional	6 random site in Queensland, Australia (Oct-Dec 2000)	OGTT; fasting insulin	Increasing quintiles of serum concentrations of α- carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, lycopene, and total carotenoids were inversely associated with 2-hr postprandial plasma glucose and fasting insulin concentration in non-smokers.	Coyne et al., [54]
serum α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/ zeaxanthin, and total carotenoids	Case-control	CARDIA Study & YALTA study (1985–2001) (18–30 yrs)	Risk of T2D; insulin resistance	All serum carotenoids concentrations were inversely associated with the risk of T2D. Year 15 serum insulin and insulin resistance values were inversely related to serum total carotenoids concentration in nonsmokers.	Hozawa et al., [94]
Dietary intake of lycopene	Prospective cohort	WHS, US (1992–2003)	Risk of T2D	Dietary intake of lycopene is not associated with the risk of T2D.	Wang et al., [254,255]
Plasma α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin	Nested case-control	WHS, US (1992–2003)	Risk of T2D	There was no prospective association between baseline plasma carotenoids and the risk of T2D in middle-aged and older women.	Wang et al., [254,255]
Total plasma carotenoid concentration	Prospective cohort	EVA Study, Nantes, France (1991–1993 9 years follow-up)	Risk of dysglycemia	Risk of dysglycemia was significantly lower in participants in the highest quartile of total plasma carotenoids concentration compared with participants in the lowest quartile.	Akbaraly et al., [8]
Serum β-carotene	Prospective cohort	ATBC study, Finland (1985–1993)	Risk of T2D	Serum concentration of β-carotene was not associated with the risk of T2D.	Kataja-Tuomola et al.,[115]
Serum lycopene, α-carotene, β-carotene, lutein, β-cryptoxanthin, zeaxanthin	Cross-sectional	The Mikkabi Cohort Study, Japan (2003 cohort I and 2005 cohort II - 2013)	Fasting plasma glucose	The fasting plasma glucose level was inversely correlated with serum lycopene and β-carotene in non-smokers. Serum β-carotene concentration was correlated with fasting plasma glucose levels in current smokers than in non-smokers.	Sugiura et al., [234]
Dietary intake of β-carotene Serum β-carotene	Prospective cohort	ULSAM study, Sweden (10-, 20-, and 27-years follow-up)	Risk of T2D	Relative risk is inversely associated to increase in dietary intake of β-carotene and serum β-carotene concentration.	Arnlov et al., [13]
		SU.VI.MAX primary prevention trial		Baseline serum concentrations of β-carotene was negatively associated with plasma glucose.	Czernichow et al.,[56]

(continued on next page)

Table 3 (*continued*)

Exposure	Study design	Cohort	Outcome assessment	Association	Ref
Serum antioxidant supplements (β-carotene, vitamin C, vitamin E, zinc, selenium)	Baseline analysis of randomized controlled trial		Metabolic syndrome components		
Dietary intake of α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin	Prospective cohort	ATBC study, Finland (1985–1993)	Risk of T2D	Dietary carotenoids were not associated with a decreased risk of T2D in middle-aged male smokers.	Kataja-Tuomola et al.,[116]
Serum zeaxanthin/lutein, β-Cryptoxanthin, lycopene, α-Carotene, β-Carotene	cross-sectional	Yakumo Study, Japan (2005–2008)	Metabolic syndrome components	Glucose was negatively associated with serum β-carotene concentration in both sexes.	Suzuki et al., [235]
Dietary intake of β-carotene:	Prospective cohort	Multi-ethnic cohort of Atherosclerosis	Risk of T2D	Risk of T2D is inversely associated to increase in dietary intake of β-carotene	de Oliveira Otto et al.,[176]
Dietary intake of α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, total carotenoids	Prospective cohort	EPIC- Netherland study (1993–2003)	Risk of T2D	High α-carotene intake and high β-carotene intake are associated with lower risk of T2D.	Sluijs et al., [229]
Serum α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, total carotenoids	Prospective cohort	The Mikkabi Cohort Study, Japan (2003 cohort I and 2005 cohort II - 2013)	Risk of T2D	The highest tercile of serum α-carotene, β-cryptoxanthin, and total provitamin A carotenoids are associated with reduced risk of T2D. Serum β-carotene and zeaxanthin are associated with borderline risk reduction, however NOT significant.	Sugiura et al., [233]
Dietary intake of α-carotene, β-carotene, lutein/zeaxanthin	Prospective cohort	NPAAS Feeding Study, US (2010–2014)	Risk of T2D	Higher dietary intake of α-carotene, β-carotene, and lutein/zeaxanthin is inversely associated with the risk of T2D.	Prentice et al., [190]
Serum carotenoids (Retinol, α-carotene, β-carotene, ζ -carotene, lutein, lycopene, phytoene, and phytofluene)	cross-sectional	2 cohorts, Sydney, Australia (2008–2013)	Insulin resistance, and serum insulin	Insulin resistance correlated inversely with serum carotenoids.	Harari et al., [83]
Plasma α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, total carotenoids	Nested prospective cohort	EPIC-InterAct study (Nested within the European EPIC study) (1993 –2003)	Risk of T2D	Plasma α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein and total carotenoids are inversely associated with the risk of T2D. Plasma zeaxanthin was NOT associated with reduced risk of T2D.	Zheng et al., [295]
Reduce the risk associated with pre-infection CVD					
Dietary intake of β-carotene	cross-sectional	NHANES 2003–2006 cohort	CVD risk factors	Dietary intake of β-carotene was inversely associated to serum concentrations of LDL-C and homocysteine.	Wang et al., [259]
Plasma and dietary intake of carotenoids	cross-sectional	CUDAS study	CVD risk factors	Plasma lycopene was negatively associated with carotid artery IMT.	McQuillan et al.,[153]
Plasma of carotenoids	cross-sectional	the Los Angeles Atherosclerosis Study	CVD risk factors	18-month change in IMT was inversely related to lutein, β-cryptoxanthin, zeaxanthin and α-carotene.	Dwyer et al., [61]

Abbreviation: 75-g oral glucose-tolerance test, OGTT; Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, ATBC; cardiovascular disease, CVD; Coronary Artery Risk Development in Young Adults, CARDIA; European Community Respiratory Health Survey, ECRHS; European Prospective Investigation into Cancer and Nutrition, EPIC; forced vital capacity, FVC; intima-media (wall) thickness, IMT; intravenous glucose tolerance test, IVGTT; low-density lipoprotein cholesterol, LDL-C; National Health and Nutrition Examination Survey, NHANES; SUpplementation en VItamines et Mineŕaux AntioXydants, SU.VI.MAX; Swedish Uppsala Longitudinal Study of Adult men Study, ULSAM; the Atherosclerosis Risk In Communities, ARIC; The Epidemiology of Vascular Ageing, EVA; The Nutrition and Physical Activity Assessment Study, NPAAS; The Perth Carotid Ultrasound Disease Assessment study, CUDAS; the ratio of forced expiratory volume in one second, FEV_1; The Young Adult Longitudinal Trends in Antioxidants, YALTA; Type 2 diabetes, T2D; Women's Health Study, WHS.

4.2. Improving glycemic control

Poor glycemic control was linked to the upregulation of ACE2 expression [197,267], which may influence susceptibility to infection (or more severe infection). This phenomenon increases the vulnerability to developing severe COVID illness among T2D patients who have poorly controlled pre-infection glycaemia which may have contributed to their poorer recovery rate [38,39,40,41]. T2D patients experience oxidative stress, including the generation of hydroxyl radicals through the glucose auto-oxidation and polyol (sorbitol) pathway, which further worsens insulin resistance and reduces insulin secretion [87]. In addition, the binding of SARS-CoV-2 to ACE2 disrupts the generation of Ang (1−7), leading to downregulation of the major glucose transporter, GLUT4 [177,218]. The double impact of viral infection and insulin resistance enhances stress-sensitive signaling pathways, such as NF-κB, c-Jun N-terminal kinase (JNK), MAPK and hexosamine [87], further exacerbating the systemic inflammation in COVID-19 patients. A small amelioration in pre-infection glycemic control (reducing HbA1c from 8.0 % to 6.0 %) can lead to a better outcome (reduced relative risk (RR) of severe COVID-19 illness from 1.0 to 0.71 (95 %CI: 0.52–0.87) in diabetic patients with COVID-19 infection [85]. The epidemiological studies of the association between dietary carotenoids or circulating carotenoids and the risk of T2D are listed in Table 3.

Among carotenoids, fucoxanthin exhibited the most promising attributes in improving glucose control. One potential mechanism of fucoxanthin in improving insulin resistance is via regulating GLUT4 [144,174]. Fucoxanthin supplementation was reported to restore the attenuated GLUT4 expression and increase the update of glucose in skeletal muscle in C57BL/6 J mice fed a high-fat diet [92,144,174], and in diabetic/obese KK-Ay mice [143]. Another plausible mechanism is that fucoxanthin may inhibit macrophage infiltration and downregulate the pro-inflammatory adipokine expression and secretion in abdominal white adipose tissue, leading to improved insulin resistance and glycemic management [92,143]. Furthermore, fucoxanthin may also improve insulin sensitivity by inhibiting protein tyrosine phosphatase 1B (PTP1B) on the cytoplasmic surface of the ER in insulin-targeted tissue (i.e. liver, fat, muscle, and pancreas) [107,246]. In addition, fucoxanthin extract (over 200 μM) from brown algae *Eisenia bicyclis* and *Undaria pinnatifida* [107] and from *Undaria pinnatifida* (*Laminaria digitata* and *Sargassum polycystum*) [287] showed α-glucosidase inhibitory effects

Table 4
Randomized controlled trials of the effect of dietary carotenoids on protecting lung function, improve glycemic control, and reduce CVD risk.

Intervention	Study participants	Dose	Duration	Main outcomes	Ref
Protect lung function					
β-carotene vs placebo	Participants with cystic fibrosis, 6.7–27.7 yr old	1 mg/kg/day (maximum 50 mg/day) for 3 months + 10 mg/day for a further 3 months	6 months	FEV_1 did not change significantly in either group	Renner et al.,[201]
Ascorbate + α-tocopherol + carrot and tomato juice	Healthy nonsmoking adults, 18–35 yr old (crossover)	250 mg of ascorbate + 50 IU of α-tocopherol + 12 oz carrot and tomato juice per day	2 weeks	O3-induced reductions in FEV_1 and FVC were 30 % and 24 % smaller, respectively, in the supplemented cohort.	Samet et al., [215]
Tomato extract (lycopene) vs tomato juice vs placebo	Asthmatic adults (crossover)	tomato juice (45 mg lycopene/d) or tomato extract capsules (45 mg lycopene/d)	10 days	Treatment with both tomato juice and extract reduced airway neutrophil influx. No significant change in FEV_1	Wood et al., [261]
Softgel of mixed carotenoids vs multivitamin control without antioxidant enrichment	Pancreatic-insufficient subjects with cystic fibrosis	lutein (5 mg/d), zeaxanthin (1 mg/d), lycopene (1 mg/d)	16 weeks	No significant differences between groups were observed in the change in mean FEV_1 or FVC.	Sagel et al., [212]
Improve glycemic control					
Crocin vs. placebo	T2D patients	15 mg/d	12 weeks	↓Plasma glucose; insulin; HbA1c; SBP; HOMA-IR ↑Insulin sensitivity	Behrouz et al.,[21]
Fucoxanthin vs. placebo	Normal-weight and obese adults	Study 1: 1 mg/d Study 2: 2 mg/d	8 weeks	↓HbA1c	Mikami et al.,[158, 157]
Reduce CVD risk					
Astaxanthin vs placebo	Non-obese subjects with fasting serum triglyceride of 120–200 mg/dl and without diabetes and hypertension	6 mg/d	12 weeks	↑HDL-C	Yoshida et al.,[286]
		12 mg/d		↓triglyceride ↑HDL-C; adiponectin	
		18 mg/d		↓triglyceride ↑adiponectin	
Astaxanthin vs placebo	Healthy adults	1.8 mg/d	14 days	No effect	Iwamoto et al.,[103]
		3.6 mg/d		↑LDL-C lag time (↓LDL-C oxidation)	
		14.4 mg/d		↑LDL-C lag time (↓LDL-C oxidation)	
		21.6 mg/d		↑LDL-C lag time (↓LDL-C oxidation)	

Abbreviation: cardiovascular disease, CVD; forced expiratory volume in one second, FEV_1; forced vital capacity, FVC; high-density lipoprotein cholesterol, HDL-C; Homeostatic Model Assessment for Insulin Resistance, HOMA-IR; low-density lipoprotein cholesterol, LDL-C; Systolic blood pressure, SBP; type 2 diabetes, T2D.

similar to acarbose, which delays the digestion and absorption of glucose. Like fucoxanthin, carotenoids such as lutein and zeaxanthin have also been shown to demonstrate α-glucosidase inhibitory effects [192].

The glycemic regulatory effect of carotenoids besides fucoxanthin has also been reported in animal models such as diabetic mice models [207,223,239,248,270], high fat-fed mice [24,25], SHR/NDmcr-cp (cp/cp), and a rat model of metabolic syndrome [98]. The PPARγ activating pathway was also implicated in glycemic control by carotenoids. Bixin and astaxanthin demonstrated the ability to attenuate blood glucose by binding and activating PPARγ (i.e. agonists of PPARγ) and enhancing carbohydrate metabolism [58,133]. Another underlining pathway for carotenoids to combat insulin resistance is by regulating serine phosphorylation of IRS-1 by blocking JNK and IKKβ [25]. Crocetin, a natural apocarotenoid in *Gardenia jasminoides*, has been reported to block JNK and IKKβ signaling pathways by inhibiting PKCθ to reduce palmitate-induced insulin resistance and increase insulin-induced glucose update in adipocytes [278].

Several epidemiological studies have revealed the negative association between serum carotenoid (β-carotene, lycopene, lutein) concentrations and fasting serum insulin [229,285] and HbA$_{1c}$ [236] (Table 3). Although human trials exploring the anti-diabetic effect of carotenoids are very limited, the results are promising (Table 4). In an 8-week RCT, a significant reduction in HbA1c levels (−0.14 % ± 0.05) was observed in obese adults who received 2 mg/d fucoxanthin compared to the placebo group [157,158]. In a recent clinical trial of diabetic patients, crocin supplements significantly improved fasting blood sugar, HbA1c, plasma insulin level, insulin resistance and insulin sensitivity [21].

4.3. Protection from CVD

Pre-infection CVD has been recognized to increase the severity and mortality of COVID-19 [16]. The Australia and New Zealand consensus statement reported COVID-19 cases were associated with acute cardiac manifestations, including left ventricular dysfunction, heart failure, arrhythmias and acute coronary syndromes [288]. A 5-fold increased mortality risk was associated with patients with pre-infection CVD (10.5 % mortality rate) compared to those with other pre-infection comorbidities (0.9 % mortality rate) [264]. A meta-analysis of over 46,000 cases in China also reported the most common co-morbidities to encompass CVD and hypertension [276,277,280]. It is hypothesized that SARS-CoV-2 targets CVD systems through various mechanisms [50]: (1) binding ACE2 suppresses the anti-inflammatory ACE2/Ang(1−7)/Mas pathway, which may lead to lung tissue damage and acute myocardial injury [135,137,269]; (2) cytokine storm causes systemic inflammation that may precipitate multiple organ damage and failure and increase coronary blood flow to cause plaque rupture (i.e., prothrombotic milieu); (3) hypoxia caused by impaired lung function may attenuate the myocardial oxygen demand-supply ratio to cause acute myocardial injury [16,138]; (4) blocking and degrading ACE2 may result in hypokalemia which increases the risk of tachyarrhythmia in patients with pre-infection CVD [38,39,40,41].

Pre-clinical evidence suggests that carotenoids such as astaxanthin could improve the circulating blood lipid profile by increasing HDL-C, reducing LDL-C, triglycerides and lipid peroxidation [103]. In human studies (Table 4), astaxanthin improved circulating triglyceride and HDL-C in a dose-response manner in a 12-week randomized placebo-controlled trial of 61 obese participants (20–65 years old) [286] and significantly inhibited LDL oxidation in 24 healthy adults (1.8–21.6 mg/d for 2 weeks) [103].

Epidemiological evidence suggests that the antioxidant properties of carotenoids may prevent the oxidation of LDL-C, which exerts proatherogenic properties (Table 3). A study reported by Wang et al. on the association between dietary carotenoids and the CVD risk biomarkers in

NHANES 2003–2006 cohort (1312 males and 1544 females) observed that the dietary intake of β-carotene was inversely associated with serum concentrations of LDL-C and homocysteine [259]. Furthermore, lutein [153] and zeaxanthin [61] were negatively associated with serum LDL-C and homocysteine and positively associated with HDL-C; lycopene and total carotenoids were negatively associated with serum homocysteine.

In addition, carotenoids also exhibit a positive effect on CVD associated conditions such as hypertension and ischemia. Animal studies have found that astaxanthin exhibits a hypotensive effect via modulating NO in spontaneously hypertensive rats [97,163] and rats with elevated blood pressure and glucose-insulin perturbation [191]. Furthermore, it is hypothesized that lutein potentially protects the myocardium from ischemia or reperfusion injury by preventing myocyte apoptosis and reducing oxidative stress [6].

Based on current evidence, carotenoids can potentially improve blood pressure, dyslipidemia and cardiovascular health with CVD comorbidity [97,163,191].

5. Conclusion and future perspectives

Carotenoids could potentially protect against COVID-19 symptoms by regulating COVID-19 induced over-production of pro-inflammatory cytokines, chemokines, pro-inflammatory enzymes and adhesion molecules, modulating PPARγ expression, and blocking the cellular receptor ACE2. Amongst the available carotenoid supplements, a moderate to high dose (4–12 mg/day) of astaxanthin for over 12 weeks as a potential anti-inflammatory adjunctive therapy for healthy subjects with no or mild medical conditions appears to show the most promising potency in immunomodulation. Further human studies are required to evaluate the clinical relevance of astaxanthin supplementation in people with more severe health conditions. Lutein, lycopene and crocin are also proposed to be potential immunomodulatory candidates. However, it can be hypothesized that either a higher effective dose (>20 mg/day) or a more extended intervention period (>16 weeks) may be required as compared to that of astaxanthin.

As clinical trials on other carotenoids are limited, well-designed future RCTs are necessary to provide robust evidence on the most appropriate choice of carotenoids to support immune homeostasis and function. To identify and research the efficacy of ACE2 inhibitors, *in silico* techniques (such as molecular docking and virtual screening) and bibliometric analysis can be efficiently used to discover and systematically screen more carotenoids that has ACEI potentials before further the in vitro and *in* vivo studies [168]. Further, a range of pharmacokinetics considerations (optimal doses, upper levels of intake, bioavailability and bioaccessibility factors), the duration of administration, characterization of the efficacy of each compound, and possible side effects remain to be determined.

In conclusion, clinical evidence pointed out that the efficacy of carotenoids immunomodulation that could potentially benefit reducing the risk of COVID-19 varies in different types of carotenoids. Nevertheless, robustly designed in vitro*, in vivo*, and human studies are required to establish a clear understanding of the interplay between isolated carotenoids and immunity before utilization of carotenoid supplementation in the management of COVID-19 could be recommended. However, encouraging increased fruit and vegetable consumption and thereby enhancing carotenoid intake remains sound advice!.

Funding

This work was supported by the National Natural Science Foundation of China (grant number 31601472); Guangdong Province Zhujiang Talent Program (grant number 2019ZT08H476); and Shenzhen Science and Technology Program (grant number KQTD20180412181334790).

CRediT authorship contribution statement

Conception of idea: LWL, JC, FC. Design of review outline: LWL, JC. Sourcing literature: LWL, JC, YG. Drafting the manuscript: LWL, JC, YG. Reviewing and revising the manuscript: SYQ, MF, CTE, ML, MW. Editing the manuscript: LWL, JC, FC. All authors approved the final version for submission.

Disclosure statement

No potential conflict of interest was reported by the authors.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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