



Utilization of Marine Seaweeds as a Promising Defense Against COVID-19: a Mini-review

M. D. T. L. Gunathilaka¹

Received: 7 March 2022 / Accepted: 4 May 2023 / Published online: 27 May 2023

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

Abstract

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which mainly affects the respiratory system. It has been declared as a “pandemic” in March 2020 by the World Health Organization due to the high spreading rate. SARS-CoV-2 binds with the angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface which leads to the downregulation of ACE2 and upregulation of angiotensin-converting enzyme (ACE) receptors. The elevated level of cytokines and ACE receptors leads to the severity of SARS-CoV-2 infection. Due to the limited availability of vaccines and recurrent attacks of COVID-19 mainly in low-income countries, it is important to search for natural remedies to prevent or treat COVID-19 infection. Marine seaweeds are a rich source of bioactive compounds such as phlorotannins; fucoidan; carotenoids; omega-3 and omega-6 fatty acids; vitamins B₁₂, D, and C; and minerals including zinc and selenium that exhibit antioxidant, antiviral, and anti-inflammatory activities. Furthermore, bioactive compounds present in marine seaweeds have the ability to inhibit ACEs by inducing ACE2 which exhibits anti-inflammatory effects in COVID-19. Correspondingly, soluble dietary fibers present in seaweeds are served as prebiotics by generating short-chain fatty acids through fermentation. Hence, seaweeds can be utilized to reduce the gastrointestinal infections associated with SARS-CoV-2 infection.

Keywords COVID-19 · SARS-CoV-2 · Marine seaweeds

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which mainly affects the respiratory system. It was initially identified in December 2019 in Wuhan City, China. The World Health Organization declared COVID-19 as a pandemic disease in March 2020 due to the high spreading rate among 194 countries, including the USA, Africa, Europe, India, and Sri Lanka (WHO, 2020). To date, the WHO has estimated 423,437,674 globally confirmed COVID-19 cases with 5,878,328 deaths (WHO 2022). According to Sri Lankan statistics, 638,043 confirmed COVID-19 cases have been identified together with 16,024 deaths to date (Amaratunga et al. 2020.; Health Promotion Bureau 2022).

SARS-CoV-2 is an airborne disease that mainly affects the respiratory system and causes mild, moderate, to severe respiratory illness which can further progress into a life-threatening condition. The severity of the COVID-19 infection is linked with the secretion of a high level of inflammatory mediators such as cytokines, interleukins, tumor necrosis factor, and C-reactive proteins which, in turn, exacerbate the inflammatory reactions in the body. The high level of cytokines which refers to the “cytokine storm” is associated with the high mortality rate of COVID-19 infections among survivors and non-survivors (Hojyo et al. 2020; Tang et al. 2020). Beyond that, SARS-CoV-2 can cause damage to multiple systems which, in turn, lead to multiorgan failure and death (Lakhani et al. 2021; Morhtari et al. 2020). The infected people are suffering from shortness of breath, sore throat, cough, fatigue, headache, fever, myalgia, and diarrhea, and furthermore, it can lead to life-threatening conditions including pulmonary edema and severe pneumonia (Hojyo et al. 2020).

As vaccination is highly effective against infectious diseases, several vaccines are developed for the prevention of COVID-19 infection. Among them, eight vaccines

✉ M. D. T. L. Gunathilaka
thilina.g@nsbm.ac.lk

¹ Department of Biomedical Science, Faculty of Health Science, NSBM Green University, Mahenwatta, Pitipana, Homagama, Sri Lanka

including AstraZeneca–Oxford, Sinopharm, Sinovac Biotech, Pfizer–BioNTech, Gamaleya, CanSino Biologics, Janssen, and Moderna are authorized and approved for public use to date (Yim et al. 2021a, b). However, due to the limited availability of COVID-19 vaccines, it is very difficult to fulfill the requirement of global COVID-19 vaccination. Even though the developed countries have the capacity to achieve full coverage of COVID-19 vaccination, statistics showed that around 4% of people who are living in low-income countries are vaccinated yet (World Bank 2020). Therefore, in place of vaccination programs, it is very important to search for natural remedies to prevent or treat COVID-19 infection.

Among the natural resources, seaweeds are a rich source of bioactive compounds including polyphenols, flavonoids, sulfated polysaccharides, proteins, peptides, vitamins, and minerals. Macroalgae are extremely diverse groups of aquatic, eukaryotic, multicellular, photosynthetic organisms possessing chlorophyll *a*, ranging in size from a few millimeters to several meters (Adl et al. 2012; Baldauf 2008; Burki et al. 2016). The bioactive compounds in seaweeds have been reported to exhibit significant pharmacological effects such as antiviral (Wang et al. 2008; Gheda et al. 2016), antibacterial (Perez et al. 2016), antidiabetic (Gunathilaka et al. 2021a, b; Gunathilaka et al. 2020), anticancer (Gunathilaka et al. 2021c; Gutierrez-Rodriguez et al. 2018), anti-inflammatory (Barbalace et al. 2019), immunomodulatory (Palstra et al. 2018), and antioxidant (Farasat et al. 2014) effects. Recent research has confirmed that the sulfated polysaccharides in seaweeds have the potential ability to act against SARS-CoV-2 (Kwon et al. 2020). Further research proved that phlorotannins extracted from seaweeds have the ability to act against SARS-CoV-2 (Kandeel and Al-Nazawi 2020; Qamar et al. 2020). Therefore, the present review mainly focuses on the utilization of bioactive compounds in marine seaweeds as a promising defense against COVID-19 infection.

Structure and Mechanism of Action of SARS-CoV-2

Structure of SARS-CoV-2

The human coronavirus was first observed and studied by two scientists: June Almeida, a Scottish virologist, and David Tyrrell, a British virologist. In 1968, the word “coronavirus” was first published referring to the characteristic appearance of virion morphology (Almeida et al. 1968) and intracellular binding site (Kathryn 1999). The morphology of the coronavirus was suggested based on the surface viral proteins (Sturman and Holmes 1983). According to epidemiological studies, five SARS-CoV-2

variants have been identified since the beginning of the pandemic as alpha, beta, gamma, delta, and omicron (Casella et al. 2022). Both COVID-19 and SARS-CoV-2 were officially published by the WHO in February 2020 (WHO, 2020).

SARS-CoV-2 belongs to the family of Coronaviridae, and it is a single-stranded positive-sense RNA virus (Neuman et al. 2006). The long single-stranded RNA is tightly packed at the center of the virus structure, and it is further encoded with capsid proteins called “nucleocapsid” (Wang et al. 2020). The RNA together with the nucleocapsid located at the core of the virus is further surrounded by an outer membrane that consists of lipids and three structural proteins including envelop proteins (E), membrane proteins (M), and spike proteins (S) as shown in Fig. 1 (Lai and Cavanagh 1997; Mittal et al. 2020). The spike proteins present in the outer membrane protrude from the viral surface and mediate the entry of coronavirus into host cells. The spike protein consists of two functional subunits called subunit 1 (S1) and subunit 2 (S2). S1 is composed of the receptor-binding domain (RBD) and N-terminal domain (NTD) which facilitate the binding of coronavirus to the receptors of the host cells. The receptor-binding domain of S1 of spike protein can specifically recognize the angiotensin-converting enzyme 2 (ACE2) receptors (Figs. 1 and 2). Similarly, S2 is composed of several components such as transmembrane domain (TM), connector domain (CD), fusion peptide (FP), central helix (CH), heptad repeat 1 (HR1), heptad repeat 2 (HR2), and cytoplasmic tail (CT) that facilitate the fusion of viral membrane with the host cells (Fig. 2) (Wang et al. 2020). Other than the structural protein, SARS-CoV-2 consists of 16 non-structural proteins which facilitate viral replication, within the host cells via a series of mechanisms, and act as a potential source for vaccine synthesis (Yadav et al. 2021).

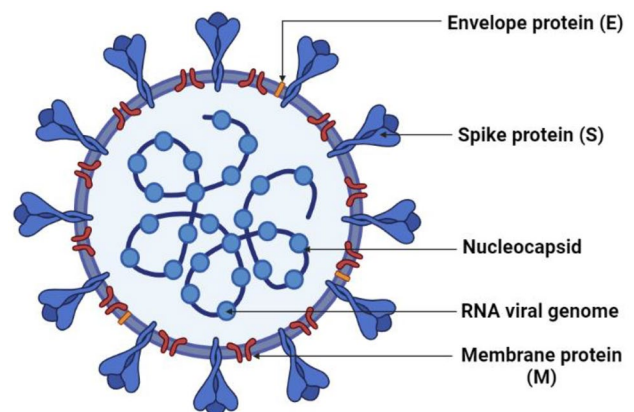
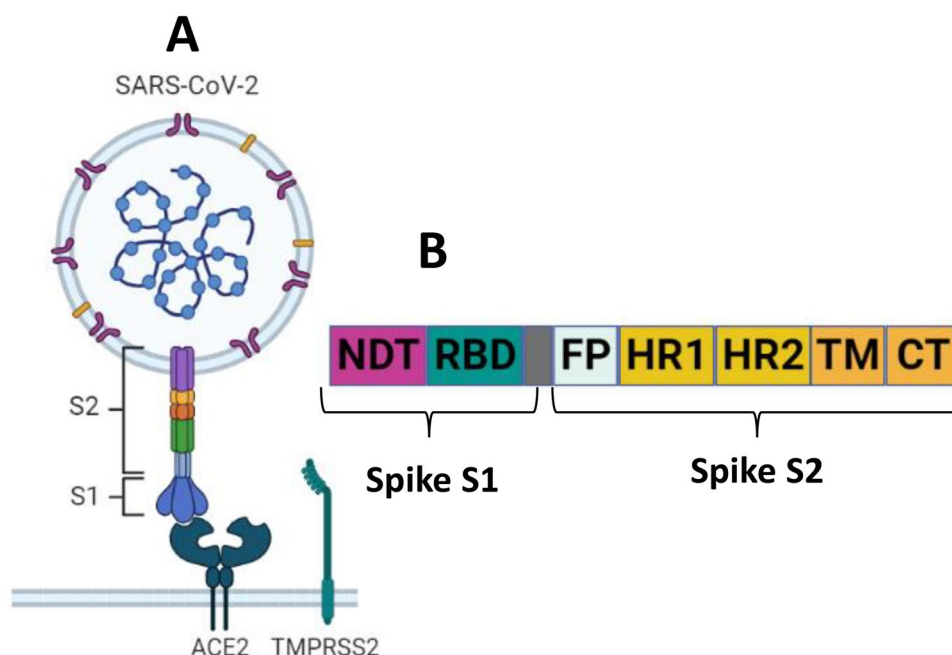


Fig. 1 The structure of SARS-CoV-2

Fig. 2 Schematic diagrams of **A** SARS-CoV-2 binding to ACE2 receptors and **B** SARS-CoV-2 spike proteins. NDT, N-terminal domain; RBD, receptor-binding domain; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; TM, transmembrane domain; CT, cytoplasmic tail



Mechanism of Action of SARS-CoV-2

SARS-CoV-2 enters the human lung cells via ACE2 receptors. Among the structural proteins, a spike protein present on the viral membrane binds with ACE2 receptors on lung cells and gains access to the entry of human lungs. During this process, human cells ingest viral cells via the process called “endocytosis” (Mittal et al. 2020). Once SARS-CoV-2 enters the host cells, S1 and S2 of spike proteins are cleaved by host proteases including trypsin and furin which release the FP present in S2 to activate the membrane fusion mechanisms within the endosome. As a result of the activation of membrane fusion mechanisms, viral RNA is released into the cytoplasm. With this process, viral RNA starts its replication process and produces thousands of viral RNA copies other than the structural and non-structural proteins and assembles into new virions within the endoplasmic reticulum-Golgi intermediate compartment. Ultimately, the synthesized new virions are transported via exocytosis and gain the capability to infect other body cells (Boopathi et al. 2021).

Therapeutic Targets for COVID-19

The therapeutic targets of SARS-CoV-2 can be discussed in three different steps as SARS-CoV-2 replication cycle, the spike protein during entry, the main protease during proteolytic activation, and RNA-dependent RNA polymerase during transcription (Krumm et al. 2021). Concerning the spike proteins present on the surface of SARS-CoV-2, angiotensin-converting enzyme 2 plays a major role as it is

the major human receptor for the S protein and facilitates viral entry (Zhou et al. 2020; Li et al. 2020).

The SARS-CoV-2 gains access to the human body via ACE2 receptors that are mainly found in the alveolar epithelial type 2 cells. Therefore, the expression of ACE2 receptors in alveolar epithelial cells determines the most vulnerable individuals to SARS-CoV-2 infection. ACE2 receptors are involved in the regulation of blood pressure and inflammatory conditions via the renin-angiotensin system (Tamama 2021). Both angiotensin-converting enzyme (ACE) and ACE2 are involved in the renin-angiotensin system which regulates blood pressure. The ACE is a carboxypeptidase that catalyzes the conversion of angiotensin I into angiotensin II which stimulates vasoconstriction and inflammatory effects. In contrast, ACE2 converts angiotensin II into angiotensin (1–7) which stimulates vasodilatation and anti-inflammatory effects (Fig. 3). Therefore, ACE2 has protective effects against severe acute lung injuries in COVID-19

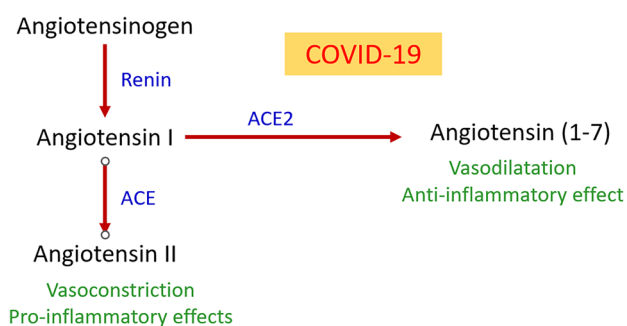


Fig. 3 The involvement of the renin-angiotensin system in the prevention of inflammatory conditions in SARS-CoV-2 infection

whereas ACE exacerbates the inflammatory conditions in lung tissues. Therefore, inhibition of the ACE leads to stimulating ACE2 which leads to producing angiotensin (1–7) that exerts protective effects against COVID-19 infection (Malha et al. 2020).

The infection of SARS-CoV-2 exacerbates the inflammatory condition in the body and leads to cause acute respiratory distress syndrome (ARDS) mainly by secreting high levels of cytokines which is refer to a cytokine storm. The high levels of cytokines such as chemokines, interferons, tumor necrosis factors, granulocyte–macrophage colony-stimulating factors, and interleukins are released as a result of the activation of innate immune mechanisms against the virus (Tamama 2021). The excessive secretion of cytokines attracts leukocytes via diapedesis by increasing vascular permeability and coagulability which stimulates the local inflammatory reactions and cell destruction. Furthermore, the cytokine storm induces cellular apoptosis and necrosis, lesions of the alveolar membrane, and fibrin deposition which leads to cause pulmonary fibrosis. Ultimately, all the mechanisms lead to cause multiorgan failure, ARDS, and death if inadequately treated (Krumm et al. 2021).

Similarly, reactive oxygen species act as the main stimulant in the activation of immune responses in COVID-19 infection. The SARS-CoV-2-infected lung tissues generate a high level of reactive oxygen species which stimulate the oxidation of phospholipids in pulmonary surfactants. The oxidized phospholipids stimulate alveolar macrophages to secrete cytokines mainly interleukin 6 (IL-6) via Toll-like receptor 4 that exacerbate acute lung injury (Jung and Lee 2021). Therefore, based on the literature, IL-6 together with other cytokines elevates the inflammatory condition in severe COVID-19.

Marine-derived Bioactive Compounds for the Treatment of COVID-19

Marine seaweeds have been identified as an important source of bioactive compounds comparable or superior to herbal medicines. In the last few years, marine seaweeds have been widely studied due to the presence of human-beneficial bioactive components (Gunathilaka et al. 2021a, b, c). Marine seaweeds are categorized into three groups as red algae (Rhodophyta), brown algae (Phaeophyta), and green algae (Chlorophyta) depending on the presence of accessory pigments. All groups of marine algae contain chlorophyll *a*, which assists in the process of photosynthesis. The characteristic color of different algal species is derived from accessory pigments. Marine green algae (Chlorophyta) have a characteristic green pigmentation mainly due to chlorophylls *a* and *b* that is approximately the same as in the amount present in higher plants. Phycoerythrin and phycocyanin are the pigments present in the marine red algae (Rhodophyta) which give a characteristic red color by masking the other pigments, such as chlorophyll

a, beta-carotene, and xanthophylls. Xanthophyll pigments and fucoxanthin are responsible for the brown color of brown algae (Phaeophyta) by masking the other pigments, such as chlorophylls *a* and *c*, β -carotenes, and other xanthophylls.

Bioactive compounds present in marine seaweeds including polyphenols, flavonoids, alkaloids, tannins, sterols, proteins, enzymes, essential fatty acids, peptides, vitamins, and pigments are reported to exhibit different pharmacological activities. The composition of bioactive compounds varies depending on the environmental conditions including salinity, temperature, pH, level of sunlight, and availability of CO₂ (Gunathilaka and Peiris 2022). This section mainly focuses on how marine-derived bioactive compounds are utilized for the treatment of COVID-19.

Effect of Marine-derived Polyphenolic Compounds Against COVID-19

Marine seaweeds are a rich source of polyphenols including flavonoids, phlorotannins, and bromophenols. Among different types of polyphenolic secondary compounds, phlorotannins are polyphenolic compounds that are mainly found in brown algae made up of phloroglucinol subunits. Depending on the number of phloroglucinol subunits, phlorotannins are categorized into six subunits as eckols, fucols, fuhalsols, phlorethols, fucophlorethols, and carmalols. Phlorethols are made up of two phloroglucinol subunits whereas eckols are made up of three phloroglucinol subunits (Gunathilaka et al. 2020). Figure 4 shows the structure of the repeating unit phloroglucinol and the different groups of phlorotannins.

Phlorotannins are reported to exhibit potential bioactivities including antioxidant, antimicrobial, antiviral, anti-allergic, antidiabetic, anti-inflammatory, anticancerous, and neuroprotection (Catarino et al. 2021). Further several studies have proved the anti-inflammatory activities of the phlorotannins isolated from marine seaweeds (Kwon et al. 2020; Ryu et al. 2021). Similarly, Bharathi et al. (2022) investigated the interactivity of algal molecules on SARS-CoV-2-RBD/ACE2 and SARS-CoV-2 spike/TMPRSS2 receptors using a silica model. Phlorotannins are reported to exhibit anti-inflammatory effects mainly by reducing the level of proinflammatory cytokines and reactive oxygen species (Catarino et al. 2021). Furthermore, phlorotannins have the ability to reduce cytokine storm in SARS-CoV-2 infection (Tamama 2021; Hu et al. 2021). Similarly, oxidative stress is one of the important mechanisms in the COVID-19 antiviral immune response (Wieczfinska et al. 2022). As phlorotannin exhibits several antioxidant mechanisms, it can be utilized to enhance the antiviral immune response in COVID-19 infection. Previous studies confirmed that phlorotannins exhibited potent antioxidant activity as determined by several mechanisms including DDPH and ABTS radical scavenging activity. Further studies reported that the phlorotannins isolated from

Ecklonia stolonifera, *Ecklonia kurome*, and *Eisenia bicyclis* including phlorofucofuroeckol A, dieckol, and eckol exhibited potent antioxidant activity compared to the α -tocopherol, catechin, and ascorbic acid (Shibata et al. 2008). Phlorotannins extracted from *Fucus vesiculosus*, *Fucus serratus*, and *Ascophyllum nodosum* reduced the oxidative degradation of DNA in stress-induced cells (Kang et al. 2012). Other than that, phlorotannins have the ability to induce auto-antioxidant defenses present in cells by activating detoxifying enzymes including superoxide dismutase and catalase. Studies confirmed that the phlorotannin-rich extracts of *F. vesiculosus*, *F. serratus*, and *A. nodosum* activated superoxide dismutase and catalase (O'Sullivan et al. 2012). Similarly, phlorotannins exhibit anti-inflammatory effects mainly by reducing the levels of proinflammatory cytokines and also by inhibiting angiotensin-converting enzymes. Previous studies have proved that phlorotannin extract of *Ecklonia cava* reduced the levels of proinflammatory cytokines including interleukins (IL-6 and IL-1 β) and tumor necrosis factor (TNF- α) (Kim et al. 2019). Furthermore, a previous study has confirmed that phlorotannins mainly dieckol isolated from *E. cava* have the ability to inhibit SARS-CoV competitively except for the monomeric phloroglucinol (Park et al. 2013). Therefore, phlorotannins in *E. cava* could be potential against SARS-CoV-2 as well. Correspondingly, phlorotannins inhibited ACE which is another target to reduce the inflammatory condition in COVID-19 infection. Phlorotannins extracted from brown seaweeds reduced inflammatory conditions by inhibiting ACE. Dieckol (IC₅₀: 1.47 Mm) extracted from *E. cava* inhibited ACE in a non-competitive manner. Furthermore, phlorotannins extracted from *Ecklonia stolonifera* including eckol, dieckol, and phlorofucofuroeckol A exhibited a potent inhibitory activity on angiotensin-converting enzymes with IC₅₀ values of 70:82 \pm 0:25 μ M, 34:25 \pm 3:56 μ M, and 12:74 \pm 0:15 μ M, respectively (Gunathilaka et al. 2021a, b, c). Among the isolated phlorotannins, dieckol inhibited the ACE non-competitively. Similarly, dieckol, 8,8-bieckol extracted from *Ecklonia cava*, acts as a protease inhibitor (Silva et al. 2020). Furthermore, phloroglucinol (IC₅₀: 56.96 μ g/ml) extracted from *Sargassum wightii* inhibited ACE compared to the reference drug captopril (IC₅₀: 51.79 μ g/ml) (Gunathilaka et al. 2021a, b, c).

Phlorotannins are unique compounds present in marine brown algae and can be extracted by several methods. Phlorotannin can be extracted by 30% ethanol–water solvent with a solid (freeze-dried seaweed powder/liquid ratio of 1:5 at a temperature of 25 °C for 30 min (Li et al. 2017).

Effect of Marine-derived Proteins and Peptides Against COVID-19

Most edible marine seaweeds are rich in proteins and peptides that exhibit an inhibitory effect on ACE. Therefore,

marine-derived proteins and peptides can also be utilized to reduce inflammatory conditions in COVID-19 infection. *Enteromorpha clathrata* is an edible green seaweed that can be utilized to inhibit ACE by the action of its protein-derived hydroxylate (Gunathilaka et al. 2021a, b, c). Furthermore, protein-derived hydroxylate of the red seaweed *Palmaria palmata* inhibited ACE, thereby reducing inflammatory conditions in COVID-19 (Admassu et al. 2018). Furthermore, a protein hydroxylate of *Gracilariopsis lemaneiformis*, *Porphyra dioica*, *Neopyropia yezoensis*, *Pyropia columbina*, *Palmaria palmata*, *Bangia fuscopurpurea*, *Sargassum maclurei*, *Laminaria japonica*, *Undaria pinnatifida*, *Ulva intestinalis*, *Ulva rigida*, *Ulva lactuca*, *Enteromorpha clathrata*, and *Caulerpa lentillifera* inhibited ACE, thereby reducing the inflammatory conditions in severe COVID-19 infection (Echave et al. 2022). Marine peptides are present in all three types of marine algae and extracted mainly by using bioassay-guided fractionation using methanol or ethyl acetate which has been subjected to partition with hexane or dichloromethane. The partially purified extract was subjected to silica gel column chromatography, and final purification was conducted using the reverse-phase HPLC technique (Cheung et al. 2015).

Effect of Marine-derived Sulfated Polysaccharides Against COVID-19

The sulfated polysaccharides are present in the cell walls of marine seaweeds and possess human-beneficial biological activities including anticoagulant, antiviral, antioxidant, anticancer, and anti-inflammation, hence utilized in many industries of cosmetics, foods, and pharmaceuticals. The unique properties of sulfated polysaccharides are based on the chemical structure, molecular weight, and chain conformations. The brown algae contain fucoidan, alginates, and laminaran as sulfated polysaccharides with beneficial biological effects (Gunathilaka et al. 2021a, b, c). Similarly, red seaweeds contain carrageenans and agarans as sulfated polysaccharides while ulvan is present in green seaweeds. The chemical structure of repeating dimeric units of fucoidan, carrageenan, and ulvan are shown in Fig. 5.

Marine-derived sulfated polysaccharides are found in the cell wall of marine seaweeds and are reported to exhibit antiviral activity. Fucoidan is a sulfated polysaccharide that exhibits antiviral activity by reducing the secretion of proinflammatory cytokines mainly interleukins (Tamama 2021). Further studies proved that fucoidan reduced lung fibrosis in a mouse model (Yu et al. 2018). Therefore, it can be utilized to prevent pulmonary fibrosis in severe COVID-19 infection. Furthermore, a study conducted by Kwon et al. (2020) reported that fucoidan isolated from *Saccharina japonica* exhibited potent antiviral activity against SARS-CoV-2 by binding with spike glycoprotein of the virus which inhibits

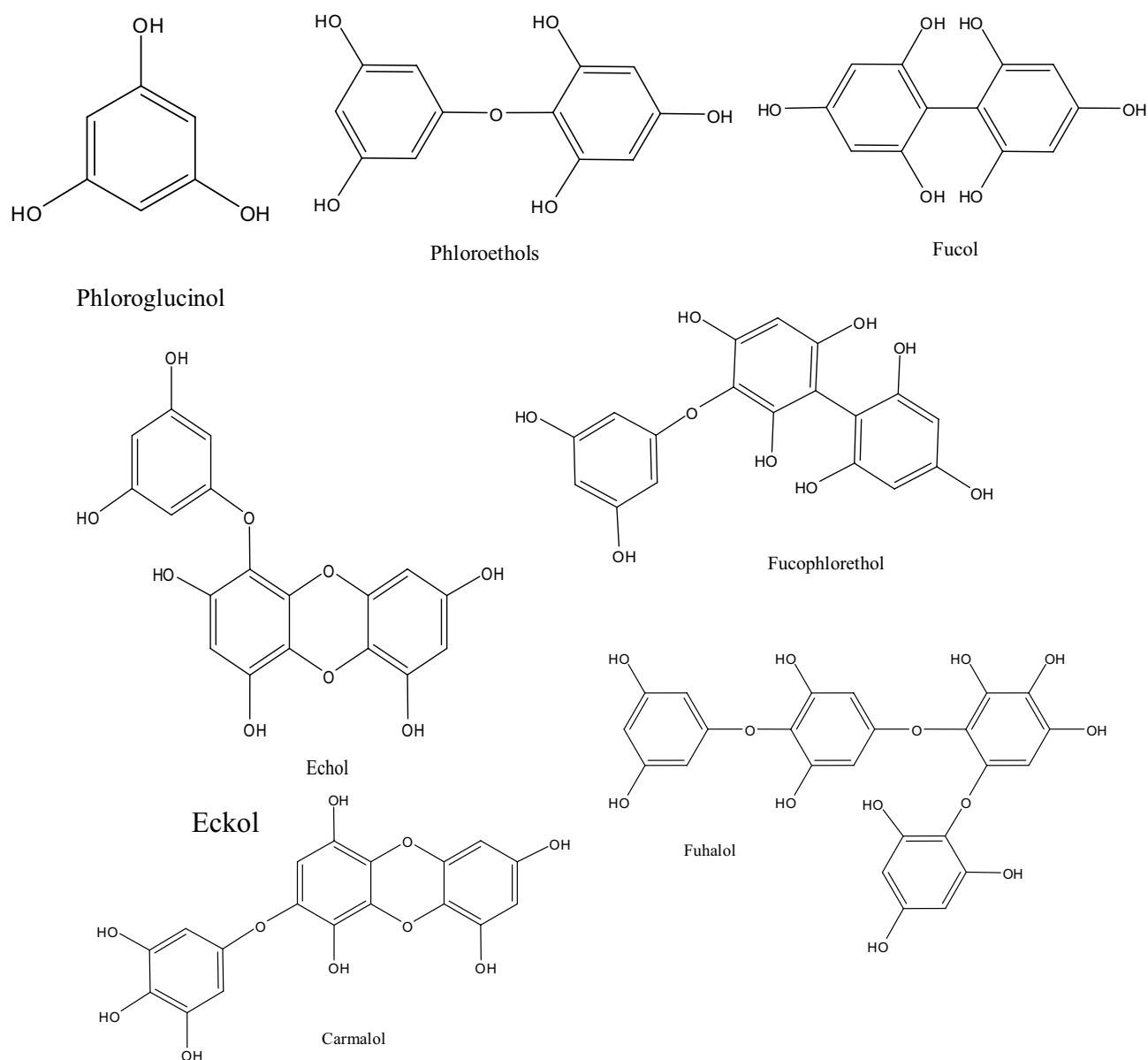


Fig. 4 Chemical structure of phloroglucinol and groups of phlorotannin

the binding of spike glycoprotein with ACE2 receptors of host cells. Furthermore, fucoidan extracted from *Adenocystis utricularis*, *Cystoseira indica*, *Fucus vesiculosus*, and *Undaria pinnatifida* exhibited anti-inflammatory activity by inhibiting adhesion and blocking reverse transcriptase enzyme (Kuznetsova et al. 2020; Krylova et al. 2020). Similarly, galactans are the main polysaccharide found in different marine seaweeds (Kumar et al. 2022a, b). Galactans extracted from *Agardhiella tenera*, *Schizymenia binderi*, and *Callophyllis variegata* exhibited antiviral activity by blocking the viral adhesion and replication into host cells (Ohta et al. 2009). Carrageenan, a sulfated polysaccharide found in marine red seaweeds, has the ability to inhibit viral

infections mainly by obstructing the entry of viral particles into the host cells (Singh et al. 2021). Another study has reported that the carrageenan nasal spray was effective against the common cold caused by a human coronavirus (Koenighofer et al. 2014). Furthermore, lozenges (medicinal tablets) prepared using carrageenan were effective for throat problems caused by the human coronavirus OC43. This study has further proved that carrageenan has effectively inactivated the viral glycoproteins (Morokutti-Kurz et al. 2017). Moreover, carrageenan extracted from *Gigartina skottsbergii* exhibited antiviral activity via the inhibition of binding or internalization of viruses into host cells (Nagle et al. 2020; Grassauer et al. 2011). Therefore, based

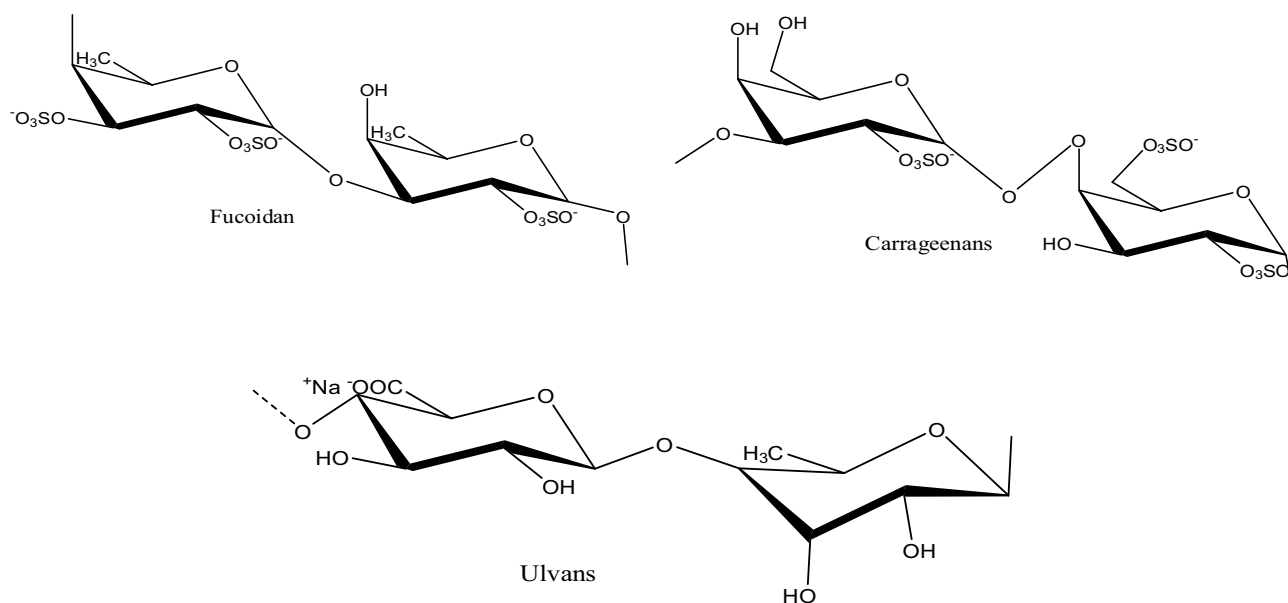


Fig. 5 The chemical structure of repeating dimeric units of fucoidan, carrageenan, and ulvan

on the previous studies, carrageenan can be effective against SARS-CoV-2 as well.

Alginates are natural anionic polymers extracted from brown seaweed (Serrano-Aroca et al. 2021). Based on the previous studies, alginate extracted from *Laminaria japonica* and *Laminaria digitata* exhibited antiviral activity by inhibiting inverse transcriptase in the RNA virus (Tran et al. 2014). As SARS-CoV-2 is an RNA virus, alginate can be effectively utilized to inhibit the action of SARS-CoV-2.

Sulfated polysaccharides present in red, green, and brown algae were extracted using several methods. Sulfated polysaccharides present in brown seaweeds, mainly fucoidan, were extracted by precipitating with ethanol followed by different steps including acid precipitation, size-exclusive chromatography, or filtration to obtain pure fucoidan. Similarly, sulfated polysaccharides present in red algae, mainly carrageenan, were extracted using two conventional extraction procedures separately to extract refined carrageenan and semi-refined carrageenan. The refined carrageenan was extracted by solubilizing in hot water containing alkali whereas semi-refined carrageenan was extracted by boiling in hot potassium chloride (Jonsson et al. 2020).

Effect of Marine-derived Carotenoids Against COVID-19

Marine seaweeds are rich in carotenoids that include zeaxanthin, neoxanthin, α-carotene, β-carotene, lutein, fucoxanthin, astaxanthin, and siphonaxanthin and are reported to exhibit potent antioxidant and antiviral activities. Fucoxanthin is the most abundant type mainly found in brown algae including *Undaria pinnatifida*, *Laminaria japonica*,

Sargassum sp., and *Fucus* sp. Similarly, astaxanthin and siphonaxanthin are mainly present in green algae such as *Codium cylindricum*, *Caulerpa lentillifera*, and *Codium fragile* (Yim et al. 2021a, b). Previous studies have confirmed that fucoxanthin exhibited potent anti-inflammatory activity mainly by reducing the levels of proinflammatory cytokines including interleukins (Tamama 2021). Furthermore, a molecular docking simulation study conducted by Yim et al. (2021) reported that fucoxanthin extracted from *Undaria pinnatifida* and siphonaxanthin extracted from *Codium fragile* have the ability to bind with the ACE2 receptors which is the binding site of SARS-CoV-2 spike protein with host cells (Yim et al. 2021a, b). During COVID-19 infection, SARS-CoV-2 induces oxidative stress that assists their replication inside the host cell. As marine algae are a rich source of natural antioxidants, it can be utilized against COVID-19 infection to maintain redox homeostasis in the body. Fucoxanthin, a natural carotenoid present in brown algae, has the ability to scavenge free radicals due to the presence of a specific allenic bond in its structure. Furthermore, studies reported that fucoxanthin extracted from *Sargassum siliquastrum* inhibited oxidative DNA damage by increasing the production of glutathione peroxidase (Singh et al. 2021).

Carotenoids present in marine seaweeds can be extracted using different methods including ultrasound-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction. Among the different techniques, the Soxhlet extraction method is a conventional method that delivers the highest yield of carotenoids (Ramesh and Young, 2018).

Table 1 Summary of tested algae and possible active agents responsible for the anti-inflammatory/antiviral properties

Algal species	Antiviral/anti-inflammatory metabolites	Effective concentration	Mechanism of action
Algae extracts/compounds exhibited antiviral activity against SARS-CoV-2			
<i>Laminaria japonica</i>	Sulfated polysaccharides	12 ~ 289 µg/ml	Inhibitory activity against SARS-CoV-2 virus entry (Yim et al. 2021a, b)
<i>Undaria pinnatifida</i>		12 ~ 289 µg/ml	
<i>Hizikia fusiforme</i>		12 ~ 289 µg/ml	
<i>Sargassum horneri</i>		12 ~ 289 µg/ml	
<i>Codium fragile</i>		12 ~ 289 µg/ml	
<i>Porphyra tenera</i>	Fucoidan	> 1000 µg/ml	Inhibit the replication of viral particles (Krylova et al. 2020)
<i>Fucus evanescens</i>		25–110 µg/ml	
<i>Agardhiella tenera</i>	Galactan	4.7–16 µg/ml	Blocking of virus adhesion and replication into host cells (Ohta et al. 2009)
<i>Schizymenia binderi</i>			
<i>Callophyllis variegata</i>			
<i>Codium fragile</i>	Siphonaxanthin	87.4 µM	Bind with the ACE2 receptors which is the binding site of SARS-CoV-2 spike protein with host cells (Yim et al. 2021a, b)
<i>Undaria pinnatifida</i>	Fucoanthin	> 100 µM	Bind with the ACE2 receptors which is the binding site of SARS-CoV-2 spike protein with host cells and reduce the levels of proinflammatory cytokines including interleukins (Yim et al. 2021a, b; Tamama 2021)
Algae extracts with antiviral activity			
<i>Gigartina skottsbergii</i>	Carrageenan	–	Inhibition of binding or internalization of viruses into host cells (Nagle et al. 2020)
<i>Porphyridium aerugineum</i>	Sulfated polysaccharides	–	Selectively inhibit binding of many enveloped and non-enveloped viruses (Grassauer et al. 2011)
<i>Adenocystis utricularis</i> , <i>Cystoseira indica</i> , <i>Fucus vesiculosus</i> , <i>Undaria pinnatifida</i>	Fucoidan	–	Inhibition of adhesion and blocking of reverse transcriptase (Kuznetsova et al. 2020; Krylova et al. 2020)
<i>Saccharina japonica</i>	Fucoidan	–	Inhibits the binding of spike glycoprotein with ACE2 receptors of host cells (Kuznetsova et al. 2020)
<i>Ecklonia cava</i>	Phlorotannin extract	–	Reduce the levels of proinflammatory cytokines (Catarino et al. 2021)
<i>Undaria pinnatifida</i>	Dieckol; 8,8-bieckol	–	Anti-inflammatory activity (Schwalfenberg 2006; Penalver et al. 2020)
<i>Calliblepharis jubata</i>	Omega-3 (EPA & DHA)	–	
<i>Bifurcaria bifurcate</i>			
<i>Durvillaea antarctica</i>			
<i>Agarophyton chilense</i>			
<i>Ulva lactuca</i>	Vitamin D ₃	–	Anti-inflammatory activity (Leandro et al. 2020)
<i>Fucus spiralis</i>			
<i>Gelidiella acerosa</i>	Vitamin B ₁₂	–	Antiviral activity (Leandro et al. 2020)
<i>Ascophyllum nodosum</i>			
<i>Laminaria digitata</i>			
<i>Undaria pinnatifida</i>			
<i>Palmaria palmata</i>			
<i>Porphyra umbilicalis</i>	Vitamin C	–	Enhance the cellular immune responses and vascular integrity (Uddin et al. 2021; Simat et al. 2020)
<i>Himanthalia elongate</i>			
<i>Crassiphycus changii</i>			
<i>Ecklonia arborea</i>	Alginate	–	Inhibition of inverse transcriptase in the RNA virus (Tran et al. 2014)
<i>Laminaria digitata</i>			

Table 1 (continued)

Algal species	Antiviral/anti-inflammatory metabolites	Effective concentration	Mechanism of action
<i>Palmaria palmate</i>	Protein hydroxylates	–	ACE inhibitor (Echave et al. 2022; Gunathilaka et al. 2021a, b, c)
<i>Enteromorpha clathrata</i>			
<i>Gracilariopsis lemaneiformis</i>			
<i>Porphyra dioica</i>			
<i>Neopyropia yezoensis</i>			
<i>Pyropia columbina</i>			
<i>Palmaria palmata</i>			
<i>Bangia fuscopurpurea</i>			
<i>Sargassum maclurei</i>			
<i>Laminaria japonica</i>			
<i>Undaria pinnatifida</i>			
<i>Ulva intestinalis</i>			
<i>Ulva rigida</i>			
<i>Ulva lactuca</i>			
<i>Enteromorpha clathrata</i>			
<i>Caulerpa lentillifera</i>	Dieckol	1.47 Mm	ACE inhibitor (Silva et al. 2020)
<i>Ecklonia cava</i>			
<i>Sargassum wightii</i>			
	Phloroglucinol	56.96 µg/ml	ACE inhibitor (Gunathilaka et al. 2021a, b, c)

Effect of Marine-derived Omega-3 and Omega-6 Against COVID-19

Seaweeds are rich in both omega-3 and omega-6 which are long-chain polyunsaturated fatty acids. Previous studies reported that both omega-3 and omega-6 fatty acids are involved in the regulation of inflammatory conditions. Omega-3 fatty acids play a key role in regulating the membrane fluidity of neutrophils by incorporating omega-3 fatty acids into the phospholipid bilayer which stimulates the secretion of prostaglandins and leukotrienes to enhance the immune response. Furthermore, it enhances the phagocytic function of macrophages and induces an antiviral response by inhibiting viral replication through the secretion of interferon. Similarly, omega-6 fatty acids stimulate the secretion of cytokines and leukotrienes which enhance the immune response against pathogen invasion (Hathaway et al. 2020). Previous studies have reported that both red and brown seaweeds are rich in omega-3 fatty acids that include linolenic acid, linoleic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Further research proved that brown algae *Undaria pinnatifida*, *Calliblepharis jubata*, *Bifurcaria bifurcata*, and *Durvillaea antarctica*; red algae *Agarophyton chilense*; and green algae *Ulva lactuca* are rich in omega-3 polyunsaturated fatty acids including EPA and

DHA which are beneficial to reduce oxidative stress and acute respiratory distress in COVID-19 (Schwalfenberg 2006; Penalver et al. 2020).

Effect of Marine-derived Vitamins Against COVID-19

Seaweeds are a rich source of vitamins including vitamins A, C, D, E, B, and K. As reported, vitamins D, B₁₂, and C have been reported to reduce the inflammatory conditions in COVID-19 infection. Vitamin D₃, known as cholecalciferol, modulates the inflammatory responses by reducing the secretion of proinflammatory cytokines. Jayawardena et al. (2021) have reported a significant positive correlation between vitamin D deficiency and COVID-19 infection (Jayawardena et al. 2021). Similarly, previous studies have reported that vitamin B₁₂ inhibited RNA-dependent RNA polymerase activity of SARS-CoV-2 (Narayanan and Nair 2020). Furthermore, vitamin C has the ability to scavenge reactive oxygen species which, in turn, enhances the cellular immune responses and vascular integrity to minimize the severe respiratory infections in COVID-19 (Uddin et al. 2021). Among the edible seaweeds, *Fucus spiralis* and *Gelidiella acerosa* are reported to exhibit high vitamin D₃

content whereas *Ascophyllum nodosum*, *Laminaria digitata*, *Undaria pinnatifida*, *Palmaria palmata*, *Porphyra umbilicalis*, and *Ulva* sp. are rich in vitamin B₁₂ (Leandro et al. 2020). Seaweeds including *Himanthalia elongate*, *Crassiphycus changii*, and *Ecklonia arborea* are reported to exhibit high vitamin C content (Simat et al. 2020).

Effect of Marine-derived Minerals Against COVID-19

Seaweeds are a rich source of essential minerals including calcium, magnesium, zinc, selenium, sulfate, phosphorus, chloride, sodium, and potassium which are acquired from the marine environment (Penalver et al. 2020). Among the available minerals, zinc is associated with the regulation of immune responses during SARS-CoV-2 infections. Previous studies have reported that zinc level is important to maintain lung integrity to prevent respiratory distress conditions in COVID-19 infections. Furthermore, it was reported that Zn inhibited the entry of SARS-CoV-2 into cells by downregulating the ACE2 receptors and also by inhibiting the fusion of SARS-CoV-2 with the host cell membrane. Furthermore, Zn has the ability to conquer RNA-dependent RNA polymerase of the SARS-CoV-2 (Jahromi et al. 2021). Therefore, seaweeds rich in Zn including *Caulerpa lentillifera*, *Ulva rigida*, *Chondrus crispus*, *Palmaria palmata*, *Porphyra umbilicalis*, *Fucus vesiculosus*, and *Himanthalia elongate* can be utilized for the treatment of COVID-19 infection (Penalver et al. 2020).

Effect of Marine-derived Prebiotics and Probiotics Against COVID-19

Furthermore, the gut microbiota is also important to prevent gastrointestinal infections associated with COVID-19 infection. SARS-CoV-2 gains access through the ACE receptors on intestinal endothelial cells and cause gastrointestinal infections. Both prebiotics and probiotics are involved in the maintenance of commensal gut microbiota by producing short-chain fatty acids through fermentation which exhibit anti-inflammatory effects. Similarly, soluble dietary fibers present in marine seaweeds are produced from short-chain fatty acids through fermentation by gut microbiota. Previous studies have reported that oral administration of fucoidan increased gut microbiota including *Lactobacillus* and *Bifidobacterium*. Similarly, laminarin, alginate, and agar serve as prebiotics (Kurian et al. 2021). Therefore, seaweeds rich in soluble dietary fibers can be utilized to reduce gastrointestinal infections associated with SARS-CoV-2. These findings are summarized in Table 1.

Furthermore, sulfolipids and glycolipids present in marine seaweeds are reported to exhibit antiviral activities against the SARS-CoV-2 infection (Kumar et al. 2022a, b).

Conclusion

Marine seaweeds are a rich source of bioactive metabolites that exhibited potent antioxidant, antiviral, and anti-inflammatory effects. Among the bioactive compounds present in marine seaweeds, phlorotannins; fucoidans; fucoxanthin; astaxanthin; omega-3 and omega-6 fatty acids; vitamins B₁₂, D, and C; minerals including zinc and selenium; and soluble dietary fibers exhibited direct or indirect antiviral effects against SARS-CoV-2 infection. Therefore, the present mini-review mainly focused on the contribution of marine bioactive compounds to lower the severity of SARS-CoV-2 infection.

Declarations

Conflict of Interest The author declares no competing interests.

References

- Adl SM, Simpson AG, Lane CE, Lukes J, Bass D, Bowser SS, Brown MW, Burki F, Dunthorn M, Hampl V, Heiss A, Hoppenrath M, Lara E, Le Gall L, Lynn DH, McManus H, Mitchell EA, Mozley-Stanridge SE, Parfrey LW, Pawlowski J, Rueckert S, Shadwick L, Schoch CL, Smirnov A, Spiegel FW (2012) The revised classification of eukaryotes. *J Eukaryot Microbiol* 59:429–493
- Admassu H, Gasmalla MAA, Yang R, Zhao W (2018) Bioactive peptides derived from seaweed protein and their health benefits: antihypertensive, antioxidant, and antidiabetic properties. *J Food Sci* 83:6–16
- Almeida JD, Berry DM, Cunningham CH, Hamre D, Hofstad MS, Mallucci L, McIntosh K, Tyrrell DA (1968) Virology: coronaviruses. *Nature*. 220 (5168): 650. Bibcode: 1968Natur.220.650.
- Amaratunga D, Fernando N, Haigh R, Jayasinghe N (2020) The COVID19 outbreak in Sri Lanka: a synoptic analysis focusing on trends, impacts, risks and science-policy interaction processes. *Prog Disaster Sci* 8:100133. <https://doi.org/10.1016/j.pdisas.2020.100133>
- Baldauf SL (2008) An overview of the phylogeny and diversity of eukaryotes. *J Syst Evol* 46:263–273
- Barbalace MC, Malaguti M, Giusti L, Lucacchini A, Hrelia S, Angeloni C (2019) Anti-inflammatory activities of marine algae in neurodegenerative diseases. *Int J Mol Sci* 20:3061
- Bharathi M, Sivamaruthi BS, Kesika P, Thangaleela S, Chaiyasut C (2022 Feb 17) In Silico Screening of Bioactive Compounds of Representative Seaweeds to Inhibit SARS-CoV-2 ACE2-Bound Omicron B.1.1.529 Spike Protein Trimer. *Mar Drugs* 20(2):148. <https://doi.org/10.3390/md20020148>. PMID: 35200677; PMCID: PMC8877529
- Boopathi S, Poma AB, Kolandaivel P (2021) Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. *J Biomol Struct Dyn* 39:3409–3418
- Burki F, Kaplan M, Tikhonenkov DV, Zlatogursky V, Minh BQ, Radaykina LV, Smirnov A, Mylnikov AP, Keeling PJ (2016) Untangling the early diversification of eukaryotes: a phylogenomic study of the evolutionary origins of Centrohelida, Haptophyta and Cryptista. *Proc R Soc B* 283:2015–2802
- Cascella M, Rajnik M, Aleem A et al (2022) Features, evaluation, and treatment of coronavirus (COVID-19) In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554776/>
- Catarino MD, Amarante SJ, Mateus N, Silva AMS, Cardoso SM (2021) Brown algae phlorotannins: a marine alternative to break the oxidative stress, inflammation and cancer network. *Foods* 10:1478

- Cheung R, Fai C, Ng TB, Wong JH (2015) Marine peptides: bioactivities and applications. *Mar Drugs* 13(7):4006–4043. <https://doi.org/10.3390/md13074006>
- Echave J, Otero P, Garcia-Oliveira P, Munekata PES, Pateiro M, Lorenzo JM, Simal-Gandara J, Prieto MA (2022) Seaweed-derived proteins and peptides: promising marine bioactives. *Antioxidants* 11:176
- Farasat M, Khavari-Nejad RA, Nabavi SM, Namjooyan F (2014) Antioxidant activity, total phenolics and flavonoid contents of some edible green seaweeds from northern coasts of the Persian Gulf. *Iran J Pharm Res: IJPR* 13:163–170
- Ghedda SF, El-Adawi HI, El-Deeb NM (2016) Antiviral profile of brown and red seaweed polysaccharides against hepatitis C virus. *Iran J Pharm Res: IJPR* 15:483–491
- Grassauer A, Prieschl-Grassauer E (2011). Antiviral composition comprising a sulfated polysaccharide. U.S. Patent Application US 12/673, 145
- Gunathilaka T, Peiris D (2022) Algae functional compounds, reference module in food science. Elsevier. <https://doi.org/10.1016/B978-0-12-823960-5.00012-3>
- Gunathilaka T, Keertthirathna LR, Peiris D (2021a) Advanced pharmacological uses of marine algae as an anti-diabetic therapy. In: *Pharmacognosy - medicinal plants*. IntechOpen. <https://doi.org/10.5772/intechopen.96807>
- Gunathilaka TL, Samarakoon K, Ranasinghe P, Peiris LDC (2020) Anti-diabetic potential of marine brown algae-a mini review. *J Diabetes Res* 1230218. <https://doi.org/10.1155/2020/1230218> [PubMed]
- Gunathilaka MDTL, Keertthirathna R, Peiris D (2021b) Advanced pharmacological uses of marine algae as an anti-diabetic therapy. In (Ed.) *Natural medicinal plants*. IntechOpen. <https://doi.org/10.5772/intechopen.96807>
- Gunathilaka TL, Dilrangi KH, Ranasinghe P, Samarakoon KW, Peiris LDC (2021) Mechanistic insight into apoptotic induction in human rhabdomyosarcoma and breast adenocarcinoma cells by *Chnoospora minima*: a Sri Lankan brown seaweed. *Pharmaceuticals* 14:1154
- Gutiérrez-Rodríguez AG, Juárez-Portilla C, Olivares-Bañuelos T, Zepeda RC (2018) Anticancer activity of seaweeds. *Drug Discovery Today* 23:434–447
- Hathaway D, Pandav K, Patel M, Riva-Moscato A, Singh BM, Patel A, Min ZC, Singh-Makkar S, Sana MK, Sanchez-Dopazo R, Desir R, Fahem MMM, Manella S, Rodriguez I, Alvarez A, Abreu R (2020) Omega 3 fatty acids and COVID-19: a comprehensive review. *Infect Chemother* 52:478–495
- Health Promotion Bureau (2022). <https://www.hpb.health.gov.lk/en>. Accessed 25 Feb 2022
- Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, Hirano T (2020) How COVID-19 induces cytokine storm with high mortality. *Inflamm Regen* 1:37
- Hu B, Huang S, Yin L (2021 Jan) The cytokine storm and COVID-19. *J Med Virol* 93(1):250–256. <https://doi.org/10.1002/jmv.26232>. Epub 2020 Sep 30. PMID: 32592501; PMCID: PMC7361342
- Jahromi RS, Tabriz HM, Togha M, Ariyanfar S, Ghorbani Z, Naeeni S, Haghighi S, Jazayeri A, Montazeri M, Talebpour M, Ashraf H, Ebrahimi M, Hekmatdoost A, Jafari E (2021) The correlation between serum selenium, zinc, and COVID-19 severity: an observational study. *BMC Infect Dis* 21:899
- Jayawardena R, Jeyakumar DT, Francis TV, Misra A (2021) Impact of the vitamin D deficiency on COVID-19 infection and mortality in Asian countries. *Diabetes Metab Syndr* 5:757–764
- Jönsson M, Allahgholi L, Sardari R, Hreggviðsson GO, Nordberg Karlsson E (2020) Extraction and modification of macroalgal polysaccharides for current and next-generation applications. *Molecules* (Basel, Switzerland) 25(4):930. <https://doi.org/10.3390/molecules25040930>
- Jung HE, Lee HK (2021) Current understanding of the innate control of Toll-like receptors in response to SARS-CoV-2 infection. *Viruses* 13:2132
- Kandeel M, Al-Nazawi M (2020) Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. *Life Sci* 25:117627. [CrossRef] [PubMed]
- Kang SM, Heo SJ, Kim KN, Lee SH, Jeon YJ (2012) Isolation and identification of new compound, 2,7'-phloroglucinol-6,6'-bieckol from brown algae, *Ecklonia cava* and its antioxidant effect. *J Funct Foods* 4:158–166
- Kathryn VH (1999) Coronaviruses (Coronaviridae). In: *Encyclopedia of virology* (Second Edition), Elsevier, pages 291–298, ISBN 9780122270307. <https://doi.org/10.1006/rwvi.1999.0055>
- Kim S, Choi S, Kim G, Imm J (2019) Anti-inflammatory effect of *Ecklonia cava* extract on *Porphyromonas gingivalis* lipopolysaccharide-stimulated macrophages and a periodontitis rat model. *Nutrients* 11:1143
- Koenigshofer M, Lion T, Bodenteich A, Grassauer A, Unger H, Mueller CA, Fazekas T (2014) Carrageenan nasal spray in virus confirmed common cold: individual patient data analysis of two randomized controlled trials. *Multidiscip Respir Med* 9:57
- Krumm ZA, Lloyd GM, Francis CP, Nasif LH, Mitchell DA, Golde TE, Giasson BI, Xia Y (2021) Precision therapeutic targets for COVID-19. *Virol J* 18:66
- Krylova NV, Ermakova SP, Lavrov VF, Leneva IA, Kompanets GG, Iunikhina OV, Nosik MN, Ebralidze LK, Falynskova IN, Silchenko AS et al (2020) The comparative analysis of antiviral activity of native and modified fucoidans from brown algae *Fucus evanescens* in vitro and in vivo. *Mar Drugs* 18:224
- Kumar A, Singh RP, Kumar I, Yadav P, Singh SK, Kaushalendra SPK, Gupta RK, Singh SM, Kesawat MS, Saratale GD, Chung S-M, Kumar M (2022) Algal metabolites can be an immune booster against COVID-19 pandemic. *Antioxidants* 11:452
- Kumar A, Singh RP, Kumar I, Yadav P, Singh SK, Kaushalendra Singh PK et al (2022b) Algal metabolites can be an immune booster against COVID-19 pandemic. *Antioxidants*, 11(3), 452. MDPI AG. Retrieved from: <https://doi.org/10.3390/antiox11030452>
- Kurian SJ, Unnikrishnan MK, Miraj SS, Bagchi D, Banerjee M, Reddy BS, Rodrigues GS, Manu MK, Saravu K, Mukhopadhyay C, Rao M (2021) Probiotics in prevention and treatment of COVID-19: current perspective and future prospects. *Arch Med Res* 52:582–594
- Kuznetsova TA, Smolina TP, Makarenkova ID, Ivanushko LA, Persyanova EV, Ermakova SP, Silchenko AS, Zaporozhets TS, Besednova NN, Fedyanina LN et al (2020) Immunoadjuvant activity of fucoidans from the brown alga *Fucus evanescens*. *Mar Drugs* 18:155
- Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K, Hong JJ, Linhardt RJ, Dordick JS (2020) Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. *Cell Discov* 6:50. <https://doi.org/10.1038/s41421-020-00192-8>
- Lai MM, Cavanagh D (1997) The molecular biology of coronaviruses. *Adv Virus Res* 48:1–100
- Lakhani JD, Kapadia S, Choradiya R, Gill RP, Lakhani SJ (2021) COVID-19 and multiorgan dysfunction syndrome. In (Ed.), *Fighting the COVID19 pandemic*. IntechOpen. <https://doi.org/10.5772/intechopen.99676>
- Leandro A, Pacheco D, Cotas J, Marques JC, Pereira L, Gonçalves AMM (2020) Seaweed's bioactive candidate compounds to food industry and global food security. *Life* 10:140. PMID: 32781632; PMCID: PMC7459772
- Li Y, Fu X, Duan D, Liu X, Xu J, Gao X (2017) Extraction and identification of phlorotannins from the brown alga, *Sargassum fusiforme* (Harvey) Setchell. *Mar Drugs* 15(2):49. <https://doi.org/10.3390/md15020049>
- Li H, Liu SM, Yu XH, Tang SL, Tang CK (2020) Coronavirus disease 2019 (COVID-19): current status and future perspectives. *Int J Antimicrob Agents*, 55(5), 105951

- Malha L, Mueller FB, Pecker MS, Mann SJ, August P, Feig PU (2020) COVID-19 and the renin-angiotensin system. *Kidney Int Rep* 5:563–565
- Mittal A, Manjunath K, Ranjan RK, Kaushik S, Kumar S, Verma V (2020) COVID-19 pandemic: insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. *PLoS Pathog* 16(8):e1008762
- Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G (2020) COVID-19 and multiorgan failure: a narrative review on potential mechanisms. *J Mol Histol* 51:613–628
- Morokutti-Kurz M, Graf C, Prieschl-Grassauer E (2017) Amylmetacresol/2,4-dichlorobenzyl alcohol, hexylresorcinol, or carrageenan lozenges as active treatments for sore throat. *Int J Gen Med* 28:53–60
- Nagle V, Gaikwad M, Pawar Y, Dasgupta S (2020) Marine red alga *Porphyridium* sp. as a source of sulfated polysaccharides (SPs) for combating against COVID-19. Preprints, 2020040168
- Narayanan N, Nair DT (2020) Vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the SARS-CoV-2 virus. *IUBMB Life* 72:2112–2120
- Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P et al (2006) Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. *J Virol* 80:7918–7928
- O'Sullivan AM, O'Callaghan YC, O'Grady MN, Queguineur B, Hanniffy D, Troy DJ, Kerry JP, O'Brien NM (2012) Assessment of the ability of seaweed extracts to protect against hydrogen peroxide and tert-butyl hydroperoxide induced cellular damage in Caco-2 cells. *Food Chem* 134:1137–1140
- Ohta Y, Lee JB, Hayashi K, Hayashi T (2009) Isolation of sulfated galactan from *Codium fragile* and its antiviral effect. *Biol Pharm Bull* 32:892–898
- Palstra AP, Kals J, Blanco Garcia A, Dirks RP, Poelman M (2018) Immunomodulatory effects of dietary seaweeds in LPS challenged Atlantic salmon *Salmo salar* as determined by deep RNA sequencing of the head kidney transcriptome. *Front Physiol* 9:625
- Park JY, Kim JH, Kwon JM, Kwon HJ, Jeong HJ, Kim YM, Kim D, Lee WS, Ryu YB (2013) Dieckol, a SARS-CoV 3CL(pro) inhibitor, isolated from the edible brown algae *Ecklonia cava*. *Bioorg Med Chem* 21:3730–3737
- Penalver R, Lorenzo JM, Ros G, Amarowicz R, Pateiro M, Nieto G (2020) Seaweeds as a functional ingredient for a healthy diet. *Mar Drugs* 18:301
- Perez MJ, Falqué E, Domínguez H (2016) Antimicrobial action of compounds from marine seaweed. *Mar Drugs* 14:52
- Qamar MTU, Alqahtani SM, Alamri MA, Chen LL (2020) Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *J Pharm Anal* 10: 313–319. [CrossRef]
- Ramesh KS, Young SK (2018) Carotenoid extraction methods: A review of recent developments. *Food Chem* 240:90–103. <https://doi.org/10.1016/j.foodchem.2017.07.099>
- Ryu B, Kim Y-S, Jeon Y-J (2021) Seaweeds and their natural products for preventing cardiovascular associated dysfunction. *Mar Drugs* 19(9):507. <https://doi.org/10.3390/md19090507>
- Schwalfenberg G (2006) Omega-3 fatty acids: their beneficial role in cardiovascular health. *Can Fam Physician* 52(6):734–740
- Serrano-Aroca Á, Ferrandis-Montesinos M, Wang R (2021) Antiviral properties of alginate-based biomaterials: promising antiviral agents against SARS-CoV-2. *ACS Appl Bio Mater* 4:5897–5907
- Shibata T, Ishimaru K, Kawaguchi S, Yoshikawa H, Hama Y (2008) Antioxidant activities of phlorotannins isolated from Japanese Laminariaceae. *J Appl Phycol* 20:705–711 [Google Scholar] [CrossRef]
- Silva JKR, Figueiredo PLB, Byler KG, Setzer WN (2020) Essential oils as antiviral agents, potential of essential oils to treat SARS-CoV-2 infection: an in-silico investigation. *Int J Mol Sci* 21:3426
- Simat V, Elabed N, Kulawik P, Ceylan Z, Jamroz E, Yazgan H, Cagalj M, Regenstein JM, Ozogul F (2020) Recent advances in marine-based nutraceuticals and their health benefits. *Mar Drugs* 18:627. PMID: 33317025; PMCID: PMC7764318
- Singh R, Chauhan N, Kuddus M (2021) Exploring the therapeutic potential of marine-derived bioactive compounds against COVID-19. *Environ Sci Pollut Res* 28:52798–52809
- Sturman LS, Holmes KV (1983) Lauffer MA, Maramorosch K (eds.). *The molecular biology of coronaviruses*. *Adv Virus Res* 28:35–112. ISBN 9780120398287
- Tamama K (2021) Potential benefits of dietary seaweeds as protection against COVID-19. *Nutr Rev* 79:814–823
- Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C (2020) Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 11:1708
- Tran NM, Dufresne M, Helle F, Hoffmann TW, François C, Brochot E, Paullier P, Legallais C, Duverlie G, Castelain S (2014) Alginate hydrogel protects encapsulated hepatic HuH-7 cells against hepatitis C virus and other viral infections. *PLoS ONE* 9:e109969
- Uddin MS, Millat MS, Baral PK, Ferdous M, Uddin MG, Sarwar MS, Islam MS (2021) The protective role of vitamin C in the management of COVID-19: a review. *J Egypt Public Health Assoc* 96:33
- Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM (2020) SARS-CoV-2: structure, biology, and structure-based therapeutics development. *Front Cell Infect Microbiol*. 10:587269
- Wang H, Ooi EV, Ang PO Jr (2008) Antiviral activities of extracts from Hong Kong seaweeds. *J Zhejiang Univ Sci B* 9:969–976
- Wieczfinska J, Kleniewska P, Pawliczak R (2022) Oxidative stress-related mechanisms in SARS-CoV-2 infections. *Oxid Med Cell Longev* 2022:5589089
- World Bank (2020) World Bank approves \$12 billion for COVID-19 vaccines. <https://www.worldbank.org/en/news/press-release/2020/10/13/world-bank-approves-12-billion-for-covid-19-vaccines>. Accessed on 27 Jan 2022
- World Health Organization (2020). Naming the coronavirus disease (COVID-19) and the virus that causes it. [Accessed on 30th May 2022]
- World Health Organization (2022) Coronavirus disease (COVID 19). https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed 27 Feb 2022
- World Health Organization (WHO). 2020. WHO Director-General's opening remarks at the media briefing on COVID-19 — 11 March 2020. See <https://www.who.int/director-general/speeches/detail/who-director-general-sopening-remarks-at-the-media-briefing-on-covid-19—11-march-2020> (accessed 30 May 2022)
- Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P, Sharma A, Kumar A, Handu S (2021) Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19. *Cells* 10:821
- Yim SK, Kim I, Warren B, Kim J, Jung K, Ku B (2021a) Antiviral activity of two marine carotenoids against SARS-CoV-2 virus entry in silico and in vitro. *Int J Mol Sci* 22(12):6481. <https://doi.org/10.3390/ijms22126481>
- Yim SK, Kim K, Kim IH, Chun SH, Oh TH, Kim JU, Kim JW, Jung WH, Moon HS, Ku BS, Jung KJ (2021b) Inhibition of SARS-CoV-2 virus entry by the crude polysaccharides of seaweeds and abalone viscera in vitro. *Mar Drugs* 19:219
- Yu HH, Chengchuan KE, Chang CL, Yuan KS, Wu ATH, Shan YS, Wu SY (2018) Fucoidan inhibits radiation-induced pneumonitis

and lung fibrosis by reducing inflammatory cytokine expression in lung tissues. *Mar Drugs* 16:392

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579:270–3. <https://doi.org/10.1038/s41586-020-2012-7>

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.