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Biomedicine & Pharmacotherapy 132 (2020) 110886

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Potential of natural astaxanthin in alleviating the risk of cytokine storm in COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Cytokine storm
Acute respiratory distress syndrome
Astaxanthin
Antioxidant
Anti-inflammatory

ABSTRACT

Host excessive inflammatory immune response to SARS-CoV-2 infection is thought to underpin the pathogenesis of COVID-19 associated severe pneumonitis and acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Once an immunological complication like cytokine storm occurs, anti-viral based monotherapy alone is not enough. Additional anti-inflammatory treatment is recommended. It must be noted that anti-inflammatory drugs such as JAK inhibitors, IL-6 inhibitors, TNF-α inhibitors, colchicine, etc., have been either suggested or are under trials for managing cytokine storm in COVID-19 infections. Natural astaxanthin (ASX) has a clinically proven safety profile and has antioxidant, anti-inflammatory, and immunomodulatory properties. There is evidence from preclinical studies that supports its preventive actions against ALI/ARDS. Moreover, ASX has a potent PPARs activity. Therefore, it is plausible to speculate that ASX could be considered as a potential adjunctive supplement. Here, we summarize the mounting evidence where ASX is shown to exert protective effect by regulating the expression of pro-inflammatory factors IL-1β, IL-6, IL-8 and TNF-α. We present reports where ASX is shown to prevent against oxidative damage and attenuate exacerbation of the inflammatory responses by regulating signaling pathways like NF-κB, NLRP3 and JAK/STAT. These evidences provide a rationale for considering natural astaxanthin as a therapeutic agent against inflammatory cytokine storm and associated risks in COVID-19 infection and this suggestion requires further validation with clinical studies.

1. Introduction

The recent emergence of Coronavirus Disease-2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is highly contagious and has resulted in a global public health emergency. According to the World Health Organization (WHO), the pandemic has more than 27 million confirmed cases worldwide with over 8,97,000 deaths, as of the first week of September 2020. These numbers are changing rapidly and regularly updated in the WHO website at https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Treatment has been empirical and there are no licensed COVID-19 vaccine or drugs for humans so far. Without any definitive treatment, the current standard care is supportive treatment.

SARS-CoV-2 is a β-coronavirus containing positive-sense single stranded RNA and belongs to the family Coronaviridae of order Nidovirales [1]. SARS-CoV-2 is partially related to SARS-CoV (~79 % similarity) and MERS-CoV (~50 % similarity), according to genome sequence analysis [2]. Although the underlying pathophysiology of COVID-19 has not been completely understood yet, available evidence suggests that COVID-19 clinical features are more or less similar to SARS-CoV and MERS-CoV infections [2–7]. SARS-CoV-2 infection triggers a local or systemic inflammation via activation of immune

Abbreviations: ALT, alanine transaminase; AST, aminotransferase; CCL-3, chemokine (C-C motif) ligand 3; COX-2, cyclooxygenase-2; CRP, C-reactive protein; dsRNA, double stranded ribonucleic acid; FOXO3, forkhead box O3 gene; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSH, glutathione; HCFs, human cardiac fibroblasts; HDAC4, histone deacetylase 4; HGF, hepatocyte growth factor; HIF-1α, hypoxia inducible factor 1α; ICAM-1, intercellular adhesion molecule-1; IkB, inhibitor nuclear factor-kappa B; IL-1ra, interleukin-1 receptor antagonist; LDH, lactate dehydrogenase; LFA-1, leukocyte function antigen 1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MDA, malondialdehyde; MIP, macrophage inflammatory protein; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; MSCs, mesenchymal stem cells; NO, nitric oxide; NT, nitrotyrosine; PDGF, platelet-derived growth factor; PGE2, prostaglandin E_2; PPARs, peroxisome proliferator-activated receptors; SOD, superoxide dismutase; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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https://doi.org/10.1016/j.biopha.2020.110886
Received 3 May 2020; Received in revised form 5 October 2020; Accepted 12 October 2020
Available online 16 October 2020

inflammatory signaling pathways. Mounting evidences suggest that in addition to direct viral damage, uncontrolled inflammation due to dysregulated host immune response contributes to disease severity and death [2–7]. Consistent with this hypothesis, patients with severe COVID-19 have been noted to have significant increase in serum level of inflammatory markers, including inflammatory cytokines and chemokines, C-reactive protein (CRP), ferritin and D-dimer, hepatic dysfunction, disseminated intravascular coagulation (DIC) and thrombotic tendency, thereby indicating the occurrence of immunological complications like, macrophage activation syndrome (MAS) or cytokine storm syndrome (CSS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH) [2–6]. The pathogenic inflammation, also referred to as CSS bears similarities with the cytokine release syndrome (CRS) observed in cancer patients treated with chimeric antigen receptor modified T cells (CAR-T) [6]. Due to the hyperactive nature of the immune responses with severe COVID-19, repurposing of several disease-modifying anti-rheumatic drugs (DMARDs), such as tocilizumab (IL-6 receptor inhibitor), baricitinib (JAK inhibitor) and anakinra (IL-1 receptor antagonist), have been proposed as potential treatments for COVID-19 [2–6].

ASX (3,3′-two hydroxyl-4,4′-two ketone-beta, beta'-carotene), an oxycarotenoid of predominantly microalgal origin, is a potent antioxidant with immunomodulatory, anti-inflammatory and anticancer properties. ASX has been shown to exert diverse health benefits therapeutically [8–15]. ASX has been shown to be an effective inhibitor of oxidative damage [14]; its immunomodulatory and anti-inflammatory effects have also been clearly demonstrated [9,11–17]. Previous studies have documented the positive effects of ASX in alleviating ALI/ARDS caused due to hyper-inflammatory complications [12,13]. The inhibitory action of ASX on macrophage activation, phosphorylation of nuclear factor kappa B (NF-κB), JAK (Janus kinase)/STAT (signal transducer and activator transcription), CRP, interleukin (IL)-6, IL-1β, cyclooxygenase (COX)-2 and TNF-α have been well documented [8,9,11–17].

In this context, the microalgae derived ASX was anticipated to be useful in the management of cytokine storm (CS) in COVID-19. Here, we provide an overview of the available evidence on the protective role of ASX against damages due to oxidative stress and inflammatory conditions indirectly indicating its possible benefits in the management of inflammatory CS in COVID-19 infection.

2. Pathogenesis of COVID-19 infection

The majority (about 80 %) of the SARS-CoV-2 infections is asymptomatic or exhibit mild to moderate symptoms of COVID-19. However, approximately 15 % of the infections, progress to severe pneumonia and about 5% eventually develop ARDS, septic shock and multiple organ failure [3]. Symptomatic COVID-19 patients typically exhibit fever, fatigue, myalgia, non-productive cough, headache, sore throat and shortness of breath [3]. At severity, the disease is characterized by significantly high serum levels of D-dimer, LDH, CRP and ferritin as well as a tendency for monocytosis, lymphopenia, a low number of natural killer (NK) and cytotoxic T cells. There is also a tendency for DIC, reflecting the involvement of MAS and CSS [2–6,18–23]. It has been generally recognized that the COVID-19 disease exaggeration till the late stage is not only attributed to direct viral damage, but also to a consequence of immune-mediated inflammatory injury induced by SARS-CoV-2 [2–7].

Host immune response clearly plays a crucial role in the host defense against SARS-CoV-2 infection and progression of COVID-19 disease [4,6]. Notably, SARS-CoV-2 infection activates both innate and adaptive immune response, thus sustaining the resolution of COVID-19 [4]. While a rapid and well-coordinated immune response represents the host's first line of defense against viral infection, an excessive inflammatory innate response coupled with a dysregulated adaptive immune defense may cause severe tissue damage both at the site of virus entry and at the systemic level [18,22]. Clinical evidence suggests that excessive pro-inflammatory response is the cause for induction of an immune pathology that results in the development of ALI, ARDS, acute cardiac injury, sepsis and multiorgan failure in COVID-19 (Table 1) [3,7,18–23].

The relevant changes that occur in both innate and adaptive immune systems during SARS-CoV-2 infection have been highlighted by several authors [2–6,18,20–23]. Lymphocytopenia and a modulation in total neutrophils have been reported as common hallmarks and are likely to be directly correlated with disease severity and death [3,4,7,18]. Significant decrease in serum levels of absolute number of CD4+ cells, CD8+ cells, B cells and NK cells as well as a decrease in monocytes, eosinophils and basophils have been reported in patients with severe COVID-19 [3,18–21,23]. In addition, most of patients with severe COVID-19 have been reported to display significantly high serum levels of pro-inflammatory cytokines (e.g. IL-1β, IL-2, IL-6, IL-8, IL-17 and TNF-α) and chemokines (e.g., MCP-1, IP-10, MIP1-α, G-CSF, GM-CSF and CCL-3) [3,18–21,23].

Additionally, the presumed ability of SARS-CoV-2 to evade the host's antiviral immune response also has raised a critical aspect concerning the disease severity [4,18]. For example, SARS-CoV and MERS-CoV escape and suppress the signaling pathways mediated by type I Interferon (IFN) to heighten their anti-viral defenses [4]. Based on the genomic identity of SARS-CoV-2 with SARS-CoV, it is speculative that SARS-CoV-2 can also adopt similar strategies to modulate the host innate immune response, thus suppressing immune detection and dampening anti-viral immune defenses [4].

2.1. Inflammatory cytokine storm and tissue damage

Accumulating clinical evidence from severe COVID-19 patients suggests that CS plays a crucial role in the pathogenesis of COVID-19 [3,18–23]. CS refers to a systemic acute-inflammatory manifestation characterized by an upsurge in immune cells and cytokine levels. This has been proposed as one of the key leading factors that trigger the pathological process leading to plasma leakage, vascular permeability and DIC as observed in severe COVID-19 patients [18–23]. Huang et al. [3] reported that plasma concentrations of IL-1β, IL-7, IL-8, IL-9, IL-10, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNF-α and VEGF were higher in both ICU (intensive care unit) patients and non-ICU patients than in healthy adults. Moreover, plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α and TNF-α in ICU patients were reported higher than non-ICU patients, thus indicating that the CS might be correlated with disease severity [3]. Plasma levels of 15 cytokines, namely IFN-α2, IFN-γ, IL-1ra, IL-1α, IL-2, IL-4, IL-7, IL-10, IL-12, IL-17, IP-10, G-CSF, M-CSF, HGF and PDGF-BB have been reported to linearly associated with lung injury based on Murray score and this could be used to predict the severity of COVID-19 [23]. In another study, Chen et al. [21] found that macrophage-related pro-inflammatory cytokines, particularly IL-6, IL-10 and TNF-α, were significantly higher in majority of severe COVID-19 cases. The immunological features, such as significant increase in serum levels of IL-6, TNF-α, IL-2R, IL-10, CD14+ and CD16+ along with the significant decrease of lymphocytes are clearly distinguishable in severe COVID-19 patients (Table 2) [3,18,20,21].

Evidence from literature indicates that the CS observed in COVID-19 resembles that occurring in CRS, a form of Systemic Inflammatory Response Syndrome (SIRS) and in sHLH, a hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia with multiorgan failure [2,4,6,23]. Blocking of pro-pathogenic cytokines has been used clinically for the treatment of autoimmune or auto-inflammatory diseases [23]. Therefore, existing modulators of inflammatory cytokines have been repurposed as a therapeutic strategy to alleviate the risk of hypercytokinemia or CS in COVID-19 patients.

2.2. Putative inflammatory signaling pathways triggered by SARS-CoV-2

The structural similarities of SARS-CoV-2 as well as the analogies in

Table 1
Patterns of symptoms along with cytokines and chemokines, and T cell lymphopenia in patients related to the severity of COVID-19 [3,7,18–23].

State of COVID-19	Asymptomatic/pre-symptomatic	Mild or moderate	Severe
Symptoms	No symptoms	Fever, headache, dry cough, myalgia, fatigue, dyspnea	Fever, dry cough, fatigue, ALI, ARDS or MOF
Cytokines & chemokines	No change	↑IL-6, ↑IL-10, ↑TNF-α	↑↑IL-2, ↑↑IL-6, ↑↑ IL-10, ↑↑TNF-α, ↑↑MCP-1, ↑↑CRP, ↑GM-CSF
T cell lymphopenia	No change	↓Lymphocytes (CD4 + T, CD8 + T)	↓↓Lymphocytes (CD4 + T, especially CD8 + T)

↑ increased; ↑↑ severe increased; ↓ decreased; ↓↓ severe decreased.

Table 2
Immunological characteristics of patients with moderate and severe COVID-19.

COVID-19 non-severe/ moderate	COVID-19 severe	References
↓Lymphocytes, ↑PMNs	↑IL-2, ↑IL-7, ↑IP-10, ↑MIP1A, ↑TNF-α	Huang et al. [3]
↓Lymphocytes, ↓Monocytes,	↓↓ Lymphocytes	Zhou et al. [18]
↓CD4+, →PMNs, →B, →NK, ↑Monocytes CD14+, ↑Monocytes CD16+	↓↓ Monocytes, ↓CD4+ (↑CD69+ CD38+ CD44+) ↑CD8+, ↑IFN-γ+, ↑GM-CSF+ ↑↑ Monocytes CD14+ ↑↑ Monocytes CD16+	
	↑↑ CD4+ HLADR+, ↑↑ CD8+ CD38+, ↑↑ CD4+ CCR6+ Th17	Xu et al. [20]
Lymphocytes↓	↓↓ Lymphocytes,	Chen et al. [21]
↑IL-2R, ↑IL-6, ↑IL-10, ↑TNF-α, →IL-1β, →IL-8	↓CD4 + T, ↓CD8 + T, ↑↑ IL-2R, ↑↑ IL-6, ↑↑ IL-10, ↑↑ TNF-α	

→ normal values, ↓ decreased, ↓↓ severe decreased, ↑ increased, ↑↑ severe increased.

the infection mechanisms with SARS-CoV [24] give reason to speculate that SARS-CoV-2 infection may induce the activation of shared intracellular pathways, such as IRF3 (IFN regulatory factor-3), NF-κB and JAK/STAT signaling pathways [4]. However, it is yet to be demonstrated that such similarities between SARS-CoV and SARS-CoV-2 can be directly translated into pathological outcomes [4].

The innate immunity, which acts as the first defense barrier against any pathogen and determines the activation of immune response, could play an important role in the development of CS and be responsible for boosting more severe forms [25,26]. Toll like receptors (TLRs) that recognize pathogen-associated molecular patterns (PAMPs) are involved in the activation of innate immunity [25,26]. Upon entry of SARS-CoVs into the host cell by entry receptor angiotensin-converting enzyme-2 (ACE2), the viral RNAs, as PAMPs, are detected by the pattern recognition receptors (PRRs), such as TLRs and consequently results in immune cell activation [4,26,27]. The viral genomic RNA or the intermediates during viral replication, including dsRNA, are recognized by TLR3 and TRL7/8, and cytoplasmic RNA sensors, namely retinoic acid-inducible gene-I (RIG-I)/melanoma differentiation-associated protein 5 (MDA5) [25]. Consistently, TLRs have been reported to activate different signaling pathways in human CD14+ monocytes, correlating with differential type I IFN and cytokine secretion involved in CD4 + T cell polarization [4,25]. As a result, downstream transduction pathways in antiviral response, such as IRF3, NF-κB and JAK/STAT, are activated [4,25].

TLR3 is highly expressed on dendritic cells, placenta and pancreas, and its activation through TRIF (TIR-domain-containing adaptor-inducing interferon-β) pathway, determines the activation of NF-κB [25,26]. TLR7 is expressed in human plasmacytoid (pDCs), B cells, epithelial cells, keratinocytes and hepatocytes [26]. TLR7 activates myeloid differentiation primary response 88 (MyD88) pathway, with consequent activation of mitogen-activated protein kinase (MAPK) cascade, NF-κB and other pathways resulting an enhanced expression of TNF-α, IL-1β, IL-6, IL-12 and IFN-α [26]. TLR8 is expressed in myeloid cells and pDCs, thereby activating MyD88 with a downstream pathway like TLR7 [26]. TLR4 plays a pivotal role for the response to the lipopolysaccharide (LPS) of gram-negative bacteria as well as oxidized phospholipids induced by virus infection including SARS-CoV and associated with the activation of NF-κB and IRF3 like TLR3 [26]. The potential mechanism has been reviewed extensively [26]. All these elements, including the interlinking of various mechanisms of innate immunity, lead to an overactivation of the inflammatory response.

Another potential mechanism of CS in COVID-19 via hyperactivation of the NF-κB pathway caused by the angiotensin-II (Ang II) pathway was proposed [27]. One of the major pathways for NF-κB activation after coronavirus infection is the MyD88 pathway through PRRs, leading to the induction of a variety of pro-inflammatory cytokines, including IL-6 and TNF-α [27]. Hoffmann et al. [24] showed that SARS-CoV-2 endocytosed ACE-2 as its cell entry receptor, resulting in reduction of ACE-2 on cells, followed by an increase of serum Ang II [27]. Ang II acts both as a vasoconstrictor and pro-inflammatory cytokine via the Ang II-angiotensin receptor type 1 (AT1R) [27]. The Ang II-AT1R axis activates NF-κB and induces TNF-α, epidermal growth factor receptor (EGFR) and soluble form of IL-6Rα (sIL-6Rα) via disintegrin and metalloprotease 17 (ADAM17) [27]. IL-6 binds to sIL-6Rα through a glycoprotein (gp130) to form the sIL-6Rα-IL-6 complex, which activates STAT3 in non-immune cells [27]. Both NF-κB and STAT3 can activate the IL-6 amplifier (IL-6 Amp) to induce various forms of proinflammatory cytokines and chemokines, including VEGF, MCP-1, IL-8 and IL-6. STAT3 is required for full activation of NF-κB and IL-6 is the main activator of STAT3 [27]. Therefore, SARS-CoV-2 infection in the respiratory system can activate both NF-κB and STAT3, which in turn can activate IL-6 Amp, a mechanism for the hyperactivation of NF-κB by STAT3, leading to multiple inflammatory and autoimmune diseases [27]. IL-6 Amp induces various proinflammatory cytokines and chemokines, including IL-6 and recruits lymphoid cells and myeloid cells, such as activated macrophages, in the lesion to strengthen the IL-6 Amp in a positive feedback loop [27]. Collectively, the impaired acquired immune responses and uncontrolled inflammatory innate responses to SARS-CoV-2 infection may cause CS.

This suggests that in addition to antiviral therapeutics during the initial phase of the infection, appropriate therapies targeting the cytokine pathways, particularly the NF-κB and JAK/STAT signaling pathways, may be required to dampen the risk of CS due to dysregulation of inflammatory responses in the later phase of COVID-19 infection [4,6,26,27].

3. Management of immunological complications of COVID-19

Currently, there are no Food and Drug Administration-approved drugs or vaccines for the treatment of COVID-19 [28]. Repurposing of existing antivirals and supportive management with specific respiratory and ventilator supports are current approaches for treatments for severe cases [27,28]. The lack of any effective drug for the treatment of

COVID-19 leads to a sense of urgency to develop new therapeutic strategies based on pathophysiological assumptions [27–30].

Besides antiviral agents, the treatment of immunological complications, such as CS using appropriate host-directed therapies that include immunosuppressive and immunomodulatory drugs has been suggested to be essential [2,4,6,22,23,26–30]. A range of marketed drugs, such as DMARDs, metformin, pioglitazone, fibrates and atorvastatin, including nutrient supplements and biologics have been proposed to reduce immunopathology, boost immune responses and prevent or curb ARDS [2,6,28,30]. These could be used as adjuncts to monotherapy or as combinatorial therapies with repurposed antivirals targeting SARS-CoV-2 induced COVID-19 [28,30,31].

As CS is a relatively common manifestation of COVID-19 infection and often leads to exacerbation with progression to ARDS, ALI and other serious organ damages, intervention with appropriate anti-inflammatory treatment should be considered in addition to antiviral treatment to prevent further injury [6,18,21–23,26–36]. Table 3 provides a representative list of potential targeted processes and examples of candidate agents which are currently entering clinical trials or have been proposed [28,30,32–34].

In addition, alternative drugs and interventions have been proposed for potential prevention and treatment of CS, and possible lung fibrosis after COVID-19 pneumonia [30–36]. The mesenchymal stem cells (MSCs)-based immunomodulation treatment has been proposed as a suitable therapeutic approach [34]. Chan et al. [32] have reported the potential benefits of Traditional Chinese Medicine (TCM), which includes symptomatic relief, reduction in fever duration, reverting radiological changes and speedy recovery with shortening of hospital stay. Recently, Zhang et al. [36] have proposed melatonin as a potential adjuvant for COVID-19 based on its known anti-inflammatory and antioxidant properties. It was speculated that use of melatonin as an adjuvant may exert beneficial effects in COVID-19 by the regulation of anti-inflammation, antioxidant and immune responses [36]. Colchicine, commonly used for the treatment of gouty arthritis and Behçet's syndrome based on its anti-inflammatory and immunomodulatory properties as well as its ability to inhibit IL-1β, has been proposed to be useful for the treatment of some complications of COVID-19 infection [34].

We anticipated that ASX derived from the microalgae *Haematococcus pluvialis*, with its potent antioxidant, anti-inflammatory and immunomodulatory actions could be useful as a potential adjunctive supplement in the management CS and associated risk in COVID-19.

Table 3
Potential process in COVID-19 amenable to therapeutic targets with examples of candidate agents [27–30].

Potential Targeted Process	Candidate Agent
Antiviral/anti-inflammatory	Convalescent serum (patients with COVID-19), type I interferon, immunoglobulins, mesenchymal stem cells
ACE2 entry inhibitor	Soluble recombinant ACE2
TMPRSS2 protease priming	Protease inhibitor (chemostat mesylate)
Receptor endocytosis	Chloroquine or Hydroxychloroquine
RNA polymerase for replication	Remdesivir, favipiravir
Viral proteases	Lopinavir/vitonavir
Importin nuclear transport	Ivermectin
IL-1 excess activation	Anakinra, Canakinumab, Colchicine
Angiotensin II excess	ACE inhibitors/angiotensin receptor blocker, recombinant ACE2
Cytokine storm	Tocilizumab, sarilumab, or siltuximab (IL-6 inhibitors) or baricitinib (JAK inhibitor), lenzilumab (GMCSF inhibitor)
Oxidative stress	Deferoxamine, vitamin C
Fibrosis	Nintedanib
Inflammation	Dexamethasone, metformin, pioglitazone, statins

4. Astaxanthin as a potential adjunctive supplement in COVID-19

H. pluvialis derived ASX is a natural oxycarotenoid with anti-inflammatory, immunomodulatory and potent antioxidant properties [8–14]. The potent antioxidant property of ASX implicating to its various biological activities has been demonstrated in both preclinical and clinical studies [8,10]. ASX is not a known viricide. However, it has been shown to suppress features of viral infection owing to its potent antioxidant, anti-inflammatory and immunomodulatory actions [11–17]. Studies including human trials have shown that ASX effectively regulates immunity and disease etiology, suggesting its wide array of potential therapeutic and nutritional support in prevention and treatment of various pathogenic diseases and metabolic disorders, all of which have elements of oxidative stress and/or inflammation in the pathogenesis [8,10,17]. The potential pharmacological effects of ASX include antioxidant [12,9–14,37–46], anti-inflammatory [9,12,14,54–60] and immune-modulating [11,14,15,61–63] as well as cardiovascular, neuro-, ocular- and skin-protective effects [8,17,37,64]. ASX has been suggested as a potential therapeutic agent against atherosclerotic cardiovascular disease [8,37], oral lichen planus (OLP) [9], gouty arthritis [55], ALI [12,43], sepsis [44], cancers [47–50], diabetes mellitus [51–53], etc. The biological activities of ASX is reported to originate from its potent singlet oxygen quenching and lipid peroxidation suppressing activities [65]. Recent human trials elaborating on the safety perspectives have found no negative effects of ASX consumption as a dietary supplement [66]. Results from clinical studies have shown that treatment with ASX improves blood flow in humans [67] and enhances blood rheology by increasing the flexibility of erythrocyte membranes [68].

With its unique molecular structure [10], ASX stretches through the bilayer cell membrane providing resilient protection against oxidative stress [38]. As a potent and efficient antioxidant, ASX can prevent genotoxicity and cytotoxicity mediated by ROS, stimulate hepatic xenotoxic-metabolizing enzymes and enhance tumor immunity [14,15]. Unlike most antioxidants, which works either in the inner side of the membrane (e.g., vitamin E and β-carotene) or on the outer side (e.g., vitamin C), ASX can scavenge and quench reactive oxygen species (ROS) and free radicals (superoxide anion, hydrogen peroxide, singlet oxygen, etc.) in both the inner and outer layers of the cell membrane [10]. The ROS scavenging effect of ASX is approximately 6000 times higher than that of vitamin C, 800 times than that of coenzyme Q10 and 550 times than that of vitamin E [65].

These pleiotropic protective effects of ASX owing to its potent antioxidant, anti-inflammatory and immunomodulatory actions may support its potential adjunctive use in alleviating and management of CS and associated risks in COVID-19 patients. A representative list of potential targeted clinical characteristics of COVID-19 and possible functional role of ASX is provided in Table 4. As there is no direct evidence of applying ASX against COVID-19, we propose in Table 5 a summarized outcome of available *in vitro* and *in vivo* studies related to ASX treatment in alleviating the risk of inflammatory cytokine, thereby supporting its likely therapeutic benefits against CS in COVID-19 infection.

4.1. Astaxanthin protects against inflammation by inhibiting proinflammatory cytokines via regulating intracellular signaling pathways

Inflammation and oxidative stress are implicated in the pathogenesis of many chronic diseases, including diabetes, atherosclerosis, hypertension [8,16], gouty arthritis [55] and oral lichen planus (OLP) [9]. Hyperinflammation due to an uncontrolled inflammatory response is also considered to be a major cause of COVID-19 pathogenesis [6,22,27]. Inhibiting the production of intracellular ROS is a general way to suppress the pro-inflammatory signals and thus modulators of redox balance are considered the key regulators of inflammatory responses, where macrophages (M1 and M2) play a central role in inflammation

Table 4
Potential functional role ASX related to targeted clinical characteristics of COVID-19.

COVID-19 clinical characteristics	Relation to astaxanthin	References
Elevated production of pro-inflammatory cytokines (IL-2, IL-1β, IL-8, etc.)	Inverse correlation, Downregulates	[2,6,12]
Increased production of IL-6 & TNF-α	Inverse correlation, Inhibits/downregulates	[2,6,12]
Increased production of CRP	Inverse correlation, reduces	[2,23,12]
NF-kB/MAPK signaling pathway activated	Inverse correlation, inhibits/downregulates	[2,4,12,13, 26,27,40]
Activate JAK/STAT-3 signaling pathway	Inverse correlation, inhibits	[6,50,127]
Increase expression of TLRs signaling	Inverse correlation, downregulates	[26,27,70,74, 75]
Dysregulate cytokine production	Regulate cytokine production	[4,6,12,13]
Imbalance RAS signaling pathway induce ROS, inflammation	Inverse correlation, inhibit inflammation	[27,42,51, 82,83]
Induce oxidative damage	Inverse correlation, prevents	[12,43,46,71, 72,75]
Increase VEGF	Inverse correlation, decreases	[6,23,50]
Decrease lymphocytes, NK cells	Inverse correlation, modulates, increase NK cells	[14,15,23, 92,93]
Increase risk of sepsis	Inverse correlation, prevents	[3,6,12,103]
Increase risk of ALI/ARDS	Inverse correlation, prevents	[6,12,43,99]
Increase risk of heart failure	Inverse correlation, prevents	[67,103,106]
Increase risk of CNS injury	Inverse correlation, prevents	[39,96,80]
Increase risk of renal fibrosis	Inverse correlation, prevents	[3,19,97]
Increase risk of liver fibrosis	Inverse correlation, prevents	[3,19,99]

[16,45]. In inflammation states, M1 macrophages are activated by IFN and LPS, which produce excess amounts of matrix-degrading enzymes, pro-inflammatory cytokines (including IL-1β, IL-6 and TNF-α), nitric oxide (NO), COX-2 and matrix metalloproteinases (MMPs). These are responsible for the degradation of extracellular matrix and mediate tissue remodeling in various pathological conditions [16,45]. Alternatively, M2 macrophages are activated by IL-4 and IL-13 and modulate the inflammatory reactions by producing anti-inflammatory cytokines, such as IL-10 [45]. The balance between M1/M2 phenotype is, therefore, important for regulating immune and inflammatory processes [45].

The NF-κB signaling pathway promotes inflammation by increasing the release of ROS and pro-inflammatory cytokines in macrophages [45]. Inversely, the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway plays a critical role in the endogenous antioxidant defense mechanism and prevents oxidative stress by stimulating the production of antioxidant enzymes [39]. Additionally, Nrf2 inhibits inflammatory responses associated with NF-κB in macrophages [39,45]. Moreover, Nrf2 exerts a reduction in intracellular ROS levels and inhibits pro-inflammatory signals in macrophages [45]. Thus, a bioactive compound with antioxidant property and ability to activate Nrf2 may have therapeutic potential to prevent the development of inflammation.

Treatment with ASX exhibits anti-inflammatory actions by remarkably suppressing the activity of inflammatory mediators, such as inducible nitric oxide synthase (iNOS), COX-2 and expression of MMPs. ASX also exerts its anti-inflammatory actions by inhibiting the expression of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6 in THP-1 macrophages [16,40]. ASX exerts anti-inflammatory actions by suppressing the expression of pro-inflammatory cytokines via regulation of the NF-κB dependent signaling pathway in alveolar macrophages, neutrophils and lymphocytes [40,41,45]. Numerous *in vitro* and *in vivo* studies have shown that ASX significantly suppresses the production of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α [9,12,40,43, 50]. Also, Cai et al. [12] have shown that ASX administration significantly inhibits the MAPK/NF-kB signaling pathway mediated secretion of pro-inflammatory cytokines IL-6 and TNF-α in LPS-stimulated mouse prime macrophages (MPM) and serum of LPS-induced septic mouse. LPS-stimulation markedly increases the degradation of IkB-α and phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), p38 and c-Jun N-terminal kinase (JNK) along with activation of the NF-κB pathway resulting in the secretion of pro-inflammatory factors. Treatment with ASX has been reported to prevent LPS-induced ALI and sepsis by attenuating LPS-induced inflammation *in vitro* and *in vivo* [12]. Pretreatment with ASX suppresses LPS-induced degradation of IkB-α and phosphorylation of ERK1/2, p38 and JNK in LPS-induced experimental sepsis resulting downregulation of pro-inflammatory cytokine production [12].

Miyachi et al. [9] found that the administration of ASX provides both preventive and curative anti-inflammatory effects against LPS-induced inflammation in the human gingival keratinocyte line NDUSD-1 by suppressing the production of IL-6 via inhibiting activation of the NF-κB signaling pathway. Translocation of NF-κB/p65 and the levels of IL-6 and TNF-α were reported to decrease markedly following ASX treatment [9]. Similarly, ASX was demonstrated to inhibit the production of NO and prostaglandin (PGE2) by suppressing the expression of iNOS, COX-2, TNF-α and IL-1β in both LPS-stimulated primary macrophages and RAW264.7 cells [40]. ASX also inhibited the serum levels of NO, PGE2, TNF-α and IL-1β in LPS-treated mice [40]. Lee et al. [40] demonstrated that LPS-stimulated expression of pro-inflammatory cytokine and mediators was inhibited by ASX via regulation of the NF-kB activation. ASX inhibits nuclear translocation of NF-κB/p65 subunit, degradation of IκBα and IKK activation [40]. In addition, ASX was reported to reduce plasma levels of NO, PGE2, TNF-α and IL-1β in an animal model of sepsis [40]. In a recent study, Bi et al. [43] have shown that ASX treatment alleviates cecal ligation puncture (CLP)-induced acute lung injury by suppressing the oxidative stress-induced secretion of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β. This study also reported that ASX treatment noticeably attenuated CLP-induced lung histopathological injury, inflammatory infiltration, total protein and albumin concentration as well as total cell and neutrophil counts in bronchoalveolar lavage fluid (BALF) [43]. Treatment with ASX was reported to significantly downregulate the expression of iNOS, nitrotyrosine (NT) and NF-κB/p65 in the lung tissues and alleviate CLP-induced ALI [43]. Moreover, ASX treatment was also found to reduce serum levels of LDH, blood urea nitrogen, creatinine, IL-1β, IL-6 and TNF-α, and also attenuated multi organ damage in CLP-induced septic rats [44]. Similarly, Farruggia et al. [45] have demonstrated that ASX significantly decreases LPS-induced mRNA expression of IL-6 and IL-1β by inhibiting the NF-κB/p65 signaling pathway in RAW 264.7 macrophages. Besides its role in inhibiting the nuclear translocation of NF-κB, ASX also exerts its anti-inflammatory effect by altering the splenic macrophages to be less inflammatory and by modulating macrophage phenotype to be less inflammatory [45]. Furthermore, the anti-inflammatory effect of ASX was reported to be mediated by both Nrf2- dependent and -independent mechanisms [45].

The cytokine IL-6 is one of the major pro-inflammatory cytokines produced by activating macrophages and monocytes. IL-6 mediates the innate-adaptive immunity interface and is involved in autoimmune disorders and chronic inflammation [56]. An elevated serum level of IL-6 has been discussed in COVID-19 disease progression [3,6,20,21,23], suggesting the use of IL-6 inhibitors as potential therapeutics in the management of CS in COVD-19 [6,28]. Numerous studies as discussed above have demonstrated that ASX could effectively modulate IL-6 levels *in vitro* and *in vivo*. Kim et al. [56] demonstrated that ASX significantly suppressed the production of IL-6 in both LPS- and stomatal derived factor (SDF)-1α stimulated microglial cells via downregulation of ERK1/2-MSK- and NF-κB/p65 signaling pathway. Additionally, in a

Table 5
Preclinical *in vitro* and *in vivo* studies investigating effect of astaxanthin on inflammatory or oxidative stress.

Experimental model	Role of Astaxanthin	Molecular mechanism involves	Outcome of the study	References
LPS-induced human gingival keratinocyte line NDUSD-1	Anti-inflammatory, Antioxidant	- Inhibits translocation of NF-kB/p65 - Regulation of NF-kB	- Inhibits IL-1β, IL-6, TNF-α - Inhibits NF-kB/p65 signaling pathway - Prevents & cure inflammation	[9]
LPS-induced mouse prime macrophages (MPM), RAW264.7 cells, male C57BL/6 mice	Anti-inflammatory	- Inhibits phosphorylation of IkB-a, ERK1/2, p38, and JNK - Regulation of MAPK/NF-kB	- Suppresses IL-6, TNF-α - Inhibits MAPK/NF-kB - Attenuates ALI/ARDS - Protects against LPS-induced Sepsis	[12]
THP-1 macrophages	Antioxidant, anti-inflammatory	- Suppresses expression of CD36 - Regulation of NF-kB	- Suppresses MMP-1, -2, -3, -9, -12, & -14 expressions and activations - Suppresses IL-1β, IL-6, TNF-α - Suppresses iNOS, COX-2 - Inhibits macrophage activation	[16]
LPS & H2O2 stimulated RAW264.7 & primary macrophages	Antioxidant, anti-inflammatory	- Inhibits IkB-a degradation - Inhibits iNOS promoter activity - Regulation of NF-kB	- Downregulate NF-kB signaling pathway - Inhibits IL-1β, TNF-α - Suppresses serum levels of NO, PGE2, iNOS, COX-2	[40]
H2O2-, or bleomycin (BLM) induced alveolar epithelial cells type II, human lung tissue or Sprague-Dawley rats	Antioxidant, anti-apoptosis, anti-fibrotic	- Modulation of Nrf2 signaling - Inhibits cytochrome c (Cyt c) - Regulates P13 K/Akt pathway	- Activates Nrf2, caspase-9, caspase-3 - Improves cellular defense against ROS, ameliorates oxidative stress - Prevents translocation of Bcl-2 family proteins - Prevents pulmonary fibrosis	[42]
CLP-induced wild-type C57BL/6 J mice	Antioxidant, anti-inflammatory, protects against ALI	- Regulation of NF-kB/p65 pathway	- Downregulates expression of NF-kB/p65 - Prevents vascular leakage, inhibits infiltration of neutrophil, macrophages, and monocytes - Suppresses IL-1β, IL-6, TNF-α - Reduces oxidative stress, decreases ROS, MDA, MPO, iNOS & NT - Alleviates ALI	[43]
CLP-induced sepsis in Sprague-Dawley rats	Antioxidant, anti-inflammatory, protects against sepsis-induced multi organ injury	Suppresses oxidative stress marker MDA, increases SOD activity, downregulates IL-6, IL-1β, TNF-α, reduces peritoneal bacterial load	- Inhibits IL-1β, IL-6, TNF-α - Decreases MDA, LDH, BUN, Cr - Reverses SOD activity - Attenuate oxidative damage induced by sepsis - Reduces peritoneal bacterial load - Protects against sepsis	[44]
LPS-induced RAW264.7 macrophages	Antioxidant, anti-inflammatory effects in macrophages	Inhibits NF-kB/p65, prevents ROS accumulation & pro-inflammatory gene expression in Nrf2 dependent and independent manner	- Inhibits NF-kB - Downregulates expression of IL-1β, IL-6 - Increase Nrf2 nuclear translocation - Decreases NADP oxidase-2 expression - Decreases macrophage polarization	[45]
EC304 Human umbilical vein endothelial cells, Male Syrian hamster	Antioxidant, anti-inflammatory, anti-tumor	- Regulation of JAK/STAT3 pathway - Prevents phosphorylation STAT3	- Inhibits production IL-6 - Inhibits JAK/STAT signaling pathway - Suppresses expression of HIF-1α, VEGF, VEGFR2 - Suppress expression MMP2, MMP9 - Inhibits angiogenesis	[50]
Pre-chiasmatic cistern induced mice and rat model	Anti-inflammatory	- Inhibition of TLR4 activation - Inhibition IL-6production - Regulation of NF-kB signaling pathway - Modulation of sirtuin1	- Inhibits IL-6 production - Inhibits TLR4 activation & group box expression of MyD88 - Inhibits translocation high mobility group box expression of MyD88 - Downregulates NF-kB - Increases expression of sirtuin1 - Suppresses cerebral inflammation - Reduce neuronal death	[54]
MSU-induced J774A.1 murine macrophage	Anti-inflammatory, antioxidant, anti-arthritis	Regulation MAPK pathway	- Inhibits induction of COX-2 - Inhibits IL-6 - Downregulates MAPK pathway	[55]

(*continued on next page*)

Table 5 (*continued*)

Experimental model	Role of Astaxanthin	Molecular mechanism involves	Outcome of the study	References
			- Suppresses inflammation in gouty arthritis	
LPS-, SDF-1a induced RAW264.7 macrophage, BV-2 microglial cells	Anti-inflammatory	- Regulation of p-ERK1/2-MSK1-and p-NF-kB/p65 signaling pathway - Regulation of IL-6 production	- Downregulates p-ERK1/2, p-MSK1 pathways - Downregulates p-NF-kB/p65 pathway - Inhibits IL-6 production - Suppresses IKKα, IkBα	[56]
Iohexol-induced human proximal renal tubular epithelial cells	Antioxidant, anti-inflammatory	Regulation of NLRP3 inflammasome	- Downregulates NLRP3 inflammasome - Decrease ROS, oxidative stress - Suppresses IL-1β, IL-8 - Inhibits apoptosis & inflammation - Exerts protection against inflammasome induced renal injury	[59]
Streptozotocin-induced diabetic rats, Male Sprague-Dawley rats;	Antioxidant, reno-protective	Modulation of Nrf2/ARE signal	- Promotes nuclear translocation of Nrf2/ARE signaling - Increases HO-1 and SOD1 expression and activity - Decreases MDA - Alleviates accumulations of fibronectin and collagen IV - Exerts reno-protective effects	[74]
Ochratoxin induced oxidative damage and inflammation in mice lung tissue	Antioxidant, anti-inflammatory, protect against lung injury	Modulation of Nrf2/NF-kB signaling pathways	- Elevates expression of Nrf2, HO-1 & MnSOD - Decreases MDA, Keap-1 expression, - Inhibits TL4/MyD88 expression - Regulate NF-kB - Suppresses IL-1β, IL-6 & TNF-α - Protects against oxidative damage & inflammation - Alleviates lung injury	[75]
H2O2-induced U937 cell line	Antioxidant, anti-inflammatory	Regulates NF-kB, Restore SHP-1	- Inhibits NF-kB - Suppresses IL-1β, IL-6, TNF-α - Modulate SHP-1 expression - Prevents against oxidative damage	[79]
H2O2-induced I/R in human tubular epithelial cell (HTEC)	Antioxidant, anti-inflammatory, protects against I/R induced renal injury	Scavenges ROS, restore SOD, decreases MPO	- Inhibits IL-1β, IL-6, TNF-α - Increases SOD activity - Reduces MDA, MPO - Prevents I/R induced renal injury	[84]

mouse model of experimental choroidal neovascularization, it was demonstrated that ASX treatment led to significant inhibition of macrophage infiltration into the process [57]. Moreover, ASX suppressed IkB-α degradation and NF-κB nuclear translocation, thereby resulting in subsequent downregulation of IL-6, VEGF, intercellular adhesion molecule-1 (ICAM-1) and MCP-1 [57].

ASX also provides neuroprotection against secondary brain injury through suppression of cerebral inflammation [54]. In a prechiasmatic cistern subarachnoid (SAH) model, activation of TLR4 increases downstream molecules MyD88 and NF-κB and induces pro-inflammatory markers along with ICAM-1, causing direct damage to the surrounding neural cells and neutrophil migration [54]. Reportedly, post-treatment with ASX after SAH significantly inhibited the TLR4 activation, increased sirtuin 1 expression, reduced neutrophil infiltration, suppressed the activity of NF-κB and inhibited subsequent inflammatory response by downregulating IL-1β, TNF-α and ICAM-1 both *in vivo* as well as *in vitro* [54]. Furthermore, administration of ASX after SAH had reportedly ameliorated secondary brain injury cascades, brain edema, neuronal death and improved neurologic function [54].

The mechanism underlying ASX regulation of pro-inflammatory cytokines has been extensively investigated and engages diverse signaling pathways, among which the NF-κB pathway plays an essential role [9,12,16,40,43,45]. Besides, ASX modulations of Nrf2 and sirtuin1 signaling pathways play significant roles in its anti-inflammatory mechanism [45,54].

The NF-κB signaling pathway plays a seminal role in immunity by activating pro-inflammatory genes encoding iNOS, COX-2, TNF-α, IL-1β and IL-6 [40]. Aberrant NF-κB activity is associated with the pathogenesis of multiple inflammatory diseases as well disease associated with viral infection and most anti-inflammatory drugs suppress inflammatory cytokine expression by inhibiting the NF-κB pathway [40,56]. Anti-inflammatory drugs such as dexamethasone, colchicine, prednisone and aspirin prevent inflammatory diseases by suppressing the production of pro-inflammatory cytokines and expression of iNOS and COX-2. As discussed here, numerous *in vitro* and *in vivo* studies suggest that ASX inhibits the expression of iNOS and COX-2, resulting in reduced production of IL-1β, IL-6 and TNF-α in macrophages as well as reduces serum levels of IL-1β, IL-6 and TNF-α in experimental animal models. It has been well documented that ASX exerts broad-spectrum anti-inflammatory actions mostly via downregulation of the NF-κB signaling pathway, supporting our hypothesis that ASX could have a therapeutic effect in alleviating inflammatory responses in COVID-19.

4.2. Astaxanthin protects against oxidative damage by regulating ROS generation and endogenous antioxidant response

Oxidative stress plays a crucial role in the inflammatory response and cytokine outbreak during various pathological and non-pathological diseases, including in the pathogenesis of viral infections [12–14,69]. Virus-induced activation of phagocytes is associated with oxidative stress and is correlated with the viral infection that modulates the intracellular redox sensitive signaling pathways to promote viral

replication and pathogenesis [69]. Oxidative stress is not only due to ROS released, but also due to pro-oxidant cytokines, such as tumor necrosis factor (TNF) and IL-1 released by activating phagocytes [69]. Recent evidence suggests that much of the ALI caused by SARS-CoV and H5N1 can be attributed to excessive ROS generation initiated by an overactive innate immune response [70]. In SARS-CoV, H5N1 avian flu and chemical agent induced ALI/ARDS models, oxidized phospholipids activate the innate immune response by the overproduction of IL-6 in alveolar macrophages via the TLR4-TRIF-TRAF6-NF-kB signaling pathway, thereby leading to ALI [70]. Stimulation of TLR4 can trigger the activation of two downstream signaling pathways: MyD88-dependent or TRIF-dependent pathways [70]. TLR4 belongs to the TLR receptor family for the innate immune system and it is also a therapeutic target for ASX.

Recently, numerous studies have highlighted the possible role of oxidative stress in the progression and severity of COVID-19 [71–73]. Free radicals, such as O_2^-, ClO^-, NO and $ONOO^-$ could be the cause of virus induced pneumonia death [71]. Oxidative stress reportedly plays a crucial role in the pathogenesis of COVID-19, perpetuates the CS and DIC as well as exacerbates hypoxia, including mitochondrial dysfunction [72]. The interplay between ROS and CS generates a self-sustaining cycle between the CS and oxidative stress produced, leading to multi-organ failure in severe COVID-19 patients who progress to sepsis and shock [71,72]. It has been speculated that SARS-CoV-2 infection interferes with the equilibrium between the expression of NF-κB (involved in expression of cytokine) and Nrf2 activation (responsible for expression of antioxidant enzyme) [73]. Studies have also implicated Nrf2 as a regulator of susceptibility to respiratory and non-respiratory viral infections, including influenza virus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), dengue virus (DENV), rotavirus, herpes simplex virus, Zika virus and HIV [73]. These suggest that a compound or drug having antioxidant actions with the capability to activate Nrf2 could be a potential therapeutic agent against COVID-19 [73].

Antioxidant action of ASX cooperates with its anti-inflammatory effect by downregulation of pro-oxidative enzymes (e.g. nitric oxide synthase) and upregulation of antioxidant enzymes (e.g. superoxide dismutase) [38]. ASX regulates intracellular oxidative stress by modulating the Nrf2/ARE (antioxidant response element) signaling [42,74,75]. Activation of Nrf2/ARE signaling pathway by ASX exerts various cytoprotective effects and leads to an endogenous antioxidant response [39]. ASX promotes the nuclear translocation of Nrf2, increases expression of heme oxygenase-1 (HO-1) and superoxide dismutase (SOD)-1 expression [74]. In addition, ASX has been reported to increase the activity of SOD, decrease MDA levels in the serum and alleviate fibronectin as well as collagen IV accumulation in the kidneys of diabetic rats, thereby exerting a reno-protective effect [74]. Moreover, ASX has been shown to protect against lung injury due to oxidative damage and inflammation induced by ochratoxin (OTA) in mice via the modulation of Nrf2/NFκB pathway [75]. Exposure to OTA has been reported to induce immunotoxicity of the TLR4/MyD88 pathway by inducing ROS overproduction followed by activation of NF-κB, resulting in elevated levels of inflammatory markers IL-1β, IL-6 and TNF-α. Pretreatment with ASX has been reported to significantly reduce the inflammation [75]. In OTA exposed mice, ASX significantly upregulated the expression of Nrf2, HO-1 and MnSOD (Manganese superoxide dismutase), while the expression of Kelch-like ECH-associated protein 1 (Keap1), TLR4 and NF-κB was significantly downregulated [75]. Similarly, ASX was shown to inhibit apoptosis in alveolar epithelial cells type II (AECs-II) *in vitro* and *in vivo* by activation of the Nrf2/ARE signaling pathway in experimental animal model, suggesting potential therapeutic value in the treatment of lung fibrosis caused by oxidative stress [42]. Treatment with ASX also regulates the Bax/Bcl2 expression via modulation of the PI3K/AKT signaling pathway, resulting inhibition of cytochrome c (Cyt c) release and activation of caspase-9, caspase-3, Nrf2 and other cytoprotective genes [42].

In the immune system, SHP-1 plays critical roles in the regulation of many receptor-mediated signaling cascades [76]. The deficiency of SHP-1 in mice causes spontaneous inflammation and autoimmunity [77]. Moreover, SHP-1 deficiency was reported to increase inflammatory gene expression and enhance activation of transcription factor STAT6, STAT1 and NF-κB in peripheral blood mononuclear cells (PBMC) and macrophages in patients with multiple sclerosis [78] Treatment with ASX has been shown to be effective in re-establishing SHP-1 negative regulation on oxidative stress induced NF-κB mediated pro-inflammatory cytokine production in U-937 cell line [79]. ASX modulates inflammatory response by inhibiting the release of IL-1β, IL-6, TNF-α, MCP-1 and ICAM-1 through the activation of SHP-1, which suppresses the NF-κB expression and IkB degradation [79].

Nod-like receptor protein (NLRP)-3 inflammasomes play important role in various inflammatory diseases including viral induced pathologies [80]. Most viruses, including SARS-CoV-1, have been shown to modulate the cellular anti-viral interferon (IFN) responses and can either interact directly with NLRP3 inflammasome in macrophages or in cells lacking NLRP3, where the viral sensing machinery can be modulated by viral protein aggregates in the cytosol [80,81]. Intracellular ROS mediated activation of NLRP3 stimulates upregulation of pro-inflammatory cytokines and chemokines synthesis [55,59]. Interestingly, numerous studies have shown that ASX effectively attenuates NLRP3 activation [55,59]. In a recent study, Peng et al. [55] have reported ASX as a potential treatment for gouty arthritis. Treatment with ASX has been found to inhibit the MAPK pathway, which in turn suppresses the expression levels of IL-1β, COX-2 and NLRP3 in monosodium urate crystal (MSU)-induced murine macrophage J774A.1 cell [55]. In addition, ASX has also been shown to attenuate ROS-induced acute kidney injury by inhibition of ROS/NLRP3 inflammasome signaling pathway [59]. In this study, Gao et al. [59] found that treatment with ASX significantly decreases the levels of ROS, NLRP3, caspase 1, IL-1β and IL-8, as well as the rate of apoptosis in iohexol-induced human proximal renal tubular epithelial cells.

Furthermore, the protective action of ASX against oxidative stress mediated ischemia-reperfusion (I/R) induced injury has been studied extensively [82–86]. I/R is a multifactorial process that includes major oxidative stress induced by ischemia and hypoxia [83]. Excessive release of ROS plays important role in I/R injury process and scavenging ROS could be a potential target [83,84]. Numerous studies applying different *in vivo* models of induced I/R injury, such as myocardial, cerebral, liver and renal injury, have confirmed the protective actions of ASX after oral or intravenous administration [82]. Li et al. [82] found that treatment with ASX prevents hepatic I/R induced injury by reducing the release of ROS and pro-inflammatory cytokines TNF-α and IL-6, leading to inhibition of apoptosis and autophagy via downregulation of the MAPK pathway. In addition, ASX has been shown to have protective effects against I/R-induced renal [84] and lung injury [85]. The protective role of ASX in I/R-induced hepatorenal injury has been reconfirmed recently in rat models [86]. In acute lower extremity I/R, ASX has been reported to reduce the I/R-induced elevation of endothelial nitric oxide synthase (eNOS) and decrease the ischemic injury in liver and renal tissues by protecting the microcirculation and providing a cytoprotective effect with vasodilatation [86]. Moreover, ASX has been reported to reduce blood coagulation and platelet aggregation, and also promote fibrinolytic activity in high-fat diet-induced hyperlipidemic rats [56,87]. These positive effects are correlated with the decrease of serum lipid and lipoprotein levels, antioxidant actions and protection of endothelial cells [87].

Oxidative/nitrative stress is an imbalance between oxidation and anti-oxidation mainly caused by excessive detrimental ROS production, MDA, MPO, iNOS and NT, and by depletion of SOD, GSH, etc. [43], that exacerbates inflammation and causes direct mitochondrial damage in ALI [88]. ROS dependent mitochondrial signaling pathway plays critical role in pulmonary apoptosis in the process of ALI [42]. The aforesaid discussion on numerous studies has shown that ASX can reduce

oxidative/nitrative stress through multiple signaling pathways to protect against ROS induced cell and tissue damages. In addition, ASX could inhibit ROS-dependent mitochondrial signaling pathways to protect pulmonary endothelial cells [42]. Additionally, treatment with ASX has been reported to decrease significantly the levels of MDA, MPO, iNOS and NT in CLP-induced ALI in mice [43]. Moreover, there is evidence that suggests protective effects of ASX against oxidative damage in other disorders such as neurodegenerative diseases, cardiovascular disease, diabetes, cancers and obesity [8,10,17,39,48,50].

4.3. Astaxanthin exerts immunomodulatory actions

Viral lung infections leading to ALI/ARDS are the leading cause of morbidity and mortality. Once the virus infects respiratory epithelial cells, dendritic cells phagocytose the virus and present antigen to T cells. Effector T cell functions by killing the infected cells and cytotoxic CD8 + T cells produce and release pro-inflammatory cytokines, which induce cell apoptosis [89]. Effective immune responses to these infections require precise immune regulation to preserve lung function after viral clearance [89]. The exacerbation of cytokine production and the excessive recruitment of immune cells along with uncontrollable epithelial cell damage generates a vicious circle for infection leading to ALI/ARDS [90]. Clinical characteristics of COVID-19 suggest a reduced level of neutrophils, lymphocytes, CD4 + T and CD8 + T cells in peripheral blood [18,20,21].

The immunomodulatory actions of ASX have been well documented and supported by pre-clinical and clinical trials, including in human subjects [11,14,15,49,61–63,91,92]. ASX possesses antioxidant, free radical scavenging and anti-inflammatory properties that may affect human immune system and resistance to pathogens [17]. ASX exerts regulatory actions on the immune system by stimulating mitogen-induced lymphocyte proliferation, increasing NK cell cytotoxicity and delayed-type hypersensitivity response, and increasing the number of total T- and B-cells in the peripheral blood [14]. Supplementation of ASX in mice has been shown to increase *ex vivo* splenocyte antibody response to T-dependent antigens [92], lymphoblastogenic response and cytotoxic activity [63]. Reportedly, ASX was found to have a stimulatory effect on the production of polyclonal antibodies IgM and IgG on mouse spleen cells [93]. Dietary supplementation with ASX was found to increase IgM and IgG secreting cells *in vivo* in T dependent antigen (TD-Ag) primed mice but had no effect on *in vitro* and *in vivo* antibody production in response to T-independent antigen [63]. These indicate significant immunomodulating actions of ASX for humoral immune responses to TD-Ag, suggesting that ASX supplementation could be beneficial in restoring humoral immune responses in aged animals [63]. ASX has also been reported to produce immunoglobulins in human cells [15]. Moreover, in LPS- and concanavalin-activated primary cultured lymphocytes, Lin et al. [62] found that treatment with ASX modulates lymphocytic immune response *in vitro* and exerts *ex vivo* immunomodulatory effects by enhancing IFN-γ and IL-2 production without inducing cytotoxicity.

Furthermore, several studies have highlighted the ability of ASX to modulate the forkhead box O3 gene (FOXO3), which has been recognized as a critical controller of cell fate and function, such as metabolism, resistance to oxidative stress, DNA damage, autophagy and apoptosis [39]. Besides FOXO3 response being a crucial factor in mitigating aging and age-related diseases, including cardiovascular diseases, type II diabetes, cancers and neurodegenerative disease [39], the gene also regulates the CD8 T cell response to viral infections [94]. FOXO3 is known to promote apoptosis of T cells and to limit clonal expansion of CD8 T during an acute viral infection [94]. A deficiency of FOXO3 results in a dendritic cell-specific increase in the production of IL-6 [95]. These studies suggest that the transcription factor FOXO3 is a potential negative regulator of virus -specific CD8 T cell during chronic viral infection. Although, at this stage, a possible role of FOXO3 in SARS-CoV-2 induced COVID-19 is yet to be confirmed, it could represent a potential target for exploration of new therapeutic avenues to enhance CD8 T cell responses in COVID-19.

Numerous studies have shown that ASX efficiently activates the FOXO3 gene expression in animal models [39,96]. Reportedly, ASX modulates the expression of FOXO3 gene significantly in heart tissue, brain, skeletal muscle and blood [39]. In a study with iohexol induced-acute kidney injury in rat model, ASX was shown to upregulate FOXO3 expression in the renal tubular epithelium in both *in vitro* and *in vivo* models [96]. Treatment with ASX was found to efficiently protect against iohexol-induced acute kidney injury [96]. Recently, in mice model, oral administration of ASX has been shown to induce rapid increase of CD8 + T cell population by upregulating CCL5 macrophages and elevate expression of IFN-γ [97]. In addition, ASX exhibits marked protection against renal fibrosis by inhibiting fibroblast activation via modulating the Smad2, Akt and STAT3 signaling pathways and suppresses epithelial to mesenchymal transition in renal tubular epithelial cells via Smad2, snail and β-catenin [97]. Moreover, ASX has been reported to prevent pulmonary fibrosis [98] and liver fibrosis [99].

Perhaps, one of the important actions that ASX could act against viral infection is the ability to modulate evolutionary conserved NAD+ -dependent class III histone deacetylase enzyme sirtuins (types 1–7), primarily known as lysine deacetylases. Sirtuins modulate several signaling pathways, including insulin/IGF-1 signaling pathway, AMP-activated protein kinase, p53, NF-κB and FOXO [39,100]. With its diverse activities and localizations intracellularly, sirtuins are core regulators of cellular homeostasis and can control numerous cellular pathways required throughout the viral life cycle [100]. Sirtuins can impact the outcome of viral infection by modulating both host and viral gene expression and may represent a first line of defense against viral infection [100]. Sirtuin activation was reported to reduce influenza A virus titers, while inhibition increased titers [100,101]. Recently, several studies have highlighted the possible role of sirtuin in SARS-CoV-2 induced COVID-19 disease progression [102,103]. Reduced NAD + level and oxidative stress attenuate the protective functions of sirtuin [104]. NAD + level declines with aging and are further reduced in patients with diabetes, hypertension and obesity thereby reducing the activity of sirtuin [102–104]. Moreover, SARS-CoV-2 induced oxidative stress results in downregulation of sirtuins to further debilitate its protective functions [102,103]. Modulating sirtuin activity levels is thus emerging as a potential therapeutic in experimental models [105]. Drugs that can increase the level of NAD + and thus elevate the functioning of sirtuin in the hyperinflammatory stage may attenuate the CS [102–105].

Evidence from numerous studies has shown that ASX exerts its various protective actions via efficient regulation of the sirtuin pathway [39,106,107]. As discussed in earlier sections, ASX is a potent antioxidant and effectively protects against oxidative stress, which might be the possible mechanism of astaxanthin regulation of sirtuin pathway. In studies using a mouse model of transverse aortic constriction (TAC) induced myocardial fibrosis and cardiac dysfunction, administration of ASX was demonstrated to (a) improve the cardiac function, and (b) alleviate myocardial fibrosis, by decreasing phosphorylation and deacetylation of receptor activated-SMADs as well as increasing expression of sirtuin1 [106]. Treatment with ASX also inhibits the expression of TGF-β1 and TGF-β1-induced transformation of HCFs to myofibroblasts [106]. Furthermore, ASX was shown to enhance the activity of sirtuin1 without increasing the expression of sirtuin1 in TGF-β1 unstimulated cells, suggesting that sirtuin1 participates in the functions of ASX [106]. In another study, Gao et al. [107] found that ASX protects against acute contrast-induced renal injury via modulation of sirtuin1-p53 signaling pathway. In this study, it was also found that treatment with ASX markedly reduces the indictors of oxidative stress and significantly elevates the expression of sirtuin1 [107].

Additionally, the role of sirtuin1 in regulation of inflammatory cytokine within macrophages have been discussed [108]. In RAW264.7 macrophage/monocytic cells and primary intraperitoneal mouse

macrophages, Yoshizaki and colleagues demonstrated that sirtuin1 downregulates inflammatory pathway activity, gene expression and release of TNF-α from LPS-stimulated macrophages, and that pharmacological sirtuin1 activators exert broad anti-inflammatory effects [108]. In line with this, recently Kang et al. [109] have demonstrated that ASX inhibits alcohol induced inflammation and oxidative stress in RAW 264.7 macrophages and bone marrow-derived macrophages isolated from wild-type and mice with macrophage specific-deletion of histone deacetylase 4 (HDAC4). Treatment with ASX has been shown to attenuate the ethanol-induced decrease of sirtuin1 levels and abolish the increase in acetylated histone H3 by ethanol in macrophages [109]. Reportedly, the anti-inflammatory and antioxidant actions of ASX in ethanol treated macrophages are mediated via the elevated expression of sirtuin1 and perhaps by the crosstalk between sirtuin1 and/HDAC4 [109].

The therapeutic implications of ASX immunomodulation was demonstrated in Balb/cA mice infected with *Helicobacter pylori* [110]. Treatment with ASX was demonstrated to reduce the bacterial load and mucosal inflammation because of ASX mediated shift in cytokine release to Th2 cell response from Th1 cell response [110]. It was reported that an excessive Th1 response driven by *H. pylori* infection favors the development of cell mediated immune response leading to cytotoxic damage of the epithelium [110]. Treatment with ASX modulates the Th1 response with the shift in Th1/Th2 balance by downregulation of Th1-cells and up-regulation of Th2-cells, resulting in a protective and non-destructive immune response against *H. pylori* [110].

Evidence from these studies suggest that ASX is a potent antioxidant and a natural anti-inflammatory compound having efficient immunomodulatory action that exerts potential therapeutic benefits against oxidative and inflammation induced tissue damage.

4.4. Astaxanthin modulation of the peroxisome proliferator-activated receptors (PPARs)

PPARs are a family of PPAR-α, PPAR-γ and PPAR-β/δ subtype transcriptions factors belonging to the ligand activated nuclear hormone receptors (NR) superfamily. These are mainly expressed in immune cells and have an emerging critical role in immune cell differentiation and regulation of inflammation [111,112]. All three PPAR isoforms share a common structure, but manifest different tissue distribution, target genes and functions [112]. The PPARs primarily regulate lipid and glucose metabolism and have additional regulatory roles on cell proliferation and differentiation, cancer, vascular homoeostasis and atherosclerosis, the immune system and inflammation [113]. PPARs play important roles in antagonizing core inflammatory pathways, such as NF-κB, AP1 and STAT [114]. PPAR-α is mainly expressed in the liver, kidney, heart and skeletal muscles and is responsible for lipid metabolism and insulin sensitivity [111]. Evidence from studies also have suggested that PPAR-α might exert anti-inflammatory action by mediating a direct effect on adipocytes [112]. The probable mechanism involves sirtuin1, that suppresses the inflammatory response by inhibiting TNF-α induced CD40 expression via the sirtuin1-dependent signaling pathway [115]. PPAR-β/δ is ubiquitous throughout human body and is mainly responsible for epithelial cell growth, fatty acid oxidation and wound healing [111]. PPAR- γ is, by far, the most extensively studied PPAR isoform, is primarily found in adipose tissues and is the most common therapeutic target. PPAR-γ controls the homeostasis of immune system by regulating the fate and function of various immune cells [112]. In addition to its major role in lipid and glucose homeostasis, PPAR-γ is also associated with inflammation responses, cardiovascular diseases and cancer [111].

Recently, Ciavarella et al. [116] have highlighted the possible therapeutic implications of PPAR-γ agonists in COVID-19 cytokine storm. They suggest that the activation of PPAR-γ could represent an effective therapeutic strategy to counter SARS-CoV-2 induced cytokine storm and to prevent the effects of inflammation following COVID-19 [116]. Moreover, PPAR-γ has been reported as a key regulator of the innate immune system exhibiting a shift in production from pro-inflammatory to anti-inflammatory mediators by neutrophils, platelets and macrophages [117]. PPAR-γ modulates platelet and neutrophil function, prevents platelet-leucocyte interactions, promotes neutrophil apoptosis, alters macrophage trafficking, increases phagocytosis and promotes alternative M2 macrophages activation, suggesting its roles in adaptive immune response [117].

Considering such implications of PPAR-γ activation on inflammatory process, modulators of PPARs and specifically, agonists of PPAR-γ have been proposed among the possible therapeutic compounds that may be able to attenuate CS that typically occurs during severe respiratory viral infection such as influenza A virus (IAV), respiratory syncytial virus (RSV), etc. [116,118,119]. In this regard, Aldridge and colleagues [118] demonstrated that pioglitazone administration in mice reduces the amount of dendritic cell recruitment in infected lungs and improves the rate of CD8 + T cells, resulting in reduced morbidity and mortality due to highly pathogenic influenza virus A. Similarly, various natural and synthetic PPAR-γ agonists have been reported to downregulate significantly the RSV-induced expression of ICAM-1 on RSV-infected lung epithelial cells in a dose-dependent manner [119]. In addition to various synthetic forms, a series of natural PPAR-γ ligands including Curcumin, Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA) and Capsaicin have been discussed recently for possible use in COVID-19 [116].

ASX has a potent PPAR activity. The modulation of PPARs by ASX and its therapeutic implications in various pathophysiological conditions have been reviewed recently [111,120]. Treatment with ASX shows a differential regulatory action on PPARs. Primarily, ASX acts as an agonist of PPAR-α [121–123] and antagonist of PPAR-β/δ [123]. However, ASX exerts both PPAR-γ agonist and antagonist actions depending on the cell context [124,125]. Under normal physiological conditions, ASX acts as a PPAR-α agonist and PPAR-γ antagonist [121, 122]. Inoue et al. [124] reported that ASX acts as a PPAR-γ agonist in oxidative-stress related conditions in macrophages. ASX has been shown to induce the liver X receptor (LXR) and CD36 mRNA expression via PPAR-γ activation in macrophages in a dose-dependent manner [124]. In addition to their involvement in the metabolism of cholesterol and lipid, LXRs also suppress the expression of pro-inflammatory TNF-α, COX-2, iNOS and MMP9 [111]. From this study, it is evident that anti-inflammatory effects of ASX are mediated by PPAR-γ activation [111]. As reported, ASX exerts protective actions against *H. pylori* infection [110], which may be by preventing oxidative-stress mediated inflammation via the activation of PPAR-γ [125]. Kim et al. [125] demonstrated that *H. pylori* infection induces mitochondrial dysfunction by increasing NADPH oxidase-mediated overproduction of ROS leading to the activation of NF-κB resulting IL-8 expression and inflammation. Treatment with ASX activates PPAR-γ and its downstream target gene catalase, thereby inhibiting mitochondrial dysfunction by reducing ROS and significantly suppressing pro-inflammatory cytokine IL-8 gene expression [125]. Similar observations were also reported in ASX treated K562 human leukemia cells, suggesting ASX significantly and dose-dependently induces cellular apoptosis and PPAR-γ protein expression in K562 cells [126].

Considering the wide array of therapeutic benefits owing to its antioxidant, anti-inflammatory and immunomodulatory actions, ASX-mediated PPAR-γ modulation could represent an effective therapeutic strategy to regulate the host inflammatory and immune responses, contrast the CS and prevent the insidious inflammatory effects following COVID-19.

4.5. Astaxanthin modulation of the JAK/STAT3 pathway

The role of Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway in the initiation of interferon-stimulated response elements has been considered pivotal in the progression of SARS-CoV-2 induced COVID-19 [6,127–129]. IL-6 is an

essential pleiotropic cytokine produced by B- and T- cells, dendritic cells and macrophages to generate an immune response of inflammation. It plays a critical role in aberrant activation of JAK/STAT3 signaling pathway to confer various biological functions, including immune regulation, lymphocyte growth and differentiation, oxidative stress, etc. [128,128,129]. IL-6 binds to IL-6 receptor-subunit-α (IL-6R) and triggers a hetero-hexameric complex with IL6 receptor-subunit-B (gp130, IL-6ST) and activates the IL-6/JAK/STAT3 pathway, that includes activation of inflammation-related downstream targets [129]. In addition to its role in activation of JAK/STAT3 signaling pathway, IL-6 is one of the pivotal inflammatory cytokines highly expressed in COVID-19 cytokine storm [129]. Elevated serum levels of IL-6 has been considered as one of the main indicators of poor prognosis in COVID-19 [3,20].

Activation of the IL6/JAK/STAT3 signaling pathway results in a systemic cytokine storm involving secretion of VEGF, which contributes to vascular permeability and the extravasation of immune cells from blood vessels [6]. Attenuation of the JAK/STAT3 pathway would play a pivotal role in preventing the inflammation that occurs in COVID-19 [127–129]. Mehta et al. [127] have suggested that the inhibition of JAK/STAT pathway can affect both inflammation and cellular viral entry in COVID-19, which possibly can reduce the case fatality rate of severe COVID-19 due to sHLH or CRS. In this context, it would be pertinent to mention that the ASX modulation of the JAK/STAT3 signaling pathway has been revealed [48,50,130]. Supplementation of ASX abrogates constitutive activation of STAT3 by preventing its phosphorylation and subsequent nuclear translocation, thereby inhibition of the JAK/STAT3 signaling pathway [50]. Kowshik et al. [50] demonstrated that administration of dietary ASX inhibits JAK/STAT signaling by suppressing the levels of IL-6 and restraining the phosphorylation of STAT3. In addition, ASX administration markedly decreases the expression of MMP2, MMP9 [50]. Moreover, ASX significantly modulates the major downstream events triggered by the JAK/STAT signaling pathway. Abrogation of STAT3 by ASX was reported to be associated with the downregulation of the key mediators of angiogenesis, the VEGF and VEGF receptor 2 (VEGFR2) [50]. In addition, ASX also inhibits nuclear translocation of hypoxia inducible factor 1α (HIF-1α), a master regulator of angiogenesis responsible for transactivation of several hypoxia responsive genes including VEGF and VEGFR2 [50]. The study supports that ASX is a potent inhibitor of the JAK/STAT signaling pathway, revealing it as a promising anti-angiogenic candidate, and thus could be a potential therapeutic agent against COVID-19 as well.

Evidence suggests that ASX is a potent antioxidant and anti-inflammatory compound with immunomodulatory actions showing pleiotropic therapeutic benefits against oxidative damage, inflammation and immune dysregulation. Its modulatory actions on innate immune system via PPARs and potent anti-angiogenic activity further suggest that ASX could be a potential therapeutic agent against COVID-19. Taken together, we anticipate that ASX modulation of inflammatory pathways could exert potential therapeutic benefits against COVID-19 cytokine storm and its associated risks (Fig. 1).

5. Prospective application of natural astaxanthin in humans

Although there is no study related to the use of ASX in COVID-19 patients, there have been clinical studies that investigated the effects of ASX in human health benefits and disease involving oxidative stress

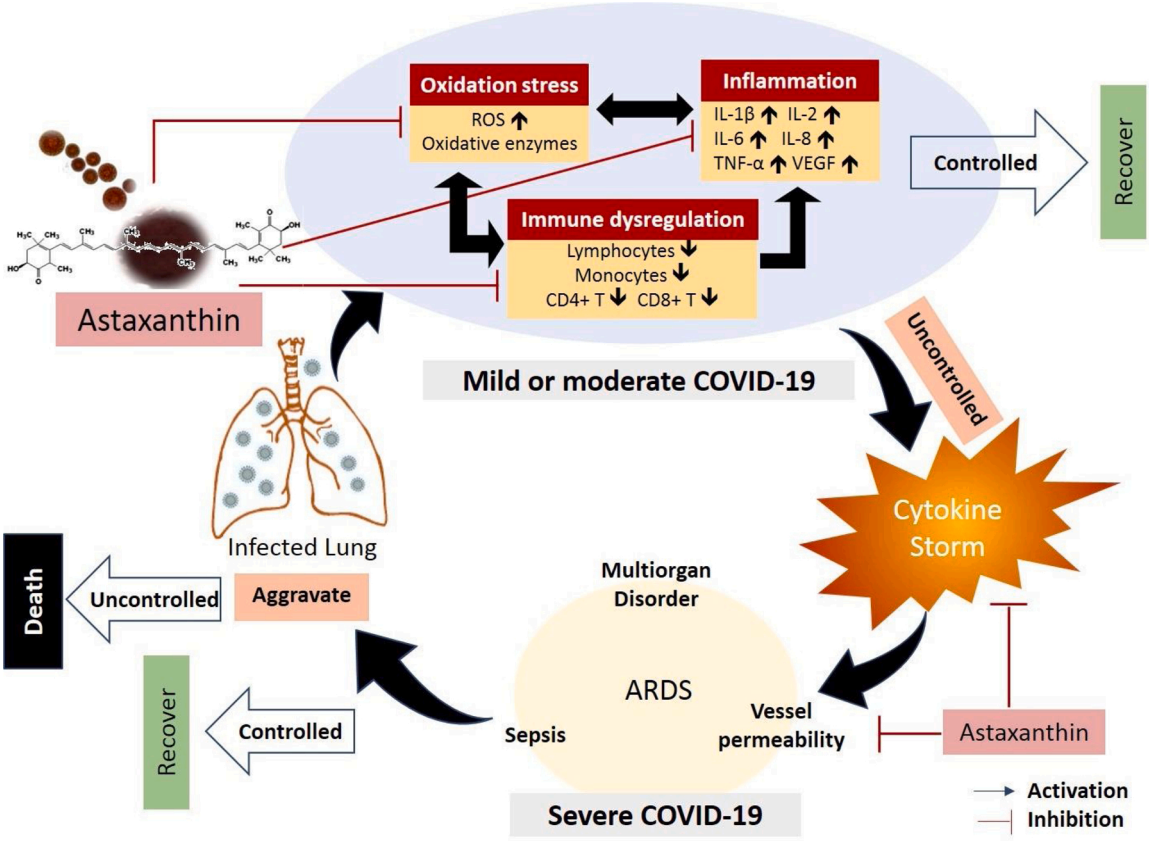

Fig. 1. Schematic representation of the putative pathogenesis of COVID-19 and hypothetical action of natural astaxanthin. We presumed that lung infected by SARS-CoV-2 elevated oxidation stress, elevated ROS mediated inflammation and a dysregulated immune response proceed unabated resulting violent cytokine storm syndrome. ARDS may ensue, accompanied by series of complications varying according to disease severity. Astaxanthin may play a vital role in regulation of the oxidative stress induced by ROS at the early stage of the infection, regulation of the immune response and downregulation of pro-inflammatory components, resulting in possible alleviation of cytokine storm. Astaxanthin may also provide supports for patients with ARDS and related complications with its anti-inflammatory properties.

and inflammation (Table 6). The most clinically demonstrated effects of ASX include antioxidation, anti-inflammation, immune modulation, lipid-metabolism-modulating and glucose lowering. In a double-blind randomized controlled trial, Choi et al. [131] reported that obese adult had higher serum levels of oxidative biomarkers (MDA and isoprostanes) and lower anti-oxidant capacity (SOD and total antioxidant capacity); however, three weeks of ASX supplementation (5 mg/d or 20 mg/d) lowered oxidative biomarkers and increased antioxidant capacity. Oxidation of low-density LDL and cell membrane lipids contributed to atherosclerosis and thrombus formation [8]. Iwamoto et al. [46] reported that ASX could protect human LDL against oxidation. The antioxidant effect of ASX against human LDL oxidation was further confirmed in an *ex vivo* study with 24 healthy adults supplemented with ASX (3.6 mg/day) for 14 days [8]. Nakagawa et al. [132] reported the effectiveness of ASX supplementation (6 and 12 mg/day) on phospholipid hydroperoxides (PLOOH) levels in erythrocytes in 30 healthy subjects. After 12 weeks of ASX administration, decreased PLOOH levels and increased ASX in erythrocytes were reported [132]. In another study involving human subjects, Karppi et al. [133] reported that supplementation of ASX for 12 weeks reduced the levels of plasma 12- and 15-hydroxy fatty acids in healthy males. These studies suggest that ASX exerts an antioxidant effect in human subjects that may potentially alleviate lipid peroxidation *in vivo*.

In a clinical study, Park et al. [14] investigated the action of dietary ASX in modulating immune response, oxidative status and inflammation in young healthy adult female human subjects. After 8 weeks of supplementation, ASX was found to enhance both cell-mediated and humoral immune responses, including T-cell and B-cell mitogen-induced

Table 6
Human clinical studies investigating safety, bioavailability and effects of astaxanthin.

Study population	Study design	Intervention (ASX mg/day) (durations)	Mechanism evaluated	Findings	References
42 healthy young women	Randomized, double-blind, placebo-controlled	Different doses: 2, 8 mg/d (8 weeks)	Immune-modulation, anti-inflammatory and antioxidant effects	- Significant decrease in CRP level - Reduced oxidative stress - Decreased plasma 8-hydroxy-2′-deoxyguanosine - Increased total T and B cell population - Enhanced NK cell cytotoxic activities - Stimulated lymphocyte proliferation - Decreased DNA damage significantly - Stimulated immune system	[14]
27 overweight and obese adults	Randomized, double-blind, placebo-controlled	20 mg/d (12 weeks)	Antioxidant effect	- Reduction of LDL, ApoA1/ApoB ratio relative to baseline - Induced TAC and SOD compared to baseline - Reduced lipid peroxidation biomarkers (MDA and ISP) compared to baseline	[131]
24 Healthy volunteers	Open-label	Different doses: 1.8, 3.6, 14.4 mg/d (2 weeks)	Antioxidant effect	- Reduction of LDL oxidation	[46]
30 healthy individuals	Randomized, double-blind, placebo-controlled	20 mg/d (12 weeks)	Antioxidant effects	- Reduced phospholipid hydroperoxide levels in erythrocytes	[132]
39 healthy men	Randomized, double-blind, placebo-controlled	8 mg/d (3 months)	Antioxidant effects	- Reduced plasma lipid peroxidation, decreased 12-hydroxy and 15-hydroxy fatty acids	[133]
61 healthy individuals with triglyceride levels between 100−200 mg/dl	Randomized, double-blind, placebo-controlled	Different doses: 6, 12, 18 mg/d (12 weeks)	Lipid metabolism	- Reduced triglyceride levels - Increased HDL - Increased adiponectin	[136]
Healthy adults	Randomized, double-blind, placebo-controlled	6 mg/d (3 × 2 mg/d) (8 weeks)	Safety	- Demonstrated safety assessed by measures of blood pressure and biochemistry	[138]
Healthy men	Open-label	40 mg/d (8 weeks)	Bioavailability	- Enhanced bioavailability with lipid-based formulation	[139]
20 healthy adult men	Single-blind	6 mg/d (10 days)	Blood rheology	- Improved blood rheology - Reduced transit time	[140]
3 healthy males	Open-label	Different doses: 10, 100 mg	Plasma appearance/ elimination half life	- C_{max} 0.28 mg/L at 11.5 h at 100 mg dose and 0.08 mg/L at 10 mg dose - Elimination half-life 52 ± 40 h - Z-isomer selectively absorbed	[141]
20 healthy postmenopausal women with high oxidative stress	Open-label	12 mg/d (8 weeks)	Antioxidant effect	- Increased antioxidant capacity - Lowered blood pressure - Reduced vascular resistance in lower limb - Reduced serum adiponectin	[144]
39 smokers 39 non-smokers	Randomized	Different doses: 5, 20, 40 mg/d (3 weeks)	Antioxidant effect	- Increased SOD and TAC - Reduced MDA and ISP	[145]
43 type 2 diabetic patients	Randomized, double-blind, placebo-controlled	8 mg/d (8 weeks)	Lipid and glucose metabolism	- Reduced triglyceride, VLDL, visceral fat mass and fructosamine - Reduced systolic blood pressure - Increased adiponectin	[146]
40 elite soccer players	Randomized, double-blind, placebo-controlled	4 mg/d (90 days)	Immune-modulation and antioxidant effect	- Increased immunoglobulin - Decreased pro-oxidant/antioxidant balance - Controlled CRP - Attenuated muscle damage	[147]

lymphocyte proliferation, NK cell cytotoxic activity, IFN-γ and IL-6 production. Moreover, the levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) and plasma CRP concentration were reported to reduce post supplementation with ASX [14]. The study also demonstrated that supplementation with ASX enhances the expression of leukocyte function antigens (LFA)-1 [14]. LFA-1 is known to control the migration of lymphocytes into inflammation sites [14].

Reportedly, in diet-induced obesity in mice, ASX significantly lowered the concentration of plasma triglyceride, alanine transaminase (ALT) and aspartate aminotransferase (AST), and increased the mRNA expression of antioxidant genes regulated by Nrf2 in the liver [134]. In addition, ASX has been reported to decrease macrophage infiltration and apoptosis on vascular cells in atherosclerosis plaques [135]. In a placebo-controlled study, Yoshida et al. [136] investigated the lipid-metabolism-modulating effect of ASX in 61 non-obese humans using ASX administration at doses of 0, 6, 12 and 18 mg/day for 12 weeks. The study showed that administration of 12- and 18 mg/day of ASX significantly reduced serum triglyceride and adiponectin levels and 6- and 12 mg/day doses significantly increased HDL-cholesterol [136]. Furthermore, in a randomized double-blind placebo-controlled study, Katagiri et al. [137] demonstrated that administration of ASX-rich *H. pluvialis* extract (6 or 12 mg/day) for 12 weeks improved cognitive function in healthy aged humans.

6. Safety of natural astaxanthin in humans

H. pluvialis sourced ASX is a potent antioxidant with many biological functions and is widely used in the fields of health food applications and biomedical research [142]. The U.S Food and Drug Administration (FDA) approved ASX as a dietary supplement [143] and notified the "generally recognized as safe" (GRAS) status to *H. pluvialis* derived ASX product [66].

Multiple preclinical and human clinical studies involving orally administered ASX in doses ranging from 4 mg to 100 mg/day have shown no adverse or toxic effects [8,138]. Human clinical studies have found ASX to be safe for human consumption and orally bioavailable [139]. *H. pluvialis* derived ASX has been reported to be more bioavailable, probably due to the presence of astaxanthin esters [17]. Maximal blood concentration of ASX has been reported to occur between 8 and 10 h after ingestion of 40 mg in healthy adults [139,140]. Following consumption of 40 mg ASX, the plasma elimination half-life period was estimated as 15.9 ± 5.3 h [139] and the same for 100 mg ASX ingestion was estimated as 52 ± 40 h [141]. No significant adverse effects of ASX have been reported so far in any published human trials. These results support the safety profile of ASX for human consumption.

7. Concluding remarks

In this review, the intricate relationship between SARS-CoV-2 induced COVID-19 infection and its immunologic complication CSS along with the possible mechanisms involved in CS development was discussed. While there is a limitation in our understanding of COVID-19 fully, it must be acknowledged that literature about COVID-19 has been evolving rapidly. It appears that oxidative stress plays a major role in the course of COVID-19 pathogenesis as well as perpetuates pro-inflammatory CS, coagulopathy and exacerbated hypoxia. Taken together, it is evident that the involvement of oxidative stress is an important factor in the pathogenesis of SARS-CoV-2 infection in all direct tissue injury, including mitochondrial dysfunction and in the activation of inflammatory signaling pathways such as NF-κB, JAK/STAT and NLRP3.

Further, CS triggered by SARS-CoV-2 infection is one of the principal causes of death. CS is exacerbated by dysregulation of ROS and pro-inflammatory cytokine production, leading to ALI, multi organ failures and eventually the host demise. Indeed, ARDS observed with SARS-CoV-2 infection is a CRS, a disorder induced by CS. Hence, in addition to antiviral therapy, additional therapy to manage the CS may require targeting of both the overlying oxidative stress and cytokine pathways, particularly NF-κB and IL-6-JAK/STAT3.

The microalgae derived ASX as a potent antioxidant and anti-inflammatory compound has been demonstrated to prevent against oxidative damage in various *in vitro* and *in vivo* studies including animal models. Mounting evidence from preclinical studies suggest that ASX is a potent inhibitor of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, regulating via intracellular cytokine pathways and modulation of PPAR-γ and endogenous anti-inflammatory mechanisms. In animal models, ASX has been demonstrated to alleviates ALI/ARDS by off-setting the cytokine storm, inhibiting subsequent fibrosis and increasing survival rates. Additionally, human clinical trials have proven its safety for human consumption with no noticeable side-effects. Furthermore, the immunomodulatory, anti-inflammatory and antioxidant actions of ASX have been demonstrated in human studies. In summary, the pre-clinical studies along with available literature reviewed here motivate a call for attention to the clinical investigation of ASX as a potential therapeutic supplement for the management of CS syndrome following COVID-19 infection.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval statement

No ethical approval was obtained as all relevant information were retrieved from publicly available literature through multiple databases and no primary data was collected or generated during the review process.

CRediT authorship contribution statement

Jayanta Talukdar: Conceptualization, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Bhaskar Bhadra:** Investigation, Data curation, Writing - review & editing. **Tomal Dattaroy:** Data curation, Writing - review & editing. **Vinod Nagle:** Investigation, Data curation. **Santanu Dasgupta:** Investigation, Data curation.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

We thank our employer for providing all necessary resources to write this article.

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