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Review Article

Therapeutic Potential of Marine Bioactive Compounds Against SARS-CoV2 Infection

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Abstract

SARS-CoV2 is now spreading all over the world and this pandemic interferes the daily life of human. The severity of this viral infection has been exceeded twice more than the previously reported viral outbreak. Scientists are trying to find out a suitable strategy to combat this viral infection and in this case they are trying to develop vaccines and side by side they are looking for specific drugs. In addition to searching new drugs, scientists are trying drug repurposing strategy. Marine areas are a vast resources of many suitable candidate drugs for human welfare and in this regard marine bioactive compounds would be a valuable source having antiviral activity that could be accepted as a suitable drug for the treatment of SARS-CoV2. In this review article, some prospects of marine drugs have been discussed though it needs further in deep research.

Introduction

The whole world is facing adverse situation due to COVID-19 pandemic. The culprit of COVID-19 (Coronavirus disease 2019) is a novel beta coronavirus, which is named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Recently, in December 2019, it was detected in Wuhan, China. The

reason of spreading of SARS-CoV-2 has been identified due to community-based contacts and travelling over the world. The COVID-19 has been declared as a pandemic disease by World Health Organization (WHO) on 11th March 2020 [3]. SARS-CoV-2 is so infectious that it reaches almost every country in the world within 6 months. USA, Italy and France have faced the severe attack of SARS-CoV-2. Until 31 July 2020, worldwide confirmed cases, deaths and recovery of COVID-19 are 17,499,750; 677183 and 10956521 respectively [4].

In the previous century, the world has seen 5 pandemic diseases (related to respiratory illness) caused by different subtypes of influenza virus. During Spanish flu in 1918, 50 million people died worldwide. The causative agent was Influenza H1N1 virus. As like COVID-19, the origin of this disease is China, which is in similar fashion like H2N2 (Asian flu) in 1957 that was also originated in China and played a devastating role of death worldwide. H3N2 virus (Hong Kong flu) was responsible for the death of 1 million people worldwide in 1968. The rest two have occurred in twenty first century, the 2005 H5N1 (Bird flu) and 2009 H1N1 (Swine flu), was responsible for the death of 1800 people worldwide. Bird flu and swine flu infected humans as well as birds and pigs [3].

SARS-CoV-2 belongs to the same family of viruses and it was named differently in two different times as like in 2003 it was severe acute respiratory syndrome coronavirus (SARS-CoV) and in 2012, it was the Middle East respiratory syndrome coronavirus (MERS-CoV) [2,5,6]. Coronavirus can cause ailment for example, the common cold, the Middle East respiratory syndrome (MERS), and the severe acute respiratory syndrome (SARS). The novel SARS-CoV-2 is considered among the other 7 well-known human coronaviruses. Four of these strains cause only mild respiratory symptoms; however, coronaviruses became harmful after outbreaks of Severe Acute Respiratory Syndrome (SARS) in 2002, which was also similar in case of Middle East Respiratory Syndrome (MERS) in 2012. The SARS-CoV-2 or 2019-nCoV coronavirus doers respiratory infection (COVID-19) and astringent pneumonia. Coronaviruses contain single-stranded RNA. The viruses are pleomorphic or, spherical, having a diameter of 80-160nm. The characteristic feature of coronaviruses is the spike projections emerging from the surface of the virion, which provide them the appearance of a crown shape. Prior to 2002, coronaviruses were considered as the causative agents of the common cold in humans and as veterinary pathogens. But the ideology has been changed dramatically from 2002 after the outbreak of SARS by a coronavirus SARS CoV. There is a remarkable difference of case fatality rate between SARS and MERS, 9.6% and 34.3% respectively. In comparison, case fatality rate of COVID19 is ~1.38-3.4% [2,7]. But SARS-CoV-2 is highly contagious compared to SARS-CoV and MERS CoV.

SARS-CoV-2

SARS-CoV-2 is considered as a eminently pathogenic member of the coronavirus family. In Baltimore classification of viruses, SARS-CoV-2 is classified as class IV positive sense single stranded RNA virus. It is a pleomorphic, enveloped, single-stranded and positive sense RNA virus. Roughly, the size of the virion is 80-120nm in diameter [8]. It shows 79.0% and 51.8% nucleotide sequence similarities to SARS- CoV and MERS-CoV, respectively. It is meticulously akin to bat-origin SARS-like coronavirus (bat- SLCoVZC45) with 87.6-89% nucleotide sequence similarities [9]. It is assumed that SARS-CoV-2 have zoonoses like

origins since it has firm genetic similarity to bat coronaviruses, suggesting it emanated from a bat- borne virus. It is believed that Pangolins are to be one of the intermediate hosts for species viral transfer to humans and the other intermediate hosts still in veil [10].

SARS-CoV-2 Molecular Structure and Genome

SARS-CoV-2 has four structural proteins such as envelope (E) proteins, nucleocapsid (N) protein, membrane "matrix" (M) protein, and spike (S) protein. The assemblage of these proteins into the virion urges infectivity of the coronavirus [11]. SARS-CoV-2 viral particles turn out as assymetrical structures with a phospholipid bilayer outer membrane containing spike protein on the surface. Inward the envelope, one strand of a 30kBp positive-sense RNA genome is carried out by the viral particles and this RNA genome codes for several non-structural proteins (nsp) as well as 4 structural proteins mentioned above. The N proteins stand for the viral genome protection. Upon host cell entry, the N protein gets unveiled and the viral genome is discharged and straightly translated by its host cell ribosomes. Viruses are unable to amalgamate their own lipids. Instead, they remodel host lipids for their own replication as well as morphogenesis. Under electron microscopy, spike proteins give the manifestation of a crown (Latin: corōna) encompassing the viral particle, which leads the virus its common name: coronavirus [12]. The M protein, a glycoprotein, is the most abundant protein on the outside of the viral envelope. M proteins operate by binding the nucleic acid to the inner facade of the host cell membrane. The C-terminal domain of trans-membrane M proteins interacts with the N protein and this step is decisive for the morphogenesis phase of the viral life cycle [13].

Structure of SARS-CoV-2 S protein has been decoded by cryo-electron microscopy. The S protein appears as a trimeric form along with two domains (S1 and S2 subunits). The upper lobular domain contains an ACE-2 (Angiotensin-converting enzyme 2) receptor-binding feature, which is causative to initiate host cell entry. The receptor binding domain is the most variable and indispensable part of the virus genome. The sequence variability is a direct impact of the intense evolutionary constrain that the host immune systems strive on the virus. The molecular machineries required for the virus to fuse with the host cell membrane are encoded by the lower domain of the S protein. The fusion domain is the most conserved part among the coronaviruses. It comprises a hydrophobic fusion peptide that is responsible to bring the two lipid bilayers close enough for fusion to be held [12].

The E protein is a small membrane protein and inconsequential component of the virus particle, it plays a pivotal role in virus assembly, virus host cell interaction, and membrane permeability of the host cell [14]. Hemagglutinin-esterase dimer (HE) has been found to be located on the surface of the viral particle. The HE protein may only be involved in viral entry instead of replication [15]. Inside the envelope, the viral particle contains one single stranded RNA genome around 30,000 nucleotide long [16].

Viral Replication

The replication of the SARS-CoV-2 into host cell can be divided into several steps such as attachment and host cell entry, transcription of viral replicase, genomic transcription and replication, translation of structural proteins, and, lastly, virion assembly and release from the host.

The Spike (S) protein of the virus plays the most important role to bind with the host cell surface receptor ACE 2, hence initiates cellular entry and infection. SARS-CoV-2 infects type 2 pneumocytes located on alveolar inner surface. Binding of S protein to the ACE 2 receptor activates the S protein by host protease. The proteolytic cleavage by transmembrane protease serine 2 (TMPRSS-2) leads to the exposure of fusion peptide of S protein [12]. The fusion peptide is the area of hydrophobic amino acids (with a hairpin like structure) and can be infused into lipid membrane. This hairpin like structure then pleats back, drags the cellular and viral membranes together to initiate fusion process. This ultimately leads to cellular entry [17,18]. Human cell ingests the virus by endocytosis. Then, the endosome opens to discharge the virus particles in the cytoplasm and unveiling of viral nucleocapsid (N) protein is started via proteasomes, which typically hydrolyzes endogenous proteins, but are also able of diminishing exogenous proteins like SARS nucleocapsid protein [19].

The replication transcription complex (RTC) is composed of the nonstructural proteins (nsp). The genomic RNA serves as template and allows the translation of ORF1a producing poly-protein pp1a. Then, an RNA pseudoknot and a slippery sequence of ORF1a leads to 25-30% of the ribosomes to undergo frame shifting leading to translation on ORF1b and producing a longer poly-protein pp1ab [20]. Then auto-proteolytic cleavage of pp1a and pp1ab leads to the generation of 15-16 nonstructural proteins (nsps), which have specific functions. The RNA dependent RNA polymerase (RdRP) is transcribed by nsp12. The nsp3 encodes papain-like protease (PLPro) and the nsp5 decodes the main protease (M^{pro}). Besides, nsp3, nsp4 and nsp6 promote the rearrangement of the cell membrane to form DMV (double-membrane vesicles) where coronavirus replication and transcription complex (RTC) is assembled and anchored [21].

The RNA genome of SARS-CoV-2 serves as a template for replicase enzyme to synthesize full- length antisense genome, which then leads to the synthesis of new positive sense genomic RNA. Most importantly, the polymerase switches templates during the transcription process at the specific sites of the genome, resulting (-) sense and (+) sense subgenomic RNA molecules (sgRNAs) synthesis [20]. The primary genomic transcription is mediated by viral replicase. The nucleopcapsid (N) protein could play important role in RNA template reading. The N proteins of SARS-CoV strains are phosphorylated by glycogen synthase kinase 3 (GSK3) that promotes the synthesis of longer sgRNAs and genomic RNA [22]. *In vitro* application of GSK 3 inhibitor in SARS-CoV infected cells showed inhibition of viral replication [23].

Coronavirus sgRNAs are monocistronic. Only the 5′- ORF is translated in a cap-reliant demeanor. Endoplasmic reticulum (ER) is the organelle where transmembrane structural proteins e.g. S, HE, M and E and some other membrane associated accessory proteins are translated. On the other hand, the N protein is translated by cytosolic ribosomes [20]. It is obvious that the structural proteins of coronavirus are subjected to post-translational modifications for the its functional activities. S protein is glycosylated so as the M protein.

Assembly of SARS-CoV2 virion takes place in the ER-Golgi intermediate compartment (ERGIC), which is arbitrated by the membrane (M) protein. The virion morphogenesis, M-S, and M-N interactions, the recruitment of structural components to the assembly site as well as the protein-protein interaction are dictated by M proteins [13]. By interacting with M proteins, E protein contributes in the viral particle assembly. Coronavirus particles burgeoned into the ERGIC are conveyed using smooth-wall vesicles,

resulting in trafficking via the secretory pathway and discharged by exocytosis. Several host proteins (cytoskeletons - tubulin, actin, filamin A) are involved in assembly and trafficking.

COVID-19 Pathobiology

The first COVID-19 pathology observed alveolar injury with cytomyxoid fibroma exudate, and subsequent analysis found a decrease in CD4+ and CD8+ T-cells but a proportional increase in the Th17 cell [24]. Th17 cells are helper T-cells, which are stimulated by interleukin-6 (IL-6) and IL-23. The neutrophil-to-lymphocyte ratio (NLR) is the preeminent indicator of cytokine storms (hypercytokinaemia), with increased NLR in the blood. Furthermore, CD8+ T-cells decreased and inflammatory cytokines such as IL-2, IL-6, IL-10, and interferon-gamma (IFNγ) are also increased in the peripheral blood in severe cases [25]. In case of COVID-19 severity, cytokine release syndrome (CRS - a cytokine storm) plays the most important role. When massive amounts of cytokines are released, this leads to increased leukocyte draft to multiple organs, most predominantly in the lung, leading to the acute respiratory distress syndrome (ARDS) in COVID-19.

CRS involves the release of a large number of cytokines including IL-6. These cytokines increases vascular permeability that results in accumulation of large amount of fluid and blood cells inside alveoli, resulting in dyspnoea and respiratory failure. A bronzed appearance of both lungs and a large amount of grey-white viscous liquid overflow was first reported from a COVID-19 death autopsy examination [26].

IL-6 is a small polypeptide having four α helices comprising 184 amino acid residues. The origin of IL-6 production are considered from almost all stromal cells and immune system cells, including T-lymphocytes, B-lymphocytes, monocytes, macrophages, dendritic cells, mast cells, and other non-lymphocytic cells such as endothelial cells, keratinocytes, fibroblasts, glomerular cells, mesangial cells and tumor cells [27]. IL-1β and tumour necrosis factor-alpha (TNFα) act as the main activators of IL-6 expression. Toll-like receptors (TLRs), prostaglandins, adipokines, stress response and other cytokines also promote the synthesis of IL-6. In the early stage of infectious inflammation, due to the activation of TLRs, monocytes and macrophages stimulated, which leads to the production of IL-6 [25].

In alveoli, there are resident macrophages, monocytes. Macrophages, dendritic cells have ACE 2 receptor thereby can be infected by SARS-CoV-2 [28]. Thus SARS-CoV-2 activates the innate immune system. Activation of adaptive immunity is also mediated by antigen-presenting cells (mainly dendritic cells). T- and B-cells not only play a pivotal antiviral role but also promote the secretion of inflammatory cytokines both in a direct and indirect way. Furthermore, under the stimulation of inflammatory stimuli, a large number of erythrocytes and inflammatory exudates enter the alveoli. Accumulation of liquids, debris in alveoli interrupts gas exchange in lungs and ultimately leads to mild or sever hypoxemia [25]. Excessive IL-6 flows towards brain and activates signaling pathway in hypothalamus leading to increased body temperature.

Because SARS-CoV-2 utilizes the ACE2 receptor for the host cell entry, it provokes over activation of the renin–angiotensin- aldosterone system (RAAS). ACE2 is an enzyme that converts angiotensin II to angiotensin 1- 7 (seven amino acid peptide) through an enzymatic reaction. Nlrp3 (NACHT, LRR- and PYD domain-containing protein 3) is an intracellular sensor that senses environmental irritants, endogenous danger signals, and a broad range of microbial motifs, resulting in the activation of the NLRP3 inflammasome.

It is expressed in many cell types including endothelial, lung epithelial, kidney, cardiac, and hematopoietic cells and bunch of evidence suggests that in response to angiotensin II stimulation, the Nlrp3 inflammasome becomes activated in these cells. Angiotensin II mediated pyroptosis due to over activation of Nlrp3 inflammasome has been reported in various organelles such as lung epithelium, kidney cells and cardiomyocytes. The SARS-CoV2-dependent Nlrp3 inflammasome hyperactivation causes multi organ failure and also leads to cytokine storm [2,6,29].

It is well known that invigoration of the Nlrp3 inflammasome provokes an immune response through caspase 1, which compels to release of robust proinflammatory cytokines, for example, interleukin 18, and interleukin-1β, and by conceiving gasdermin D (GSDMD) pore channels towards the cell membranes, arbitrating the release of danger-associated molecular pattern molecules (DAMPs). This leads a sequence of orders leading to the augmentation of the response of innate immune system and tethers of its major humoral arm, that is, the complement cascade (ComC) [30]. In conjunction with DAMPs, based on recently published report, the ComC is directly mobilized by mannan-binding lectin (MBL), which interacts to SARS-CoV2 proteins. Notably, activation of the ComC via the MBL-MASP-2 protease complex leads to the mobilization of the coagulation cascade (CoaC) in a coordinate fashion, and a worse prognosis appears in patients infected with SARS-CoV-2, when such an activation of coagulation occurs [31].

Therapeutic Possibility of Marine Bioactive Compounds

By analyzing COVID-19 pathobiology, scientists are constantly searching for various drug targets to cure or slow down the disease prognosis. Vaccines are being designed and gone through clinical trial. Monoclonal antibodies are being tested to block receptors to stop the virus infection. Drug repurposing is also considered [6]. On the other hand, alternative drug sources have also been searched and marine sources can be suggested as a vital resource.

Ocean is a huge, diversified habitat for uncountable number of living organisms. To survive in the harsh environment, organisms living in ocean produce various types of secondary metabolites that have important pharmacological values. These compounds are highly active even when present in small amount. Secondary metabolites, polysaccharides from seaweeds, ocean bacteria, fungus, sponges, crabs have recently gained researchers' attention for their various medicinal values as well as immunomodulatory specially anti-inflammatory and antioxidant activities. COVID-19 patients face severe prognosis due to cytokine storm (specially for IL6) that initiates inflammation in lungs and damages oxygen-carbondioxide exchange mechanism [2]. This cytokine storm primarily starts from alveoli due to resident macrophages. Also, monocytes, dendritic cells, neutrophils can be activated by SARS-CoV-2. So, uncontrolled response of immune cells leads to release of huge amount of cytokines and thus, organ damaging inflammation. Many marine bioactive compounds that have anti-inflammatory activities can be considered as potential candidates to treat cytokine release syndrome (CRS) in COVID-19 patients. These compounds act by various mechanisms for example inhibition of cytokine signaling pathways. Several marine derived bioactive compounds that can be used to treat CRS are described below:

Fucoidan (SF6) isolated from *Saccharina japonica* (edible brown algae in China) has been reported to have remarkable antioxidant and anti-inflammatory activity. Fucoidan, a fucose-containing sulfated

polysaccharide, appearing in the fiber pile cell walls and also in the intercellular spaces of brown seaweeds and echinoderm. SF6 strives its anti-inflammatory effect in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages through elimination of pro-inflammatory cytokine production such as IL-6, IL-1β and TNF-α, and other inflammatory mediators like COX-2 and iNOS. The anti-inflammatory ramification of SF6 is accredited to the intonation of MAPKs, NF-κB, and JAK2-STAT1/3 signaling pathways [32]. In COVID19, IL6 released from macrophage contributes to CRS. Here, Fucoidan (SF6) is suppressing not only IL6 but also its stimulators TNF-α, IL-1β (in RAW 264.7 macrophages) as well as associated signaling pathway (MAPKs and JAK2-STAT1/3 signaling) which are activated in CRS.

Very recently, the fucosterol mediated anti-inflammatory activity of has been studied [33]. In short, fucosterol exhibited anti-inflammatory effect [34] and LPS-induced inflammation in RAW 264.7 macrophage [35,36] and alveolar macrophage [37] were attenuated. *Ecklonia* spp derived bioactive compounds or phlorotannins, such as dieckol [38], phlorofucofuroeckol A [39] and phlorofucofuroeckol B [40], 6,6'-bieckol [41], and 8,8'-bieckol [42] have been reported for their anti-inflammatory activities with an established mechanism of action that governs through suppression of NF-κB and MAPK pathways.

Algal polysaccharides are also known to act as anti-inflammatory agents [43]. Red algae derived κ-Carrageenan oligosaccharides and its desulfated derivatives debilitate TNF-α production and exert anti-inflammatory activity in LPS-induced microglial cells [44]. *Porphyra yezoensis* derived porphyrans constrict nitric oxide (NO) generation in LPS-activated RAW264.7 cells through the downregulation of iNOS expression [45,46]. Based on previous reports, *Ulva lactuca* and *Enteromorpha prolifera* derived sulfated oligosaccharides treatment abates inflammatory factors and suppresses the expression of fork-head box protein O1 (FOXO1) and p53 genes and also augments the expression of Sirt1 gene in SAMP8 mice model [47]. In a previous study it was observed that alginate-derived oligosaccharide showed strong anti-inflammatory effect and in more detail it can be mentioned that the oligosaccharide interfered the expression of inflammatory enzymes and also the secretion of proinflammatory cytokines in LPS/Aβ-stimulated BV2 microglial cells. This oligosaccharide also showed suppressing effect on the expression of NF-κB and toll-like receptor 4 (TLR4) [48].

Sargassum micracanthum derived sargachromenol attenuates inflammatory response in LPS-stimulated RAW 264.7 cells [49]. It has been recorded that sargaquinoic acid of *Sargassum siliquastrum* curtailed inflammatory response in an artificially induced inflammatory condition in RAW 264.7 cells by hindering c-JNK and NF-κB pathways [50]. *U. pinnatifida* (UPGP) derived glycoprotein reduced the expression of genes involved in enzymatic activities in inflammation and NO synthesis in LPS-induced RAW 264.7 cells [51]. Furthermore, several algal alkaloids such as, caulersin, caulerpin, and racemosin A-C also exhibits anti-inflammatory activity [52].

Yondelis (from tunicate *Ecteinascidia turbinata*) reduces the *in vitro* production of inflammatory mediators IL-6 in freshly isolated ovarian tumour cells monocytes, macrophages, and tumour-associated macrophages [53].

Hymenialdisine (brominated pyrrole alkaloid from marine sponge) has been characterized as an inhibitor of NF-kB activation and its exposure to IL-1-stimulated human rheumatoid synovial fibroblasts inhibits

PGE2 (Prostaglandin E2) production. In addition, hymenialdisine inhibits IL-6 production and reduces IL-8 production dependent on synovial cell strains [54].

Gracilaria verrucosa is a common marine red alga that has anti-oxidant activity. Two enone fatty acids from *G. verrucosa* inhibit the production of inflammatory mediators (IL-6, NO, and TNF-α) by hindering the activation of NF-κB and STAT1. So it can be suggested for the treatment of severe COVID-19 cases [55].

Pseudopterane diterpene from *Pseudopterogorgia acerosa* shows anti-inflammatory activity: IC50 value of NO, TNF-α, IL-6, IL-1β were 7.54, 9.16, 12.25, 2.75 μM, respectively [56].

Briarane-type diterpenes isolated from *Briareum excavatum* showed 97.6% inhibition of IL-6 expression of LPS-activated mouse bone marrow-derived dendritic cells [57]. So briarane-type diterpenes can be a potential candidate for clinical trial in severe COVID-19.

Chaetoglobosin Fex, an alkaloid from *Chaetomium globosum* showed 56.7 and 50.1% inhibition of TNF-α and IL-6 production in LPS-activated RAW264.7 macrophages at 2μg/ml respectively [58].

In usual cases, the anti-inflammatory activity is associated with interference related action on COX-2 and iNOS expression in macrophages. Lemnalol (a sesquiterpenoid) from *Lemnalia cervicorni* showed 99.79 and 82.5% inhibition of iNOS and COX-2 expression in LPS-activated RAW264.7 macrophages at 10μM, respectively [59]. Lemnalol is noteworthy for its anti- inflammatory activity.

Pseudopterosin A (Caribbean soft coral) was found to inhibit prostaglandin E2 and leukotriene C4 production in zymosan-stimulated murine peritoneal macrophages release. The crucial roles played by prostaglandin and leukotriene in asthma (a chronic lung disease) [60].

Fucan isolated from *Fucus vesiculosus* showed inhibition of NO and PGE2 production in LPS-stimulated BV2 microglia, suppression of iNOS, COX-2, monocyte chemoattractant protein-1 and pro-inflammatory cytokine; IL-1B and TNF-alpha synthesis [61].

Diphlorethohydroxycarmalol from *Ishige okamurae* showed down-regulation of iNOS and COX-2 expression and NF-kB activation in human umbilical vein endothelial cells and RAW 264.7 cells [62].

Beside these, Halitunal, a novel diterpene aldehyde isolated from the marine alga *Halimeda tuna* also showed antiviral effect against mouse coronavirus A59 *in vitro* [63].

COVID-19 infection also exerts reactive oxygen species release (ROS) that makes the adjacent cells vulnerable to virus infection. In this regard, drugs having antioxidant activity would be a better priming tool against SARS-CoV2 infection to maintain redox homeostasis [64]. Marine algae derived few bioactive compounds have been reported to exposit strong antioxidant property (Table 1), and thus, may be protective against oxidative stress-induced damage. For example, fucoxanthin, a carotenoid derived from *Sargassum siliquastrum*, hindered H_2O_2-induced DNA damage, providing protection with increased production of GSH level, as well as higher expression of *SOD* gene [65]. Furthermore, fucoxanthin upholded antioxidant

defense system by stimulating Nrf2/ HO-1 defense axis as well as cell survival via activating cAMP-mediated protein kinase (PKA)/cAMP response element-binding (CREB) pathway and increasing BDNF secretion [66].

Table 1: *Anti-inflammatory and antioxidant effect of marine bioactive compounds.*

Compound	Source	Experimental model	Cellular effect	Reference
Fucoxanthin	*Sargassum siliquastrum*	Aβ42-induced BV2 microglia cells	Anti-inflammation, Antioxidant	65
Fucoxanthin	*Sargassum siliquastrum*	LPS-activated BV-2 microglia	Anti-inflammation, Antioxidant	66
Fucosterol	*E. bicyclis* (brown alga)	RAW 264.7 murine macrophages (t-BHP 200 μM, LPS-1μM stimulated)	Anti-inflammation	36
Fucosterol	*U. pinnatifida*	LPS-induced RAW 264.7 macrophages and THP-1 human monocyte cell line	Anti-inflammation	35
Fucosterol	*Hizikia fusiformis*	CoCl2 induced hypoxia in keratinocytes	Anti-inflammation	34
Fucosterol	*Panida. australis*	LPS or Aβ-induced BV2 (microglial) cells	Anti-inflammation	67
Fucosterol	*S. Binderi* (brown alga)	Particulate matter-induced injury and inflammation in A549 human lung epithelial cells	Anti-inflammation	68
Dieckol (phlorotannin)	*E. cava*	LPS-stimulated murine BV2 microglia	Anti-inflammation, Antioxidant	38
Phloroglucinol, eckol, dieckol, 7-phloroeckol, phlorofucofuroeckol A and dioxinodehydroeckol (phlorotannin)	*E. bicyclis* (brown alga)	LPS-stimulated RAW 264.7 murine macrophages	Anti-inflammation	36
Phlorofucofuroeckol A	*E. stolonifera*	LPS-activated BV2 and primary microglial cells	Anti-inflammation	39
Phlorofucofuroeckol B (phlorotannin)	*E. stolonifera*	LPS-stimulated murine BV2 microglia	Anti-inflammation	40
8,8'-bieckol (phlorotannin)	*E. cava*	LPS-stimulated primary macrophages and RAW 264.7 macrophages & LPS-induced septic mice	Anti-inflammation	42
6,6 -bieckol (phlorotannin)	*E.stolonifera*	LPS-stimulated BV2 and murine primary microglial cells	Anti-inflammation	41

Fucoidan (sulfated polysaccharide)	Brown seaweed	LPS-stimulated murine BV2 microglia	Anti-inflammation	61
Fucoidan	-	LPS-activated primary microglia	Anti-inflammation	69
κ-carrageenan oligosaccharides and desulfated derivatives	Red algae	LPS-activated microglia	Anti-inflammation	44
Sulfated oligosaccharides	*U. lactuca* and *E. prolifera;* (green algae)	Aging model (male senescence-accelerated prone (SAMP8) and male senescence resistant (SAMR1) mice)	Anti-inflammation	47
Alginate-derived oligosaccharide	Brown algae	LPS/Aβ-stimulated BV2 microglia	Anti-inflammation	48
Seleno-polymannuronate	Brown algae	LPS-activated primary microglia and astrocytes; mouse model of acute inflammation	Anti-inflammation	70
Sargachromenol (plastoquinone)	*Sargassum micracanthum*	LPS-stimulated RAW 264.7 macrophages	Anti-inflammation	49
Sargaquinoic acid (plastoquinone)	*Sargassum siliquastrum*	LPS-stimulated RAW 264.7 macrophages	Anti-inflammation	50
Floridoside (glycerol glycosides)	*Laurencia undulate;* (red alga)	LPS-stimulated murine BV2 microglia	Anti-inflammation	71
Glycoprotein	*U. pinnatifida*	LPS-stimulated RAW 264.7 macrophages	Anti-inflammation	51
Caulerpin (bisindole alkaloid)	*Caulerpa racemosa*	Capsaicin-induced ear edema and carrageenan-induced peritonitis	Anti-inflammation	72
Caulerpenyne (sesquiterpene)	*C. prolifera* and *C. racemosa*	Lipoxygenase (LOX) enzyme activity assay	Anti-inflammation	73
Sulfated oligosaccharides	*U. lactuca* and *E. prolifera;* (green algae)	Aging model (male senescence-accelerated prone (SAMP8) and male senescence resistant (SAMR1) mice)	Antioxidant and anti-inflammation	47
Fucoxanthin (carotenoids)	*Sargassum siliquastrum*	H2O2-induced cell damage in kidney fibroblast cells	Antioxidation	74

Fucosterol, 3,6,17-trihydroxy- stigmasta-4,7,24 (28)-triene and 14,15, 18,20-diepoxyturbinarin (sterols)	*Pelvetia siliquosa*	Rat model	Antioxidation	75
Fucosterol	*Eisenia bicyclis,* (brown alga)	RAW 264.7 murine macrophages (t-BHP stimulated)	Antioxidation	36
Fucosterol	*Ecklonia stolonifera and Eisenia bicyclis;* Brown algae	tert-Butyl hydroperoxide- and tacrine-induced HepG2cell injury model	Antioxidation	76
Fucosterol	*Sargassum Binderi;* (brown alga)	Particulate matter-induced injury and inflammation in A549 human lung epithelial cells	Antioxidation	68
Glycoprotein	*U. pinnatifida*	*In vitro* enzyme assay	Antioxidation	51
Sulfated oligosaccharides	*Ulva lactuca* and *Enteromorpha prolifera;* green algae	Aging model (male senescence-accelerated prone (SAMP8) and male senescence resistant (SAMR1) mice)	Antioxidation	47
Diphlorethohydroxycarmalol	*Ishige okamurae*	RAW 264.7 cell	Antioxidation	77
6,6′-bieckol	*Ishige okamurae*	RAW 264.7 cell	Antioxidation	77
Porphyran	*Porphyra yezoensis*	Rat liver microsome	Antioxidation	46
Halitunal	*Halimeda tuna*	Mouse coronavirus A59	Antiviral	63

Using experimental model rats, it was observed that fucosterol was able to raise cellular antioxidant enzymes, such as, CAT, SOD, and GPx [75]. It has also been recorded that fucosterol was capable to prevent ROS production in tert-butyl hydroperoxide (t-BHP)-stimulated RAW264.7 cells [36]. Beside this, fucosterol conversed safeguard from oxidative stress-induced damage of human hepatic cells, HepG2 cells, by ameliorating the level of GSH, an intracellular antioxidant [76]. In the lung epithelial cells fucosterol governed it antioxidant-induced protection by augmenting the gene expression of HO-1, SOD, and CAT, and activation of Nrf2, a master gene regulator of cellular antioxidant response pathway [68]. It is known that activated Nrf2 suppresses the inflammatory shrug by inhibiting the NLRP3 inflammasome, which is the key measure of SARS-CoV2-mediated inflammation [2]. So that, in this regard fucosterol would be very suitable drug to stop inflammasome-dependent inflammatory shrug. *U. pinnatifida* derived glycoprotein also improves SOD activity to mitigate ROS levels [51]. *Ishige okamurae* derived bioactive compounds, diphlorethohydroxycarmalol and 6,6′-bieckol manifested antioxidant activity and reduced intracellular ROS level in RAW264.7 macrophage cells, one report suggested [77].

Another report suggested that sulfated polysaccharide also manifested strong antioxidant activity and hindered intracellular ROS level in RAW264.7 macrophage cells [77]. *In vivo* study using rate liver sample showed that *Porphyra haitanesis* derived sulfated fractions had antioxidant activity and also possessed lipid peroxidation suppressing activity [78]. *Porphyra yezoensis* derived porphyran exhibits superoxide anion and hydroxyl peroxidation activity in rat liver microsome study [46].

In addition, a large number of marine algae have been found to have antioxidant activity such as *Sargassum polycystum* and *Laurencia obtusa* [79], *Gelidium foliaceum, Codium duthieae* [80], and so on.

Conclusion

SARS-CoV2 belongs to the family of Coronavirus. Active virion infects human type 2 pneumocytes in lungs and replicates inside cell. Its multiplication in host can activate innate immune cells and an uncontrolled response of host immune cells leads to cytokine storm known as Cytokine Release Syndrome or cytokine shurg that results in hypoxemia and multiple organ failure. In order to mitigate the adverse effects of COVID-19 infection, novel marine bioactive compounds having strong anti-inflammatory and antioxidant activity could be used since these are very potent, efficiently modulates several cell signaling pathways to reduce cytokine release and activates antioxidant response pathways, as reported. Naturally occurring bioactive compounds (which has immunomodulatory activities) from marine organisms would be a better option to treat severe COVID-19 infection with less side effects compared to chemically synthesized drugs. More extensive investigations and clinical trials should be focused on marine resources.

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