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Review

An insight to the therapeutic potential of algae-derived sulfated polysaccharides and polyunsaturated fatty acids: Focusing on the COVID-19

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ABSTRACT

Covid-19 pandemic severely affected human health worldwide. The rapidly increasing COVID-19 cases and successive mutations of the virus have made it a major challenge for scientists to find the best and efficient drug/vaccine/strategy to counteract the virus pathogenesis. As a result of research in scientific databases, regulating the immune system and its responses with nutrients and nutritional interventions is the most critical solution to prevent and combat this infection. Also, modulating other organs such as the intestine with these compounds can lead to the vaccines' effectiveness. Marine resources, mainly algae, are rich sources of nutrients and bioactive compounds with known immunomodulatory properties and the gut microbiome regulations. According to the purpose of the review, algae-derived bioactive compounds with immunomodulatory activities, sulfated polysaccharides, and polyunsaturated fatty acids have a good effect on the immune system. In addition, they have probiotic/prebiotic properties in the intestine and modulate the gut microbiomes; therefore, they can increase the effectiveness of vaccines produced. Thus, they with respectable safety, immune regulation, and modulation of microbiota have potential therapeutic against infections, especially COVID-19. They can also be employed as promising candidates for the prevention and treatment of viral infections, such as COVID-19.

1. Introduction

Coronavirus disease-2019 (COVID-19) is a respiratory syndrome disease caused by a new strain of the *Coronaviridae* family of viruses, the extreme acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The devastation caused by the ongoing COVID-19 pandemic on public health, the economy, and society has sped out the development of vaccines in the whole world, being a global health priority. However, the emergence of new mutant strains poses a hurdle to vaccine effectiveness. Several studies have already reported that the new strains are more than 50% more contagious than the wild-type SARS-CoV-2 virus. The approved vaccines may not be as effective against these strains, necessitating additional research to confirm the efficacy of the current vaccines [2]. Thus, preventive medications are prescribed for a disease without treatment, and immunomodulators combined with antivirals may be effective [3].

Immunomodulators are substances that influence the immune system's activity [4]. Numerous studies have evaluated the effect of using immunomodulators on improving health in severe patients with COVID-19. Despite the results, which indicate that patients are recovering, some immunomodulatory agents are correlated with an increased risk of secondary infections [5]. Some reports indicated common nosocomial

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ALA, α-Linoleic acid; ARA, Arachidonic acid; CCL2, 3, 5, C-C motif chemokine ligand 2; CD4+, Cluster of differentiation 4; CXCL8, 9, 10, C-X-C motif chemokine 8, 9, 10; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; GIT, Gastrointestinal tract; IFN- α /γ, Interferon alpha/gamma; IgG, Immunoglobulin G; IL-6 ((IL)-6), Interleukin-6 (IL 1, 7, 8 10, 12); iNOS, Inducible nitric oxide synthase; NK cells, Natural killer cells; Omega-3 LC-PUFAs, Omega-3 long-chain polyunsaturated fatty acids; Th1, T helper cell type 1; TNF-α, Tumor necrosis factor alpha; SCFAs, Short-chain fatty acids.

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infections, including bacteremia, pneumonia, and fungal infections such as invasive fungal infections [6], Herpes simplex virus (HSV) reactivation [7], and *S. stercoralis* infection [8]. Therefore, the use of natural bioactive compounds and nutraceuticals that, in addition to immunomodulatory properties, also have antimicrobial and non-toxic effects appears to be a potential panacea.

Marine resources, mainly algae, are abundant bioactive compounds with potential nutraceutical and therapeutic applications [9]. Clinical evidence of algae-based nutraceuticals' ability to boost immunity against viral diseases has already been published [10].

Sulfated polysaccharides (SPs) and polyunsaturated fatty acids (PUFAs) derived from marine sources have emerged as hotspots in the field of bioactivity research in recent years due to their exceptional immunological [10], antiviral, probiotics [9], and prebiotics [11] properties. Numerous studies have investigated the antiviral properties of these compounds, especially SPs against the SARS-CoV-2 [12,13]. SPs' diverse structure plays a vital role in enhancing the host antiviral response by interfering with virus attachment, adsorption, and replication. In addition, the mechanism of several SPs in inhibiting the various stages of viral infection within the host cell is demonstrated. They block the initial entry of the virus or inhibit their transcription and translation by modulating the host cell's immune response [12,14,15]. These compounds can also help modulate immunity against SARS-CoV-2 via several pathways. Furthermore, structurally associated entities of SPs such as carrageenan may serve as effective adjuvants for improving peptide-based vaccines' effectiveness through immune enhancement [16].

Dietary essential PUFAs play a critical role in the proper functioning of both innate and adaptive immune systems, contributing to chronic and acute inflammation control. Because omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs) are well-known metabolic precursors of specialized pro-resolving lipid mediators (SPMs), they may contribute significantly to the resolution of the inflammatory balance, thereby limiting the level and duration of the critical inflammatory period. Omega-3 LC-PUFAs may also interact with the virus at various stages of infection, most notably during virus entry and replication [1]. One study recently found that *spirulina*-based nutraceuticals and bioactive compounds can be used in current research and clinical trials for immune stimulation, disease prevention, and treatment of disorders caused by severe coronavirus infections, such as tissue repair angiotensin-converting enzyme 2-dominant (ACE2) organs and anti-inflammatory medicine [10].

In addition to the immune system, the human intestine and its microbiomes have recently become the forefront of viral infection research, such as COVID-19. The most eminent example of the link between the gut microbiota and COVID-19 infectious disease is connected to the type and regulation of microbiomes [17,18]. Recent research indicates that the gut bacteria are also an important factor in sustaining the cytokine storm [18]; therefore, regulation and improvement of microbiomes can improve immune system function and, therefore, the effectiveness of vaccines. A study stated that numerous components of dietary seaweeds include ACE inhibitory peptides, soluble dietary fibers (e.g., fucoidan, porphyran), omega-3 fatty acids, fucoxanthin, fucosterol, vitamins D3 and B12, and phlorotannins. These compounds have anti-inflammatory, antioxidant, and antiviral effects directly as well as indirectly through prebiotic effects that, for example, could minimize the ACE dominance caused by SARS CoV-2 infection. As a result, dietary seaweeds may protect COVID-19 through a variety of mechanisms [19].

The fact that natural bioactive compounds and nutrients are modulators of the immune system and gut microbiome, can be used to develop clinical nutrition concepts to improve and treat infectious diseases such as COVID-19. Therefore, this review article will examine algae derived SPs and PUFAs potential in the prevention and treatment of infectious diseases such as COVID-19.

2. COVID-19: metabolic health and nutrient status

When dealing with a life-threatening condition like COVID-19, it's critical that patients have the strength and reserves to recover from the acute phase of their illness while also preparing for the possibly lengthy rehabilitation process that will follow. Nutrition is critical at both of these stages [20]. Nutritional status appears to be a significant factor impacting the outcomes of COVID-19 patients [21]. According to studies, preventive interventions such as public health principles and nutritional support are critical at this moment in the global pandemic of COVID19 [22–24]. As a general conclusion from research, maintaining nutrient adequacy is critical for minimizing the risk of infection and disease development, either through their roles in the normal function of the immune system or through the promotion of metabolic health. Nutrient deficits, which disrupt the microbiota balance, also impact the immune system and vaccine efficiency [25]. Researchers also point to a relationship between a variety of disorders (such as obesity, diabetes, high blood pressure, and cardiovascular disease) and the possibility of hospitalization for COVID-19 patients [20], which all of these disorders are strongly linked to dietary habits and lifestyle choices [20,26]. As a result, it is expected that COVID-19 will have a multi-stage impact, necessitating research into the function of nutrition in acute treatment, recovery, and prevention of chronic diseases that enhance vulnerability to infection [20]. It should also be investigated in the prevention and treatment of COVID 19 infection. Bioactive compounds and nutrients of natural origin have therapeutic potential against a variety of disorders and infections. Therefore, due to the importance of the function of the immune system and gut microbiome against diseases and infections, this article introduces the ability of some natural bioactive compounds as nutrient to prevent and treat COVID-19.

3. COVID-19: clinical manifestations in the immune system and gut microbiome

3.1. The immune system and COVID-19 patients

COVID-19 infection begins with virus attachment to ACE2 receptors on host cells. Following COVID-19 infection occurs an active innate and adaptive immune response [27], generally, viral antigens are presented to T cells and B cells with a major histocompatibility complex (MHC) on APCs upon entry into the host, by activating innate and adaptive immunities. Innate immunity reaction in viral infections is initiated by interferon secretion from the infected cells to signal to other cells and make them ready for battle [28,29]. However, various potential SARS-CoV-2 mechanisms are being evaluated in the immune system; the research on the immune mechanisms of similar viruses such as SARS-CoV and MERS-CoV offers a great deal of insight into the immune mechanism of SARS-CoV-2 [29]. The innate immune system is the first immune response to SARS-CoV infection, which identifies pathogens and triggers pro-inflammatory cytokines to induce an immune response. The adaptive immune system then responds with T cells that can destroy virus-infected cells directly and B cells that produce pathogen-specific antibodies. During the immune response, cytokines are released, attracting pro-inflammatory cells like macrophages and neutrophils to the infection site, inducing an inflammatory response [30]. Although these responses are vital for virus clearance, they may harm normal host tissues. Studies on SARS-CoV-2 have shown that this virus interferes with normal immune responses, leading to immune system dysfunction and uncontrolled inflammatory responses in severe COVID-19 patients. These patients display lymphopenia, activation and malfunction of lymphocytes, dysfunctional granulocytes and monocytes, elevated cytokine levels, and increased immunoglobulin G (IgG) and total antibodies [31]. The immunopathology of COVID-19 is explained in detail in the figure below (**Fig. 1**).

Immunopathology studies of COVID-19 patients in China suggest a decline in lymphocytes in severe patients. After evaluating patients'

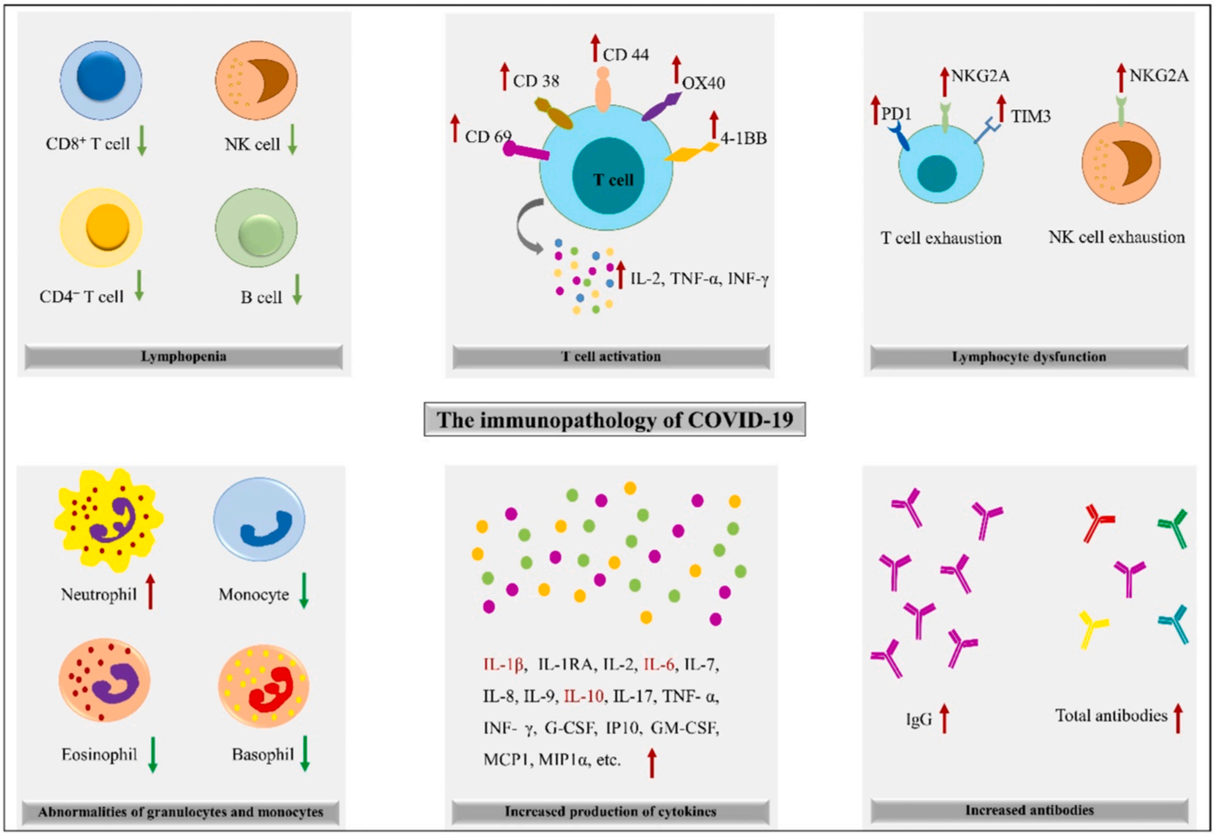


Fig. 1. COVID-19 causes lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities, increased cytokine production, and increased antibodies. Lymphopenia is a common symptom in COVID-19 patients, particularly in severe cases. CD4+ and CD8+ T cells of the patients, the expression of the levels of CD69, CD38, and CD44 increased, and virus-specific T cells from severe cases have a central memory phenotype with high levels of IFN- γ, TNF- α, and IL-2. Upregulation of programmed cell death protein-1 (PD1), T cell immunoglobulin domain and mucin domain-3 (TIM3), and killer cell lectin-like receptor subfamily C member 1 (NKG2A) in lymphocytes, however, results in an exhaustion phenotype. The number of eosinophils, basophils, and monocytes decreases in severe patients, whereas neutrophil levels are significantly higher. Another prominent characteristic of severe COVID-19 is an increase in cytokine production, especially IL-1, IL-6, and IL-10. There is also an increase in IgG levels and a higher total antibody titer [4].

symptoms, they appear to have lower lymphocyte numbers, higher leukocyte counts and neutrophil-lymphocyte ratio (NLR), and lower monocyte, eosinophil, and basophil percentages, and lower regulatory T cell levels [32]. The cluster of differentiation 4 (CD4+) T lymphocytes are also immediately activated to become pathogenic T helper cell type 1 (Th1) cells and produce granulocyte-macrophage colony-stimulating factor (GM-CSF) etc., after the COVID-19 infection [33]. Generally, substantial lymphocyte reduction and elevation of interleukin- 6 (IL-6), IL-10, and C-reactive protein (CRP) are valid markers of severe COVID-19 [34]. One of the vital features of severe COVID-19 is increased cytokine production [4]; according to clinical trials, increased levels of pro-inflammatory cytokines such as interferon alpha (IFN- α), IFN- γ, IL-1b, IL-6, IL-12, IL-18, IL-33, tumor necrosis factor alpha (TNF- α), transforming growth factor beta (TGF- β), and chemokines such as C—C motif chemokine ligand 2 (CCL2), CCL3, CCL5, C-X-C motif chemokine (CXCL8), CXCL9, CXCL10, among others, resulted in a cytokine storm in COVID-19 patients [35,36]. This cytokine storm may be accompanied by multiple organ failure and acute respiratory distress syndrome (ARDS), leading to SARS-COV-2 infected patients' death as seen in SARS-CoV and MERS-CoV infections [37–40]. As mentioned above, there is a strong indication supporting a close association between immunopathology caused by SARS-CoV-2 and poor survival of COVID-19 patients. Unfortunately, several therapies have not demonstrated a substantial change in severe COVID-19 patients [41]. Therefore, the particular immune profiles of COVID-19, such as lymphocyte enhancement or inflammation reduction, and identification of these mechanisms with immunotherapy [28], can be promising treatment strategies for severe disease cases [4].

3.2. The gut microbiome and COVID-19 patients

Infections caused by coronaviruses, such as SARS-CoV- 2, result in a variety of gastrointestinal symptoms. Virus-specific antibodies and inflammatory cytokines are created as a consequence of COVID-19 infection [30,31]; these are detectable in COVID-19 patients' stool samples [42]. Interestingly, the virus is expected to stay active in the gastrointestinal tract (GIT), maybe in a dormant condition, even when GIT signs are absent or after respiratory recovery from infection [43]. Following the outbreak of COVID-19 in 2020, researchers discovered gut microbiome dysbiosis and immune-inflammatory phenotypes that could predispose individuals to be severe/fatal COVID-19 consequences [18]. In this study, inflammatory cytokines were positively connected with the genera *Blautia*, *lactobacilli*, and *Ruminococci*, but negatively correlated with *Bacteroides*, *Streptococcus*, and order Clostridiales.

Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia are the most common gut microbial Bacteroidetes phylum [44], accounting for 90% of gut microbiota. Among the bacteria present in the gut microbiome, Firmicutes and Bacteroidetes are the most beneficial [45]. Lactobacillus, *Bacillus*, *Clostridium*, *Enterococcus*, and *Ruminicoccus* are among the more than 200 genera that make up the Firmicutes phylum. Ninety-five percent of the Firmicutes phylum is made up of the *Clostridium* genus. Bacteroidetes include well-known taxa, including *Bacteroides* and *Prevotella*. The Actinobacteria phylum has a smaller fraction of bacteria and is dominated by the *Bifidobacterium* genus [18,46]. It is also well recognized that gut bacteria have a role in influencing the host's immune system [47]. In severe patients, the pro-inflammatory cytokines IL-6, IL-10, IFN, and TNF- α are elevated during COVID-19 infection [48]. It's worth noting that several of the cytokines listed above are frequently connected to the gut bacterial population and have a role in triggering the cytokine storm [18].

COVID-19 patients have lower levels of probiotic bacteria (e.g., *Lactobacillus* and *Bifidobacterium*), according to studies [18]. This can be demanding because high *Lactobacillus* spp. Levels correlate with increased anti-inflammatory IL-10 cytokine levels [49]. The cytokine marker IL-10 may be used as a predictor for rapidly detecting patients at increased risk of COVID-19 disease worsening during infection [50]. Several gut commensals with recognized immunomodulatory capabilities, such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Bifidobacterium*, were underrepresented in COVID-19 patients and remained low in samples taken up to 30 days after the disease had resolved [51]. Furthermore, the quantity of butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium* was shown to be drastically reduced [52]. COVID-19 cases were distinguished by a lack of helpful commensals such as *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, Lachnospiraceae taxa, *Roseburia*, and *Bacteriodes* spp. such as *B. dorei*, *B. massiliensis*, *B. ovatus*, and *B. thetaiotaomicron*, which correlate with illness severity [53]. Also, SARS-CoV-2 infection reduces ACE2 expression in the GI tract and the number of circulating angiogenic cells (CACs), endangering the gut endothelium and leading to intestinal dysbiosis, which gut flora dysbiosis during COVID-19 infection results in pathogenic species outnumbering the commensal bacterial population [18,54]. Other studies have shown that opportunistic fungi (*Candida albicans*, *Candida auris*, and *Aspergillus flavus*) and bacterial pathogens (*Clostridium hathewayi*, *Clostridium ramosum*, and *Coprobacillus*) were also found in the COVID-19 patients' microbiomes [17,43]. In contrast to these results, some researchers found no correlation between microbiome composition and the severity of COVID-19 or gut inflammatory markers. Thus, only patients treated with antibiotics experience significant microbiome changes with limited microbial diversity [42]. Nevertheless, most studies point to an association between the gut microbiome and disease severity in COVID-19 patients. Such studies show the role of the microbiome in a wide range of infectious diseases, including COVID 19. Therefore, they can help identify potential treatment targets for the management and treatment of COVID-19.

4. COVID-19: prevention and treatment with natural bioactive compounds and nutrients

Many research groups worldwide are engaged in looking for new drugs and vaccines to combat SARS-CoV-2 and its adverse effects. Although the production of vaccines is efficient, it still needs a lot of effort, investment [55], and time [56]. Therefore, choosing a way to prevent and boost the immune system and gut microbiome can be considered as one of the potential perspectives for the prevention and treatment of COVID 19; thus, consumption of nutritious foods and adjuvant therapies become a requirement during the current crisis caused by the COVID-19 pandemic, and it's offered as a suggested solution [57]. Among the options of adjuvant treatment for COVID-19 infection, bioactive natural compounds can be considered as an option. They are traditionally used to help preventing and alleviating diseases since they are usually inexpensive, widely available, and rarely have undesirable side effects. Some have demonstrated antiviral activity [58,59]. To date, the varieties of bioactive compounds derived from natural resources, such as animals, plants, microorganisms, and marine organisms, have been identified and are being used to combat SARS-CoV-2 [10] and other viral respiratory infections [60]. For example, the use of natural bioactive compounds derived from mushroom [61,62], various herbal medicines [60,63–65], plant polyphenols [60,66,67], propolis [58], honey [68], and the variety of bioactive compounds derived from marine organisms such as sponge [69], and algae [70–72].

Additionally, clinical nutrition is critical for multidisciplinary management of patients infected with the known SARS-CoV-2 virus [21]. It is especially vital for patients with pathological history of cardiovascular disease, diabetes mellitus, or impaired metabolic control. These conditions may exacerbate the affection of the virus [73]. According to studies in the context of COVID-19, patients with a pathological account have a higher chance of death due to the immune system's response to inflammatory disease. Multiple variables contribute to this extreme immunological response, one of which is the degree of past inflammation experienced by the organism, which leads to premature immune system senescence [38]. However, changes in lifestyle, such as proper nutrition [74] and the correct amount of physical activity, can help prevent chronic inflammation in the body [75]. As a result, nutrition plays a vital role in responding to disease, particularly “immunonutrition,” which is a cornerstone in understanding the inflammatory response, whether as a preventative or therapeutic agent. Immunonutrition is a new and interdisciplinary field encompassing several aspects of nutrition, immunity, infection, inflammation, and tissue damage. Multiple interactions occur between the endocrine, neurological, and immune systems, the latter part, the gut microbiome [76]. Due to the role of gut microbiome in the functioning of the immune system and also its supportive role in antiviral immunity, the complex relationship between nutrient compounds, the immune system, and the gut microbiome in COVID-19 infection is the main reason for current review.

There are approximately 10^{13}–10^{14} microbial cells in the human microbiota [77,78]. This large pool of microorganisms that live on the mucosal surfaces of the GIT has both direct and indirect impacts on the host immune system, with the gastrointestinal tract accounting for an estimated 70% of the immune system response [76]. The interactions between the host and microbiota are bidirectional, complex and can potentially influence the development and function of both innate and adaptive immune systems [79]. Commensals maintain homeostasis by generating antimicrobial peptides (AMPs) and competing with pathogens for nutrients and space at the site of infection, suggesting a reciprocal link between gut microbiota and immunological homeostasis that could be utilized in the current pandemic. Gut microbiota signals can influence immune-mediated cells' pro-inflammatory (helper T cells type 17; Th17) and anti-inflammatory (regulatory T cells; Tregs) responses, affecting susceptibility to certain diseases [80,81]. Thus, coronavirus infections can be combated by a healthy gut microbiota, which protects the lungs and other important organs from an overactive immune response [79]. The impact of the gut microbiome on COVID-19 has been studied extensively. Improving the gut microbiome with nutrition, according to the findings, not only regulates immune responses [79,82], but also makes vaccines more effective [83,84]. Given the importance of the intestinal microbiota in the immune response and the fact that SARS-CoV-2 progression appears to be linked to a “cytokine storm” that results in hyper-inflammation (elevated levels of pro-inflammatory cytokines such as TNF, IL-6, and IL-1), special attention should be paid to this issue [76]. The authors attempted to investigate the mechanism by which the gut microbiota may aid or hinder SARS-CoV-2 virus transmission. There's an opportunity for a new link now that SARS-CoV-2 RNA has been discovered in feces [85]. Recent research discovered increased levels of *Clostridium ramosum* and *Clostridium hathewayi*, which are linked to the severity of SARS-CoV-2 symptomatology, as well as decreased levels of *Alistipes* spp. [86]. In addition, *B. thetaiotaomicron*, *B. dorei*, and *B. massiliensis*, which can downregulate ACE2 expression in the mouse gut, were found to correlate inversely with the SARS-CoV-2 load in patient feces in a recent study [17,43]. As a result, alterations in the gut microbiota could affect the virus's ability to gain cellular entrance into the gut [82,87]. Also, vaccine trials have indicated that improving gut microbiota with nutrients can improve vaccine efficacy against SARS-CoV-2 infections, and healthy gut microbiota is required for vaccine efficacy [83,84]. A clinical trial is currently investigating using a yeast-based probiotic as a nutrient to enhance the COVID-19 vaccine [88]. According to the findings of this study, the supplement they employ can alter the gut flora, increasing the COVID-19 vaccine's effectiveness.

Additionally, the results of a study demonstrated that vaccines are incapable of eliciting robust immune responses in germ-free mice or mice given antibiotics [89]. For the prevention of COVID-19, various vaccines against SARS-CoV-2 are now being developed. Additional focused research is warranted to further optimize their efficacy by regulating the gut microbiota. In general, according to a study on the nutritional status of patients with COVID-19 and the understanding that nutrient deficiencies can lead to severe COVID-19 and reduced efficacy of vaccines, it can be stated that supplementation with nutraceuticals that have modulating capabilities for the immune system and gut microbiome. Thus, they can be used as a preventive method and an adjunctive therapy to reduce the severity of COVID-19 infection and reduce mortality. Hence, in the next sections, we will describe the potential of natural bioactive compounds of algal origin as nutrient and modulators of the immune system and gut microbiome for the prevention and treatment of COVID-19 infection.

5. Therapeutic and preventive potential of algal compounds in COVID-19

5.1. Algae as a source of bioactive compound and their health benefits

Seaweeds or marine algae have unique structures and biochemical compositions that can be used for their versatile properties in foods and medicines [90]. They contain a variety of nutritional ingredients, including minerals, trace elements, vitamins, and lipids such as LC-PUFAs, polysaccharides, phlorotannins, and even proteins; some of them are also high in dietary fiber due to indigestible SPs [90,91], and this demonstrates seaweed's enormous potential for the extraction of bioactive compounds and nutrients [90]. According to many studies, a variety of bioactive compounds derived from algae such as polysaccharides, PUFAs, pigments, peptides, carbohydrates, vitamins, polyphenols, and phytosterols have attracted much interest in recent years due to the significant biological and chemical diversity [92–94]. These compounds reported different properties, including their antimicrobial, anti-inflammatory [93], immunostimulatory, and immunomodulatory [10] properties. They may use as immune boosters [10,95] and therapeutic agents to monitor human pathogen attacks and disease prevention [10,71]; they also have antiviral properties against various enveloped viral infections [94], such as human immunodeficiency virus (HIV) [96], herpes simplex virus (HSV) [97], and recently SARS-CoV-2 virus [94]. Additionally, research indicates that bioactive compounds derived from marine algae, such as alginate, fucoidan, laminaran, polyphenol, carrageenan, carotenoid, fatty acids, and phlorotannins, benefit the human gut microbiota by regulating metabolism, maintaining epithelial barrier integrity, and the immune system [98,99]; thus, they are referred prebiotics or nutritional food [100]. Therefore, considering their nutritional composition, together with recent studies about their health-beneficial properties, has justified the growing demand for incorporating algae into the human diet.

Among the compounds derived from algae, SPs such as agar, alginate, or carrageenan and PUFAs are highlighted because extracted SPs and PUFAs have been shown to possess a variety of biological properties such as immunomodulator [9,93,101], antioxidant [102,103], anti-inflammatory, anticoagulant, antitumor, antiviral [9,104–106], and prebiotic [107], among others [106]. These properties indicate these compounds potential for use in nutraceutical and pharmaceutical applications [108]. Therefore, due to the importance of the immune system and gut microbiome in the treatment of infections, in this study, we will investigate the mechanism of two crucial bioactive compounds from algae (SPs and PUFAs) as nutrient in modulating the immune system and gut microbiome and finally in the prevention and treatment of COVID-19.

5.2. Algae-derived SPs for immune system -based therapy and immunomodulatory activity

Algal polysaccharides are non-toxic, inexpensive, biodegradable, and biocompatible natural polymers [92]. These polymers contain sulfated esters, known as sulfated polysaccharides [109], characterized by sulfate groups substituted on the hydroxyl groups of sugar units. Following sulfation of polysaccharides, the sulfated hydroxyl groups exhibit changes in steric hindrance and electrostatic repulsion leading to flexion and extension of the chain and an increase in water solubility. These dynamics finally contribute to their ability to alter biological activities [110]. Researchers found immunomodulating SPs in several microalgae and macroalgae both in marine and freshwater environments [93,111,112] such as *Ulva intestinalis* [113], *Chloroidium ellipsoideum* [114], *Gelidum corneum* [115], and *Crassiphycus caudatus* [116] that exhibiting these properties makes them promising candidates for drug development [93]; therefore, they have acquired significance in the biomedical and pharmaceutical industries and can be further used to produce drug molecules targeting SARS-CoV-2 [102].SPs immunomodulatory activity is an important aspect of biological activity with numerous pathways, connections, and targets [110]. A number of studies have investigated their immunomodulatory properties SPs enhanced release of different cytokines and produce antibodies and activated the complementary system **(**Table 1**)**.

Also, sulfate-modified polysaccharides from algae have stimulated macrophage secretory activity, induced the development of NO, (IL)-6, and increased the secretion of cytokines and chemokines, such as TNF- α and IL-1Β [110,111]. Table 2 lists several common algal SPs with immune functions (Table 2). Extracted SPs are potential candidates to prevent and treat COVID-19 disease by affecting the immune system and therefore may be considered in developing drugs, vaccines, adjuvant therapies, and supplements to combat COVID- 19 [119].

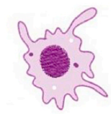
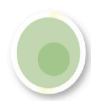
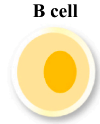
5.3. Algae-derived SPs for microbiota-based therapy and immunomodulatory activity

The crucial role of SPs in algae is associated with their potential prebiotic influence on human health, including reducing obesity and gut dysbiosis [107,135]. SPs must meet three characteristics to be considered prebiotic. First, they must not be digested in the upper gastrointestinal tract. Second, SPs must act as a selective substrate for healthy gut microbiota growth. Third, the gut microbiota's metabolites must have a beneficial effect on the host's health [107]. Many studies have been done to prove it, and according to them, algae-derived SPs are not digested in the upper gastrointestinal tract and hence reach the colon [136,137]. Also, they are impacting the populations of bacterial communities; accordingly, the researcher reported after 48 h of fermentation with SPs from *Gracilariopsis lemaneiformis*, the relative abundances of *Bacteroidetes* and *Proteobacteria* increased, but the comparable amount of *Firmicutes* and *Actinobacteria* decreased dramatically [138]. They also investigated the effect of fucoidan derived from *Laminaria japonica* and *Saccharina japonicaon* the Intestine microbiota of mice fed a high-fat diet. They discovered that fucoidan could increase *Bacteroides* and modulate the gut microbiota by selectively promoting the growth of benign bacteria [139].

Additionally, by modulating the gut microbiome, they have anti-obesity and prebiotic properties. *Bifidobacterium* and *Lactobacillus* are two genera that are frequently utilized as indicators of prebiotic action [107,135]. Consumption of SPs has been shown to boost the growth of Bacteroidetes and Actinobacteria, and Bifidobacteria [107]. After 48 h of in vitro fermentation, fucoidan produced from Saccharina japonica dramatically increased beneficial bacteria (*Lactobacillus* and *Bifidobacterium*) compared to the control group [140]. Thus, SPs may affect the gut microbiota by promoting healthy bacteria and may serve as a new prebiotic for health promotion and disease management.

Prebiotic SPs are used in the gut microbiota metabolism, producing

Table 1
The effect of some algae - derived SPs on innate and adaptive immune cells.

Immune system	Immune cell	Function		Reference
Innate immunity	 **Macrophages**	Phagocytosis	↑	[117-120]
		Cytokines	(regulation)	
		Enzyme activities (ACP)	↑	
	 **Natural killer**	Cytokines	↑	[121]
		Viability	↑	
		Activation	↑	
	 **Complement system**	Complement system	↑	[122]
Adaptive immunity	 **B cell**  **T cell** **Lymphocytes**	Proliferation	(regulation)	[118, 123]
		Cytokines	↑	
		Antibodies	↑	

↑ **indicates an increase,** (regulation) **indicates a regulation**

beneficial metabolites, particularly short-chain fatty acids (SCFAs). SCFAs are critical in maintaining the intestines' barrier function [141,142]. They also contribute to immune response modulation and inflammation reduction by controlling the activity of immune cells (Fig. 2) [107]. Recent investigations have established that SCFA level considerably increased following SPs administration, demonstrating significant physiological consequences in vivo [143]. Therefore, due to the resistance of algal SPs against digestion in the upper intestine tract and modulation of the beneficial gut microbiome, and increasing the production of essential metabolites such as SCFA, these compounds can be introduced as probiotics and prebiotics. Also, a number of studies identify SPs as a potential prebiotic based on their findings that uronic acids in SPs may lower their initial pH value, which may inhibit the growth of pathogenic bacteria and thus improve the gut microenvironment, thereby promoting gut health [138]. Because the gut microbiome and its metabolites change during COVID-19, improving them can reduce the severity of the disease and help reduce its mortality. It is concluded that both immunomodulatory and probiotic effect of SPs, may have a significant impact on prevention, treatment and mortality reduction of COVID-19 infection.

5.4. Algae-derived PUFAs for immune system-based therapy and immunomodulatory activity

PUFAs are fatty acids that contain two or more double bonds in their carbon chain. Depending on the position of the last double bond proximal to the methyl end of the fatty acids, there are two well-known groups of PUFA, namely the omega-6 (−6) and omega-3 (−3) series [93]. The class of omega 6 fatty acids includes γ-linoleic acid (GLA) and arachidonic acid (ARA), and the omega 3 fatty acid class includes eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which regarded as essential PUFAs [144,145]. These fatty acids are obtained from various plant, algal, animal, and marine sources [146]. Although fish oils remain the most practical supply of n-3 very long-chain polyunsaturated fatty acids (n-3 VLCPUFAs), there is rising concern about their ability to meet human demand. Furthermore, fish oils may include considerable levels of unwanted chemicals (e.g., dioxins, mercury). Hazardous pollutants can be eliminated, however this raises the manufacturing costs significantly [146,147]. These factors highlight the importance of algae as a source of PUFAs (especially VLCPUFAs) [148]. Many studies have evaluated the production of fatty acids in algae and confirm PUFAs' production. According to the reports, diatoms are the main omega 3 fatty acid-producing algae, especially EPA and DHA [149].

Meanwhile, many recent studies on the benefits of PUFA have focused on human health. Among the various beneficial properties the immune-stimulating properties of PUFA, and anti-inflammatory properties [93,150] have been highlighted by various authors. For example, in one study, *Ulva* species contains EPA and DHA, and their precursor α-linolenic acid (ALA; 18:3), which derived through elongation and

Table 2
Immunomodulatory activity of some SPs derived from marine algae.

No	Compound/ composition	Source	Immunomodulation	Reference
1	TSP: (Sulfated polysaccharides from *Tribonema* sp. Monosaccharides: Mannose, Rhamnose, Glucuronic acid, Galactose, Glucose, Xylose, Fucose; Mw:197 kDa)	*Tribonema* sp.	Stimulating macrophage cells, such as interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor α (TNF- α) upregulation	[120]
2	Extract: Acidic polysaccharides obtaining from protein-free water-soluble extracts (PF-WSE) of *U. rigida*, Mw ~ 2000 kDa)	*Ulva rigida*	Stimulating murine macrophages, inducing nitric oxide secretion (NO)	[121]
3	Pyruvylated sulfated galactan: (A highly ramified polysaccharide consisting of 3-linked, 3,6-linked, and non-reducing terminal d-galactose with pyruvate and sulfate groups)	*Codium fragile*	Improved development of pro-inflammatory cytokines, including interleukins-1, 6 and 12, tumor necrosis factor-α, and anti-inflammatory cytokines (IL-10).	[122]
4	CLP (*Caulerpa lentillifera* polysaccharides)	*Caulerpa lentillifera*	Increased the synthesis and secretion of IL-6, TNF-α, IL-1β, and NO	[123]
5	Crud and fraction polysaccharide: (Water-soluble sulfated polysaccharides; Monosaccharides: Rhamnose, Glucose, Galactose, Xylose, and Arabinose).	*Ulva intestinalis*	Increasing of IL-1β, TNF-α, IL-6, IL-10, IL-12, and NO	[113]
6	ESPs-CP (Ethanolic Sulfated Polysaccharide-Column Purified)	*Padina tetrastromatica*	Stimulated macrophage, increased and production of prostaglandin, NO, pro-inflammatory cytokines (IL-6, IL-1β, TNF-α), and anti-inflammatory cytokines (IL-10 and TGB-β), Enhanced concentrations of COX-2, 5-LOX, and iNOS in macrophages	[124]
7	Crude and fractionated polysaccharides (F_1, F_2, and F_3) (Monosaccharide: Rhamnose, Xylose, and Mannose. M_w: 401.7 × 10^3 to 6232 × 10^3 g/mol)	*Capsosiphon fulvescens*	Increase the production of NO	[117]
8	Polysaccharides (deproteinized (DP1–3), desulfated (DS1–3), and hydrolyzed (DH1–3) derivatives of *C. ellipsoidea* polysaccharides. M_w:51.5–193.4 kDa)	*Chlorella ellipsoidea*	Induced production of NO	[114]
9	Crude polysaccharides and fractions. (Monosaccharides: Fucose and galactose; M_w: 157.2 to 790.8 × 10^3 g/mol)	*Sargassum angustifolium*	Induced the production of high amounts of nitric oxide and cytokines by macrophage cells, including IL-1 β, TNF-α, IL-6, IL-10, and IL-12 by NF-κB and MAPKs signaling pathways	[125]
10	Extraction: Acidic polysaccharides from *L. ochroleuca*, *P. umbilicalis*, and *G. corneum)*	*Laminaria ochroleuca/ Porphyra umbilicalis, and G. corneum*	Increase in the production of TNF-α and IL-6 in macrophage cell	[115]
11	Kapa carrageenan and beta-carrageenan (Monosaccharides: Galactose: 3,6-anhydro-galactose, SO_4^{2-}/ Mw: 400 Kg/mol)	*Tichocarpus crinitus*	Increasing the serum levels of IFN-γ and IL-12	[126]
12	Crude and fraction polysaccharide (Water-soluble sulfated polysaccharides extracted from *E. prolifera* and fractionated)	*Ulva prolifera*	Stimulate macrophage cells and induce substantial development of NO and different cytokines, increase levels of IFN- α and IL-2 secretion, activate T cells by upregulating Th-1.	[118]
13	CWSP (Certain hot-water-soluble polysaccharides; Monosaccharides: Rhamnose, Glucose, Galactose, Mannose, and Xylose. High molecular weight with monosaccharides larger than 1000 kDa)	*Auxenochlorella pyrenoidosa*	Stimulated IL-1β secretion in macrophages, induced HLA-DA, -DB, and -DC, and HLADR, -DP, and -DQ cell surface expression, expression in macrophages of costimulatory family molecules such as CD80 and CD86	[127]
14	HFP and HFW (Polysaccharide fraction and hot water extract from *H. fusiforme*) (Monosaccharides: Mannose, Glucosamine, Rhamnose, Glucose, Galactose, Xylose, Fucose)	*Sargassum fusiforme*	Stimulated macrophages such as NO producing and increased pro-inflammatory cytokines	[128]
15	Focouidan (Monosaccharides: Galactose, L-fucose, Uronic acid, and Ester sulfate)	*Undaria pinnatifida*	IFN- γ levels increased, Skin edema and leukocyte migration decreased, No significant changes in IL-4, IL-6, TNF- α, and NF- κB expression	[129]
16				[130]

(continued on next page)

Table 2 (*continued*)

No	Compound/ composition	Source	Immunomodulation	Reference
	Fucoidan (Monosaccharides: Fucose and Xylose (as the main component), Glucose, Mannose, and Galactose (as minor compositions).	*Macrocystis pyrifera* *Undaria pinnatifida* (High purity fucoidan/ Sigma-Aldrich) *Ascophyllum nodosum* *Fucus vesiculosus* (Fucoidan purified from algae powder)	The production of IL-6, IL-8, and TNF-α by neutrophils was significantly boosted by all fucoidans.	
17	Alginates (Mw: 557.1 × 103 g/mol)	*Sargassum angustifolium*	Release of NO and inflammatory cytokines TNF- α, IL-1, IL-6, IL-10, and IL-12 by stimulation RAW264.7 cells	[131]
18	Fucoidan from *S. japonica* (Monosaccharides: Fucose, Galactose, Mannose, Xylose, and Glucose; Mw: 10–30 kDa)/ *S. cichorioides* (Completely sulfated Fucoidan; Mw: 40–80 kDa)/ *F. distichus* (Monosaccharides: Galactose, Mannose, and Xylose; Mw: 40–60 kDa).	*Saccharina japonica* *Saccharina cichorioides* *F. distichus*	Specific activation of Toll-like receptors (TLR) 2 and subsequent activation of NF-B pathways has been observed in *S. japonica* fucoidan (1 mg/mL), *S. cichorioides* fucoidan (100 g/mL and 1 mg/mL), and *F. distichus* fucoidan (10 g/mL1 mg/mL); activation of TLR-4 and subsequent activation of NF- κB pathways has been observed	[132]
19	Fucoidan (Monosaccharides: Galactose, Fucose, Mannose, and Xylose; Mw: 40.3 and 1254.4 × 10^3 g/mol)	*Nizamuddinia zanardinii*	Increased NO, TNF-α, IL-1, and IL-6 secretion, Stimulation of the NK cell, NF- κB, and MAPK signaling pathways, resulting in the production of TNF- α and INF- γ.	[133]
20	Fucoidan (Commercially available Fucoidan)	*F. vesiculosus*	TNF- α and IL-6 levels in spleens and blood serum had increased.	[134]

desaturation, which possess the functional property of anti-inflammatory and antioxidant activity [151]. Also, researchers have investigated the impact of dietary PUFAs on immune status for many years, with a focus on omega-3 PUFA, ALA, EPA, and DHA. According to them with several mechanisms, supplemental dietary fatty acids (FAs) may influence immune statuses, such as inhibition of the metabolic process of ARA, development of anti-inflammatory mediators, modification of intracellular lipids, and activation of nuclear receptors [101]. Also omega-3 FAs are considered PUFAs that regulate immune cell activation, specifically in neutrophils, T cells, B cells, DCs, NK cells, mast cells, basophils, eosinophils, and macrophages (Fig. 3) [152,153].

Omega-3 enhances macrophage activity via the secretion of cytokines and chemokines, the promotion of phagocytosis capabilities, and macrophages' activation through polarization [153,154]. The studies showed that by promoting APC, macrophages, or DCs, omega-3 FAs help activate T cells' function. Subsequently, it enables various T cell subgroups, such as CD4 cells, Th17 cells, and regulatory T cells [155,156]. One study examined the differential effects of marine EPA and DHA on gene expression profiles of stimulated Thp-1 Macrophages. The pathway analysis result revealed that EPA and DHA regulate genes involved in cell cycle regulation, apoptosis, immune response and inflammation, oxidative stress, and cancer pathways in a differential and dose-dependent manner [157]. Also, another study, after examining the immunomodulatory properties of the microalga *Nitzschia amabilis* derived PUFAs, concluded that rather than producing generalized immunomodulation, the administration of approximately 2 μg/mL of PUFA has more subtle effects in modulating the immune system [158]. Recently, a study examined the effects of varied dietary sources of n-3 PUFA on the immune response in broiler chickens with stress on natural killer (NK) cell activity. According to the results, the proliferative response of lymphocytes from algal biomass-fed chickens tended to be the highest. Therefore, a DHA-rich algal product might enrich chicken meat with n-3 PUFA without significant damaging effects on chicken immunity [159].

Today, given the recent COVID-19 epidemic and its resulting mortality, many researchers have attributed the cause of death to the production of inflammatory factors, inflammatory responses, and weakened immune systems [1,160]. Based on their reports, the cytokine storm phenomenon called cytokine release syndrome or macrophage over activation syndrome is the cause of the patient's death [161]. To date, because of the complex nature of this problem, the molecular events that precipitate a' cytokine storm' or the practical therapeutic strategies to prevent and manage this process are not clarified [162]. Recent articles indicate that specific nutrients such as vitamin B6, B12, C, D, E, folate, and trace elements, including zinc, iron, selenium, magnesium, and copper, have crucial role in cytokine storm management [163–166]. PUFAs such as EPA and DHA are noteworthy among these micronutrients because of their direct effect on the immunological response to viral infections [162]. Based on available evidence, PUFAs especially, EPA and DHA (omega-3 FA), have multiple inflammatory response impacts [1,152,162]. However, their role in critically ill patients has not yet been recognized by analytical data; future research may indicate that PUFAs such as omega-3 FA derived from algae may play a crucial role in the treatment of COVID-19.

5.5. Algae-derived PUFAs for microbiota-based therapy and immunomodulatory activity

PUFAs, particularly omega-3 PUFAs, can affect the gut microbial community [104,167]. Omega-3 PUFAs influence the gut microbiome in three ways: (1) modulating the type and abundance of gut microbes; (2) changing the levels of pro-inflammatory mediators like endotoxins (lipopolysaccharides) and IL17; and (3) regulating the levels of SCFAs or short-chain fatty acid salts. Omega-3 PUFAs may directly affect the diversity and abundance of the gut microbiota [167]. The effects of omega-3 PUFAs on the microbiota have primarily been studied in the *Bacteroidetes* and *Firmicutes* species [168]. Due to their predominance in the gut [169]. As a result, it has been suggested that omega-3 PUFAs may benefit the gut microbiota by inhibiting *Enterobacteria* growth, increasing *Bifidobacteria* growth, and thereby inhibiting the inflammatory response associated with metabolic endotoxemia [170].

Research has examined the effect of PUFAs from various sources on the gut microbiome.The results of one of them showed that, compared to sunflower oil, fish oil had the most significant effect on the diversity of the intestinal flora [171]. The presence of high levels of omega-3 PUFAs in fish oil alters the gut microbiota significantly, which may account for the health benefits associated with its use [172]. Fish oil with a high omega-3 PUFA content is capable of causing significant changes in the gut microbiota, which may account for some of the health benefits associated with fish oil use [173]. Given the importance of fish oil in this context, according to recent studies on various aquatic organisms and the Food and Agriculture Organization's assessment, the use of algae will become more critical in the near future due to the reduction of fish resources [174]. New research has therefore shifted to the use of these resources. Recently, one study examined the impact of algal oil high in

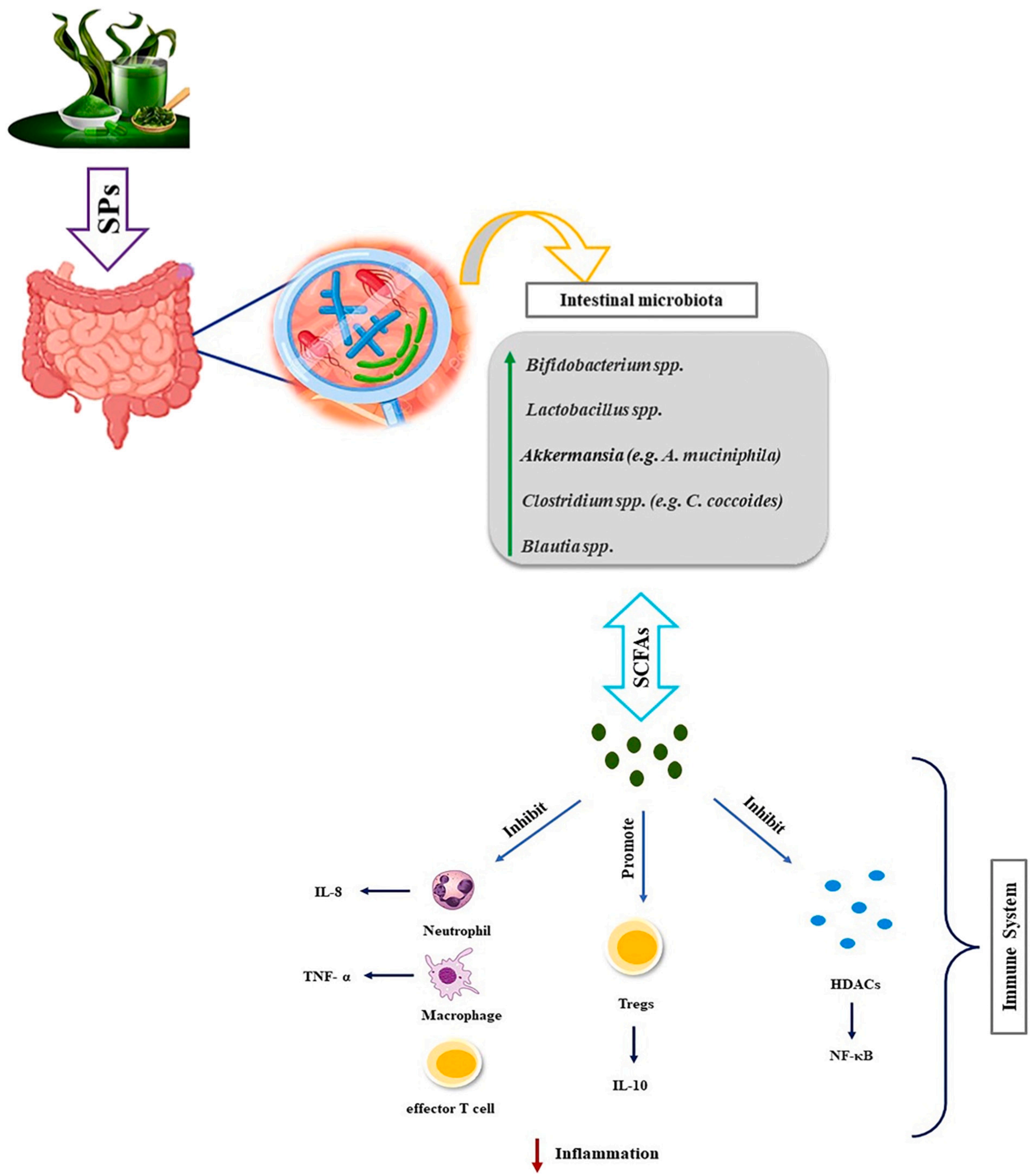


Fig. 2. The effects of SPs from algae and SCFAs produced by microbial fermentation of SPs on microbiota populations and the immune system [107].

DHA on inflammation and microbiome modulation in the gut. According to their findings, treatment with algal oil (500 mg kg^{-1} day^{-1}) significantly decreased pro-inflammatory cytokines in the colon, including IL-6, IL-1, and TNF [175].

PUFAs act synergistically on the gut microbiota and immunity as omega-3 PUFAs maintain host immunity by balancing the population of beneficial and pathogenic bacteria (Fig. 4) [167,176]. Reduced beneficial bacteria result in weakened intestinal resistance to harmful bacteria, resulting in pro-inflammatory strong signaling pathways. For example, LPS-producing bacteria activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway by binding to toll-like receptors-4 (TLR-4) on intestinal epithelial cells, resulting in the secretion of pro-inflammatory cytokines [177]. In a study, the intestinal microbiota of mice fed a high-omega-3 diet was altered, resulting in a modest increase in the anti-inflammatory cytokine IL-10 levels in both the colon and spleen. [178]. Thus, omega-3 PUFAs may play a critical role in the host's defense against infection by limiting excessive inflammation and enhancing the immune response [167]. Omega-3 LC-PUFAs may also interact with viruses during various stages of infection, most notably during virus entry and replication. As a result, the nutritional status of PUFAs plays a critical role in the inflammatory level of tissues and the overall immune response [1]. Current research on COVID-19, healthy gut microbiota can control SARS-CoV-2 infection by producing many immune cells compared to the dysbiotic gut microbiota, which produces a smaller number of immune cells. Therefore, considering the role of PUFAs affecting intestinal health in the treatment

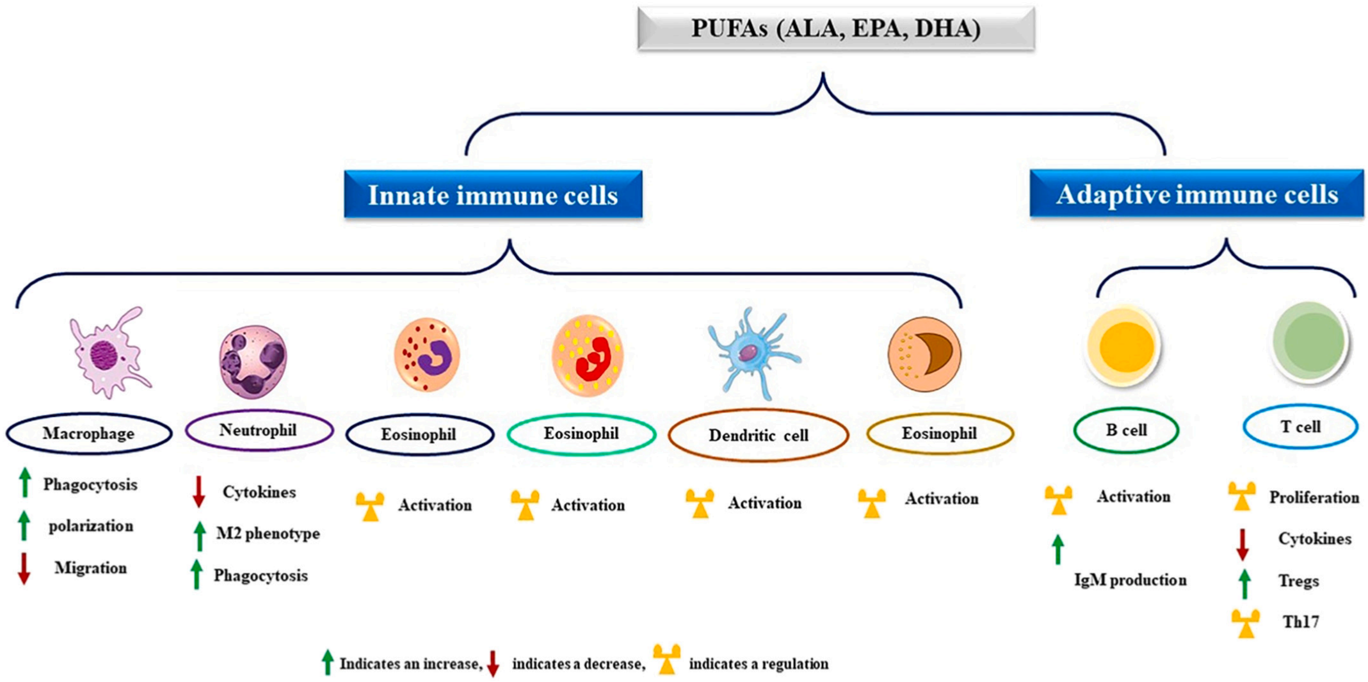


Fig. 3. The impact of n-3 PUFAs on different cells of the immune system [152,153].

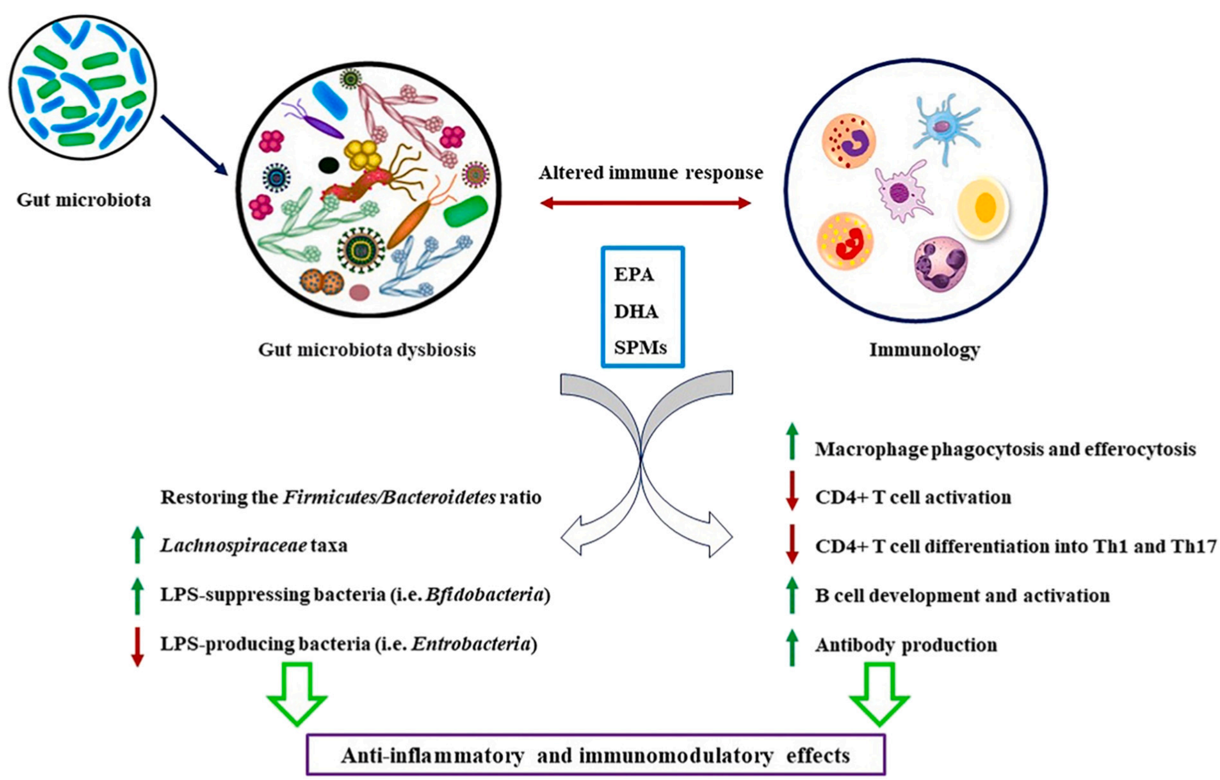


Fig. 4. Interference of n-3 PUFAs and SPMs with gut microbiota and the immune system [167,176].

of COVID-19, as well as increase in the vaccine effectiveness, they can also help in the treatment and prevention of COVID-19 infection.

6. Conclusion and perspectives

The SARS-CoV-2 pandemic has impacted negatively on people all over the world. To combat COVID-19 disease, scientists and global health experts have developed and deployed rapid diagnostics, robust and highly effective vaccines, and novel therapy procedures. Due to drawbacks like resistance, toxicity, and lack of immune responses of some available drugs, pharmaceutical companies are more concerned with discovering new safe and effective immune-stimulating alternatives; natural bioactive compounds in this regard are considered the best choices. Marine alga is a large source of natural compounds with biopharmaceutical activities that modulate the immune system and gut microbiome properties. Algae-derived biologically active constituents can be considered a unique source for the prevention and treatment of COVID-19. Algae-derived SPs and PUFAs modulate the body's immune response through various biochemical pathways. They also play an essential role in immune responses by affecting the intestinal environment and regulating its microbiomes, increasing vaccines' efficacy. SPs can also improve vaccine immunity and antiviral effects; hence COVID-19 vaccines incorporating this compound should be considered for future development. On the other hand, dietary EPA and DHA consumption can influence the cytokines storm; also, they improve the gut microbiome in the intestinal environment, alter immune responses, and reduce inflammatory factors. Hence, omega-3 intravenous PUFA administration is anticipated to lower inflammatory mediators, indicative of potentially beneficial clinical effects. In one study, it was exhibited that simultaneous use of a PUFA (ARA) and algae-derived polysaccharides (anionic macromolecules) resulted in a synergistically enhancement of production of biomarkers like NO, and iNOS gene expression in cells. Therefore, it was concluded that the combination of these compounds contributes to an improved immune response [179]. However, in our review, we focused on the immunomodulatory of each of these two compounds separately and individually in order to demonstrate that marine algae-derived metabolites are highly effective against SARS-CoV-2. Further research and clinical trials should be carried out in this context to develop the most effective natural biotherapeutics derived from marine algae. This study also serves as a turning point for using algal nutrients to develop the concept of nutritional therapy with natural compounds and a research area to accelerate the confirmation of anti-SARS-CoV-2 bioproducts.

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