



Multifaceted role of natural sources for COVID-19 pandemic as marine drugs

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Abstract

COVID-19, which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has quickly spread over the world, posing a global health concern. The ongoing epidemic has necessitated the development of novel drugs and potential therapies for patients infected with SARS-CoV-2. Advances in vaccination and medication development, no preventative vaccinations, or viable therapeutics against SARS-CoV-2 infection have been developed to date. As a result, additional research is needed in order to find a long-term solution to this devastating condition. Clinical studies are being conducted to determine the efficacy of bioactive compounds retrieved or synthesized from marine species starting material. The present study focuses on the anti-SARS-CoV-2 potential of marine-derived phytochemicals, which has been investigated utilizing in silico, in vitro, and in vivo models to determine their effectiveness. Marine-derived biologically active substances, such as flavonoids, tannins, alkaloids, terpenoids, peptides, lectins, polysaccharides, and lipids, can affect SARS-CoV-2 during the viral particle's penetration and entry into the cell, replication of the viral nucleic acid, and virion release from the cell; they can also act on the host cellular targets. COVID-19 has been proven to be resistant to several contaminants produced from marine resources. This paper gives an overview and summary of the various marine resources as marine drugs and their potential for treating SARS-CoV-2. We discussed at numerous natural compounds as marine drugs generated from natural sources for treating COVID-19 and controlling the current pandemic scenario.

Keywords SARS-CoV-2 · Marine drugs · Flavonoids · Lipids · Anti-inflammatory · Medicine

Introduction

Viruses are a big source of concern for humans in the current period since they are one of the many infectious threats they confront, creating a huge threat of pandemics over the

world. Rapidly changing global landscapes, local habitats, major population growth, and urbanization in many emerging countries, as well as advancements in transportation infrastructure, have all generated new opportunities for viral infections to start and spread. The novel virus, originally known as the 2019-novel coronavirus, was discovered to be the source of an ongoing pneumonia outbreak in Wuhan,

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China, at the end of 2019. This virus was formally connected with severe acute respiratory syndrome coronaviruses (SARS-CoVs) and designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (Viruses 2020). The respiratory sickness caused by 2019-nCoV was formally called Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) on 11 February 2020, and the disease's worldwide expansion was described as a pandemic by the WHO on 11 March 2020 (WHO 2020). The pandemic's unusual circumstances have compounded the general difficulty of controlling viral infections. Despite advances in vaccination and drug research, many viral diseases including coronavirus infections still lack prophylactic immunizations and efficient antiviral medicines (Islam et al. 2021). In this sense, the quest for novel antiviral compounds is still ongoing. COVID-19 is an infectious respiratory disease caused by SARS-CoV-2, a recently discovered coronavirus strain. By attaching to ACE-2 protein receptors on the surface of host cells, this single-stranded RNA virus can infect the respiratory tract. Spike proteins on the surface of viral particles contain a receptor-binding domain (RBD) that the human ACE-2 receptor recognizes. This one-of-a-kind RBD interacts with a lysine residue on the ACE-2 receptor, making it a potential pharmaceutical target. The virus particles invade the airways and lungs, triggering an inflammatory response in the body and causing damage to the host tissue. End-stage respiratory disease, systemic involvement, and mortality can all result from this. Although COVID-19 vaccinations have proven to be helpful in avoiding illness, control cannot rely solely on vaccines; therapies are also required.

Natural products are still one of the most common sources of antibacterial and antiviral medication prototypes (Adalja and Inglesby 2019; Pahman et al. 2021a) (Karthika et al. 2021b)(Tagde et al. 2021a). Over a thousand unique marine chemicals derived from marine species are undergoing pharmacological testing, with over forty now on the market (Khan et al. 2020a). Marine plants and microorganisms have been the focus of scientific inquiry for many decades, owing to their unique biological features. Over 12,000 natural compounds have been isolated from marine plants and microbes, and this number continues to grow (Anjum et al. 2016, 2017; Hassan et al. 2017; Hassan and Shaikh 2017; Bruno et al. 2019). In the discovery of new prototypes and the development of medicines utilizing natural marine ingredients, possible marine goods are playing a crucial role (Vo and Kim 2010; Wittine et al. 2019). Marine species span more than two-thirds of the earth, making them a significant source of new drug-like chemicals (Rong et al. 2020)(Aneiros and Garateix 2004). COVID-19 has been tested against flavonoids, alkaloids, and peptides, among other biologically active chemical groups (Rahman et al. 2020a)(Hossain et al. 2020). The enormous potential of marine organisms as raw

materials for developing innovative medicinal compounds and therapies has long been recognized in the field of marine pharmacy (Cheung et al. 2015; Malve 2016). Marine creatures have evolved a variety of anti-infective techniques and chemicals to defend themselves against microorganisms and viruses that live in the ocean (Donia and Hamann 2003). For being ecologically safe, having low toxins, and being physiologically compatible, marine resources provide a number of advantages (Bhattacharya et al. 2021b)(Sindhu et al. 2021a) (Sindhu et al. 2021b). Several natural substances derived from marine resources are now being studied for antiviral properties against COVID-19.

The resources marine organisms harbor is limitless and consistently proven efficacious at combating viruses, bacteria, cancers, and other pathogens. Their unique chemical structures and diversity introduce novel mechanisms of action, making them especially valuable against drug-resistant pathogens. Some marine compounds that do share similar mechanisms of action with other known approved drugs have shown to be more potent. Some marine compounds that do share similar mechanisms of action with other known approved drugs have shown to be more potent. As discussed above, PCBs and sulfated polysaccharides have shown to bind and inhibit RdRp with higher affinity than current standard therapy remdesivir (Abdelmohsen et al. 2014; Gentile et al. 2020; Geahchan et al. 2021). COVID-19 has been found to be protected by natural inorganic polyphosphate (polyP) derived from marine microorganisms and sponges (Sriyanto et al. 2021)(Müller et al. 2020a, 2021; Neufurth et al. 2021). Its ability to bind the spike protein on viral particles and prevent interaction with ACE-2, as well as trigger the destruction of ACE-2 on host cells, has been proven in several investigations. PolyP has also been demonstrated to have antiviral synergistic effects when used with the anti-inflammatory drug dexamethasone or the antioxidant quercetin. Moreover, numerous investigations have revealed that a variety of marine metabolites isolated from scleractinia-related animals, sponges, and algae can interact with SARS-major CoV-2's protease, M^{pro} (El-Hossary et al. 2017, 2020; Liu et al. 2019). M^{pro} is a virus-specific protein enzyme that plays a key role in viral particle replication and transcription, making it a potential therapeutic target (Zahran et al. 2020). Phycocyanobilin, for example, was discovered to bind to RNA-dependent RNA polymerase (RdRp) with similar or higher potency than remdesivir, making them an attractive alternative to standard therapy (Khan et al. 2020a; Pendyala and Patras 2020; Kwon et al. 2020).

Compounds derived from marine creatures that inhibit deoxyribonucleic acid (DNA) and ribonucleic acid(RNA) viruses, including coronaviruses, have been discovered in polysaccharides, terpenoids, steroids, alkaloids, peptides, and other structural classes (Donia and Hamann 2003; Pyrc et al. 2006; Ziłkowska et al.

2006; Barde et al. 2015; Stonik 2016; Zaporozhets et al. 2020; Gentile et al. 2020). The diverse mechanisms used by each of these chemical classes to suppress coronaviruses account for their diversity. A growing body of data demonstrates the therapeutic potential of marine-derived compounds in the discovery of new COVID-19 templates/prototypes (Yi et al. 2020). Anti-COVID-19 medicines may target SARS-CoV-2 viruses directly or host cell proteins. SARS-genome CoV-2's contain spike glycoproteins (S), matrix glycoproteins (M), nucleocapsid proteins (N), and tiny envelope proteins (E). The anti-SARS-CoV-2 medication also targets MPro and 3CLpro, which are involved in coronavirus transcription, replication, and maturation (Nyamnjoh 2020)(Tagde et al. 2021d)(Karthika et al. 2021b)(Akter et al. 2021b).

The aim of this study is to look into the possibilities of employing biologically active compounds produced from diverse chemical classes of marine organisms to cure illnesses caused by coronaviruses at various stages of the virus's life cycle. New pharmacological compounds of marine origin have been discovered in bacteria, algae, invertebrates (sponges, ophiurans, echinoderms, mollusks, soft corals, bryozoans, and tunicates), and other species. Finally, marine natural bioactive products as marine drugs could be employed as a possible SARS-CoV-2 inhibitor for better COVID-19 management. We reviewed several natural compounds as marine drugs derived from natural source for the treatment of COVID-19 as well as to control the pandemic situation at the present world. This review focuses on marine bioactive chemicals, their sources, and antiviral modes of action, with a focus on COVID-19 treatment. However, the process of marine drug development is faced with many challenges. Firstly, although the sea harbors countless organisms, accessibility to majority of these resources is limited (Montaser and Luesch 2011a). Although potential compounds are accessible close to shore, there remain other regions of the ocean that likely possess unknown organisms and, thus, new therapies. Furthermore, to continue the development of promising compounds through pre-clinical and clinical trials, there must be a continuous supply of the compounds. This presents a challenge as large-scale production may harm the marine ecosystem (Montaser and Luesch 2011a). Fortunately, rapid technological advancements in synthetic chemistry and biotechnology provide a potential solution to this problem. In addition, many potential antiviral metabolites have only been tested in vitro or visualized through molecular docking assays. More in vivo studies are needed to further investigate potential adverse effects and drug delivery requirements. Despite the challenges faced, it is clear that marine organisms serve as a promising avenue for future pharmacological intervention (Awan 2013; Khan et al. 2016; Sriyanto et al. 2021; Geahchan

et al. 2021). Table 1 shows the findings of a study on the anti-CoV effects of biologically active chemicals from marine species, as well as possible modes of action.

Coronavirus disease (COVID-19)

Coronaviruses (Latin: *Coronaviridae*) are RNA viruses that are separated into two subfamilies: *Coronavirinae* and *Torovirinae* (Boiko et al. 2022) (Payne 2017). There are four genera in the *Coronavirinae* subfamily, alpha, beta, gamma, and delta coronaviruses. HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 are human coronaviruses (Fehr and Perlman) (Tagde et al. 2021c). The coronavirus genome is wrapped in an envelope and enveloped in a spiral capsid made up of genomic RNA connected to a nucleoprotein (N). The membrane protein (M) and envelope protein (E) are essential for virus assembly, whereas the spike protein (S) promotes virus entry into host cells, and the viral envelope is made up of three structural proteins. A huge ectodomain, a transmembrane anchor, and a tiny intracellular tail make up the coronavirus spike. The receptor-binding component S1 and the membrane-fusion subunit S2 make up the ectodomain (Payne 2017).

Virology and pathogenesis of SARS-CoV-2

SARS-CoV-2 has an unusually extended survival time in the environment, lasting at least 24 days in feces and on dry surfaces at room temperature (Chen et al. 2020a). It is a positive-sense ssRNA virus with a 30 kb envelope that codes for structural, nonstructural, and accessory proteins [Table 2] (Wang et al. 2020a). Spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins are structural proteins [Fig. 2]. During viral entry, the surface S-glycoprotein facilitates proper connections between the virus and the host receptor. S-recombinant proteins receptor-binding domain (RBD) interacts with ACE2 protein specifically, mediating host cell invasion and initiating pathogenesis (Rabenau et al. 2004). SARS-CoV-2 has a 10 to 20 times higher binding efficacy, leading to increased transmissibility and contagiousness. The other three structural proteins help the virus put together. Nonstructural proteins involved in the viral life cycle include 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), helicase, and RNA-dependent RNA polymerase (RdRp) [Table 3]. The virus creates ss-positive RNA, which the host cell's translation machinery then converts into polyproteins (Khailany et al. 2020).

Table 1 Anti-CoV effects of biologically active compounds from marine organisms and their possible mechanisms

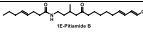
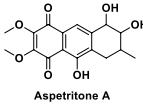
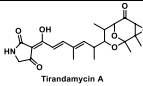
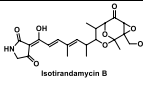
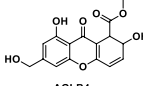
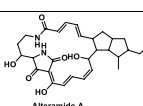
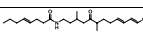
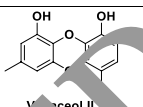
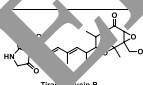
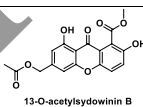
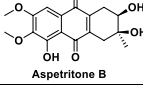
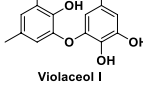
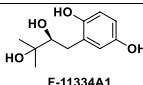
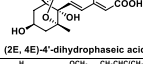
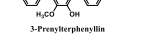
Source	Compound	Mechanism	References
Marine sponge <i>Aplysinidae</i>	Fistularin-3/11-epi-fistularin-3 (C ₃₁ H ₃₀ Br ₆ N ₄ O ₁₁)	Binding with SARS-COV-2Mpro, E _{score2} = -7.8	(Rodrigues Felix et al. 2017; Khan et al. 2020b)
Marine sponge <i>Aplysinidae</i>	15-methyl-9(Z)-hexadecenoic acid (C ₁₉ H ₄₀ O ₃) (PubChem CID 21,646,261)	Binding with SARS-COV-2Mpro, E _{score2} = -7.5	(Rodrigues Felix et al. 2017; Khan et al. 2020b)
Soft coral <i>Pterogorgia citrina</i>	(Hexadecyloxy) propane, 1,2-diol (C ₁₆ H ₃₀ O ₂) (PubChem CID 45,638)	Binding with SARS-COV-2Mpro, E _{score2} = -7.54	(Rodrigues Felix et al. 2017; Khan et al. 2020b)
Brown algae <i>Sargassumspiniuligerum</i>	Heptafuhalol A Phlorethopentafuhalol A Pseudopentafuhalol B Pseudopentafuhalol C Hydroxypentafuhalol A	Binding with SARS-COV-2Mpro, ΔGB = -15.4 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -14 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -14.6 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -14.5 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -14.6 kcal/mol	(Gentile et al. 2020)
Marine sponge <i>Petrosiastrongylophora</i> sp.	15-α-ethoxypuupehenol (C ₂₁ H ₂₆ O ₃) (PubChem CID 460,087)	Binding with SARS-COV-2Mpro, E _{score2} = -7.6	(Rodrigues Felix et al. 2017; Khan et al. 2020b)
Brown algae <i>Sargassumspiniuligerum</i>	Apigenin-7-O-neohesperidoside Luteolin-7-rutinoside Resinoside	Binding with SARS-COV-2Mpro, ΔGB = -12.3 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -12.1 kcal/mol Binding with SARS-COV-2Mpro, ΔGB = -12.2 kcal/mol	(Gentile et al. 2020)
Brown algae <i>Ecklonia cava</i>	Dieckol (6,6'-bieckol)	Binding with SARS-COV-2Mpro, ΔGB = -12.0 kcal/mol	(Gentile et al. 2020)
Axinella polypoides cultivated from <i>Streptomyces axinellae</i>	Tetromycin B	Inhibits cathepsin L, IC ₅₀ = 32.50 μM	(Ahlquist 2006)
Marine sponge <i>Plakortishalichondroides</i>	Plakortide E (C ₂₁ H ₃₄ O)	Inhibits SARS PLpro, 68% inhibition at 100 μg/mL Inhibits cathepsins B, 90% inhibition at 100 μg/mL Inhibits cathepsins L, 85% inhibition at 100 μg/mL Inhibits SARSMpro, 30% inhibition at 100 μg/mL	(Oli et al. 2014)
Marine sponge <i>Theonella cf. mirabilis</i>	Tokaramide A	Inhibits cathepsin B, IC ₅₀ = 29.0 ng/mL	(Fusetani et al. 1999)
Marine sponge <i>Theonella winhoei</i>	Miraziridine A	Inhibits cathepsin L, 60% inhibition at 100 μg/mL	(Tabares et al. 2012)
Marine sponge <i>Axinella cf. corrugata</i>	Esculetin-4-carboxylic acid ethyl ester (C ₂₄ H ₂₀ O ₁₂ Na)	Inhibits SARS-COV-23CLpro, ID ₅₀ = 46 mmol/L	(Lira et al. 2007)
Soft coral <i>Formosa gorgonian</i> <i>Erigeron</i>	Excavatolide	Binds with TMPRSS2, ΔGB = -14.38	(Rahman et al. 2020d)
Green alga <i>Dictyosphaeriaver-sluyii</i>	Decalactone 4-dictyosphaeric acid A	Binds with TMPRSS2, ΔGB = -14.02	(Rahman et al. 2020d)

Initial physiological immune response

The integrated immunological response of early cytokines releases and antiviral activation subsequent by immune-cell infiltration should result in

effective SARS-CoV-2 elimination from the pulmonary in most COVID-19 patients (Fig. 1). Yet, it has been widely documented that viral infection may proceed to serious disease as a result of a down-regulation immunological response (Bohn et al. 2020).

Table 2 SARS-CoV-2-fighting bioactive compounds generated from coral halobionts

Compound name	Structure	Source (microorganism)	Chemical category	Biological activity	References
1E-Pitamide B		<i>Phormidium corallicum</i>	Fatty acid amide	Antiproliferative	(W et al. 2016)
Asperritone A	 Asperritone A	<i>Aspergillus tritici</i> SP2-8-1	Anthraquinone derivative	Cytotoxic antibacterial	(W et al. 2017)
Tirandamycin A	 Tirandamycin A	<i>Streptomyces</i> sp	Tirandamycin derivative	Antibacterial	(Z et al. 2019)
Isotirandamycin B	 Isotirandamycin B	<i>Streptomyces</i> sp	Tirandamycin analog.	Bacteriostatic	(Z et al. 2019)
AGI-B4	 AGI-B4	<i>Scopulariopsis</i> sp.	Xanthone	Anticancer	(Elnaggar et al. 2016)
Alteramide A	 Alteramide A	<i>Pseudoalteromonas</i> sp	Tetracyclic alkaloid	Cytotoxic and antifungal	(Shigemori et al. 2002; WJ et al. 2014)
Pitamide A		<i>Phormidium corallicum</i>	Fatty acid amide	Antiproliferative	(W et al. 2016)
Violaceol II	 Violaceol II	<i>Scopulariopsis</i> sp.	Phenyl ether derivative	Cytotoxic and antioxidant	(Elnaggar et al. 2016; S et al. 2017)
Tirandamycin B	 Tirandamycin B	<i>Streptomyces</i> sp	Tirandamycin derivative	Antibacterial	(Z et al. 2019)
13-O-acetyltydowinin B	 13-O-acetyltydowinin B	<i>Scopulariopsis</i> sp	Xanthone. Stylophora sp.	Antioxidant	(Elnaggar et al. 2016; S et al. 2017)
Asperritone B	 Asperritone B	<i>Aspergillus tritici</i> SP2-8-1	Anthraquinone derivative	Cytotoxic antibacterial	(W et al. 2017)
Violaceol I	 Violaceol I	<i>Scopulariopsis</i> sp.	Phenyl ether derivative	Cytotoxic and antioxidant	(Elnaggar et al. 2016; S et al. 2017)
F-11334A1	 F-11334A1	<i>Gliomastix</i> sp.	Hydroquinone derivative	Cytotoxic antitubercular	(Chen et al. 2020b)
(2E, 4E)-4'-Dihydrophaseic acid	 (2E, 4E)-4'-dihydrophaseic acid	<i>Scopulariopsis</i> sp.	Sesquiterpene	Not mentioned	(Song et al. 2020)
3-Prenylterphenyllin	 3-Prenylterphenyllin	<i>Aspergillus tritici</i> SP2-8-1	Terphenyllin derivative G	Cytotoxic antibacterial	(Wang et al. 2017a)

Prominent symptoms of COVID-19

SARS-CoV-2 causes multiple organ failure by attacking the respiratory system, gastrointestinal system, central nervous system, kidney, heart, and liver (Zhu et al. 2020). COVID-19 symptoms vary, ranging from moderate symptoms to

severe sickness. Headache, loss of smell (anosmia) and taste (ageusia), nasal congestion and runny nose, cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties are some of the most common symptoms. People with the same virus may experience a variety of symptoms, which may change over time. A respiratory symptom cluster with

Table 3 Marine compounds for potential SARS-CoV-2 treatment

Marine compound	Source	Mechanism	References
Lambda carrageenan	Marine algae	By inhibiting viral replication, it lowers viral protein expression	
Terphenyllin Tirandamycin A	<i>Scleractinia</i> -associated organisms	Form hydrogen bonds and dock with Mpro	(Zahran et al. 2020)
Phlorotannins (17 molecules)	<i>Sargassum spinuligerum</i> brown algae	Inhibit SARS-CoV-2 Mpro through hydrogen bonding and hydrophobic interactions	(Gurung et al. 2020)
Five marine compounds ($C_{19}H_{40}O_3$, $C_{16}H_{30}O_2$, $C_{22}H_{32}O_4$, $C_{21}H_{26}O_3$, $C_{31}H_{50}Br_6N_4O_{11}$)	Aplysiidae sponge, soft coral <i>Pterogorgia</i> <i>citrina</i> , <i>Petrosia stronglyphora</i> sp.	Inhibit Mpro through hydrogen bonding and hydrophobic interactions	(Khan et al. 2020)
Phycocyanobilins (PCB)	Cyanobacteria, algae rhodophytes	- Interact with RBD of spike protein through Van der Waal interactions and hydrogen bonding - Inhibits Mpro and RNA-dependent RNA polymerase	(Pradyala et al. 2020)
Sulfated polysaccharides	Cyanobacteria, brown algae (<i>Saccharina japonica</i>)	Binds spike protein and inhibits viral entry	(Nagle et al. 2020; Song et al. 2020; Bhatt et al. 2020; Kwon et al. 2020)
Bromotyrosines	Marine sponges	- Inhibits protein synthesis, replication, and propagation of HIV-1 - Binds spike protein and prevents viral entry into cells	(Binnewerg et al. 2020; Muzychka et al. 2021)

cough, sputum, shortness of breath, and fever, a musculo-skeletal symptom cluster with muscle and joint pain, headache, and exhaustion; and a digestive symptom cluster with abdominal discomfort, vomiting, and diarrhea have all been discovered (Wang et al. 2020a; Kluytmans et al. 2020; Den Bergh et al. 2020; Sami et al. 2021).

Life cycle of coronavirus and targets for the development of antiviral agents

The S1 subunit of spike protein has an RBD that interacts with angiotensin-converting enzyme 2 (ACE2), which is expressed on the endothelial surface in the respiratory and gastrointestinal systems (Zhou et al. 2020; Hoffmann et al. 2020). This starts the SARS-life CoV-2 cycle. The virus enters the host cell through the direct fusion of the host cell and viral membranes, as well as endocytosis via the spike protein's S2 subunit (Hoffmann et al. 2020b; Bestle et al. 2020). The spike protein is made as an inactive precursor, which is then cleaved by cellular proteases, causing conformational changes in the S2 subunit, allowing it to become functional and ready for membrane fusion (Chakraborty and Bhattacharjya 2020). Once the spike protein-ACE2 complex forms, TMPRSS2 breaks the spike protein in close proximity to ACE2, causing membrane fusion with the host cell and

viral genome release (Bestle et al. 2020). Trypsin, plasmin, and factor Xa are some of the other proteases involved in this process. Another mechanism for the virus to reach the host cell is by endocytosis. Endo-lysosomes' furin and cathepsin B/L (CatB/L) appear to be involved in endosomes spike protein activation (Hoffmann et al. 2020b; Bestle et al. 2020). When the viral envelope unites with the host cell membrane, the viral RNA can be released. Infected cells' cytoplasmic genomic viral RNA can be translated into two polyproteins, pp1a and pp1ab, which are then degraded into 16 mature nonstructural proteins (NSPs) by two viral proteases, 3C-like protease (3CLpro), and papain-like protease (PLpro) (Coutard et al. 2020; Wu et al. 2020; Zhou et al. 2020; Hoffmann et al. 2020a). NSP12, also known as RNA-dependent RNA polymerase (RdRp), is responsible for viral genome replication and transcription (DMVs) (Wang et al. 2020c). DMVs carry viral RNA products, which are delivered to the cytosol across the double membrane by a molecular pore complex (Wang et al. 2020c). The endoplasmic reticulum (ER) then translates structural proteins like spike protein (S), envelope protein (E), and membrane protein (M), which are then transferred to the Golgi apparatus for virion assembly. In the cytoplasm, the viral genomic RNA and structural protein N are biosynthesized and integrated into the nucleocapsid, which is subsequently linked to the viral structural proteins to generate new virions. The mechanism by which virions

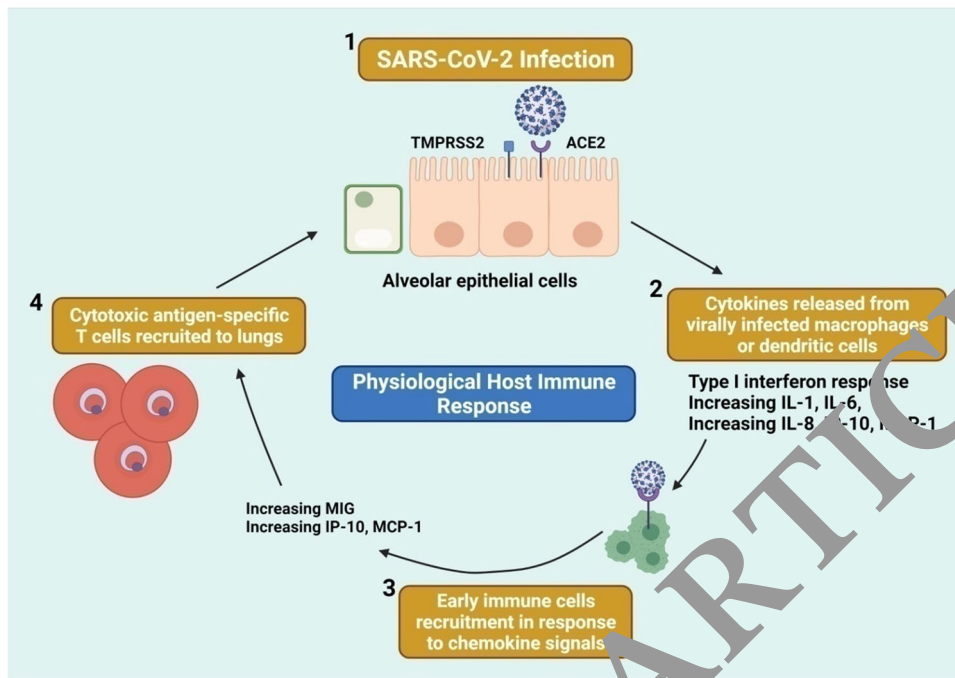


Fig. 1 Infection with SARS-CoV-2 causes a physiological immunological response in the host. 1: The surface spike (S) protein of SARS-CoV-2 assaults alveolar epithelial cells by interacting to angiotensin-converting enzyme 2 (ACE2) that is administered by the trans-membrane serine protease 2. (TMPRSS2). 2: Migration of macrophages and dendritic cells in the lungs as a result of chemokine and cytokines release (early phase). 3: It has been shown that direct viral infection of pulmonary macrophages and dendritic cells results in the production of a large number of pro-inflammatory cytokines and chemokines. 4: Dendritic cells in the lungs phagocytose virus, migrate to secondary lymphoid organs, and activate antigen-specific T lymphocytes, which subsequently go to the lungs and destroy latently infected alveoli cells (Bohn et al. 2020)

are expelled from an infected cell is known as exocytosis (Buratta et al. 2020). As a result, therapies to avoid one or more events in the SARS-life CoV-2 cycle are being developed. The discovery of drugs that target proteins involved in the viral life cycle is a possibility.

Virus entry into the host cell

The essential targets in therapeutic development are receptor binding and membrane fusion, which are early and crucial events in the coronavirus infection cycle (Fehr and Perlman, 2015). Penetration is normally initiated by nonspecific interactions between the virus and cell surface attachment factors, followed by the engagement of more specialized cellular receptors. Unspecific contact raises viral particle concentrations in the environment, which leads to higher infection rates. Attachment and penetration inhibitors bind to virus receptor molecules on the surface of susceptible cells, bind to certain proteins directly in the virion, and bind to an intermediate, “activated” version of viral protein to prevent additional structural changes (Lundin et al. 2014). Attachment and penetration inhibitors can be intelligently used

in antiviral drugs, especially those used in prophylactic situations because the ability to enter the membrane isn't always required; these substances may minimize the likelihood of virus replication from the start and so be less dangerous. Such properties are unquestionably necessary for effective drug transport across mucosal membranes (Zhou and Simmons 2014). The main advantage of utilizing penetration inhibitors for emerging viruses is that they block a large portion of the virus's material from entering the host cell, which is necessary for many of these pathogens to infect (Pyrce et al. 2006).

Inhibitors of the unspecific interaction of the virus to attachment factors on the cell surface

Lectins Non-immunoglobulin carbohydrate-binding proteins are known as lectins. They can recognize and attach to complex glycoconjugates moieties in a reversible way without affecting the covalent structure of any of the glycosyl ligands identified. Algae, fungi, marine corals, higher plants, prokaryotes, invertebrates, and vertebrates are all examples of species that include lectins. They are involved in carbohydrate recognition and binding, host–pathogen interactions, cell targeting, cell–cell communication, apoptosis activation,

cancer metastasis, and differentiation, among other biological processes. Because of the capacity to prevent virus self-assembly during replication, mannose-binding lectins (which belong to the C-type pattern recognition lectins) are a major priority for antiviral research. Given the significant degree of commonality in the presence of high mannose glycans in envelope glycoproteins across encapsulated viruses, a method based on carbohydrate-binding lectins can be applied to many of them. For example, researchers discovered that 15 of a range of plant powder lectins comprising mannose, N-acetyl glucosamine, glucose, galactose, and N-acetyl-galactosamine have anti-SARS-CoV action (Keyaerts et al. 2007; Kim 2021; Reynolds et al. 2021; Havlik et al. 2021; Jackson et al. 2021; Nguyen et al. 2021; Rauf et al. 2021; Barre et al. 2022; Lloyd et al. 2022; Spillings et al. 2022).

Glycosaminoglycan mimetics It has been shown that many microorganism employ glycosaminoglycans (GAGs), which are long sulfated polysaccharides that are expressed mostly on cell surface as well as in the extracellular matrix for cellular interaction and adherence as well as invasion and immunologic evasion (Mycroft-West et al. 2018). In order to attach to host cells, SARS-CoV and other coronaviruses utilize their GAGs (Kim et al. 2020). Cell surface glycoproteins interact with GAG mimic heparinoid polysaccharides to generate a protective barrier and prevent viral binding. In the study by Kim et al., heparin sulfate comes in contact with the GAG-binding motif in the trimeric SARS-CoV-2 spike glycoprotein at the S1/S2 location on each monomer interface and at a different location when the receptor-binding domain is open (453–459 YRIERKS).

In the marine environment, GAGs and sulfated glycans that resemble GAGs but have structurally distinct structures are common (Mycroft-West et al. 2018). Fucans from brown algae (Phaeophyta) that have been sulfated (ascophyllan, fucoidan, glucuronoxylucan, and sargassum), red algae (Rhodophyta) produce sulfated galactan (agar and carrageenan), and sulfated heteropoly saccharides derived from ulvan containing substances (agar and carrageenan) are among their analogs (Damonte et al. 2012). For the treatment of viral infections such as the human immunodeficiency virus (HIV) and herpes simplex and cytomegalovirus (HCMV), sulfated seaweed polysaccharides have been shown to have antiviral properties (Damonte et al. 2012). Fucoidans (branches of sulfated polysaccharides with a high molecular mass Research Projects Incorporated RPI-27 and RPI-28) from the marine alga *Saccharina japonica* may bind significantly to the S-protein SARS-CoV-2 in vitro using Vero-CCL81 cells that express both ACE2 and TMPRSS24, according to a study by Kwon et al. (2020) (Kwon et al. 2020). Even at the highest concentrations, none of the polysaccharides were hazardous (Kwon et al. 2020).

Inhibitors of viral lipid-dependent attachment to host cells

Because lipids are engaged in crucial phases in the virus's life cycle and can act as direct receptors or cofactors of virus entrance on the cell surface and in endosomes, they are vital in viral infection (Chazal and Gerlier 2003). They can also operate as direct receptors or cofactors of virus entrance on the cell surface and in endosomes, and they are engaged in crucial phases in the virus's life cycle. Viruses that utilize microdomains of cell membranes termed lipid rafts (membrane rafts) for some stages of their reproductive cycle rely on cellular lipid membranes as a crucial first point of interaction. Several viruses have been shown to utilize membrane rafts to aid this function (Chan et al. 2010).

Sterols Molecules that alter lipids can be used to selectively restrict viral replication. Natural substances like cyclodextrin and sterols, as well as sphingolipids (Lorizate and Kräusslich 2011), can inhibit the infectivity of many types of viruses, including the coronavirus family, by interfering with lipid-dependent attachment to human host cells. Cyclodextrins are cyclic oligosaccharides made up of a macrocyclic ring of glucose subunits connected by 1,4-glycosidic bonds that disrupt the lipid composition of the host's cell membrane, minimizing the virus's attachment to protein receptors, whereas phytosterols are cholesterol mimics that can bind to the virus instead of membrane rafts, reducing the virus's attachment to protein receptors (Fernández-Oliva et al. 2019). Sterols with important biological activity, including antiviral, have been found in algae, Porifera, Coelenterata, bryozoa, mollusks, Echinodermata, Arthropoda, Tunicata, and chordate (Stonik 2001). Porifera (sponges) have a significant position. Gauvin, for example, discovered that 5,8-epidioxy sterols isolated from the marine sponge *Luffariella variabilis* suppressed HTLV-1 (Gauvin et al. 2011). McKee investigated 22 sulfated sterols produced from marine sponges for antiviral efficacy against human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2) (McKee et al. 2002). Sulfate groups at positions 2, 3, and 6 were found among the most active sterols.

Binding to specific receptors and fusion of cytoplasmic and viral membranes

Proteolytic enzymes cleave the protease, resulting in infection surface constructions necessary for successful infection and subsequent entry into the cell after confinement to receptors, ensuring the combination of the infection's layers and the cell. Compounds that particularly interact with the S protein, as well as biological components, notably various proteases, that are essential for this process and can stop the

virus from entering the cell. As a result, antiviral specialists may target host cell surface proteins, which can act as infection sensors, and host proteases.

ACE2 inhibitors

Since ACE2 has been identified as the principal receptor of SARS-CoV-2 viruses in humans, researchers have focused on figuring out how to regulate it as a way to treat the virus. The main function of ACE2 as part of the renin-angiotensin system is to convert angiotensin II, a powerful vasoconstrictor, to angiotensin (structural forms I, III, IV, V, VI, and VII), a vasodilator that contributes to blood pressure maintenance and reduction by counter-regulating ACE. Despite the fact that it is an analog of ACE, its similarity is only about 42% (Huang et al. 2010). The use of ACE inhibitors (ACEIn) in the chronic treatment of hypertension and diabetes is a problem with ACE2 and coronavirus infections (Barbosa-Filho et al. 2006). These medications are also known to upregulate the expression of ACE2, putting the patient in the COVID-19 risk category (Zhang et al. 2020). In fact, the majority of COVID-19 diagnosed patients with severe or fatal infection had comorbidities, particularly hypertension or diabetes (Zhang et al. 2020; Wang et al. 2020b). Meanwhile, common ACEIns included in hypertension medications such as perindopril, enalapril, and losartan have little effect on ACE2 (Barbosa-Filho et al. 2006; Huang et al. 2010). The limited ability of ACEIn to cleave angiotensin I is thought to be the cause of ACE2 overexpression. As the concentration of angiotensin I rises as a result of ACE inhibition, ACE2 mRNA increases to compensate (Rice et al. 2004).

ACE inhibitory action has been found in some natural compounds that are widely utilized in ethnobotanics and, in some cases, are firmly rooted in the human diet (Barbosa-Filho et al. 2006; Daskaya-Dikmen et al. 2017). Bio-products, such as ACE inhibitors, are widely used, owing to the fact that synthetic compounds, such as enalapril, were created utilizing a natural metabolite as a scaffold. This illustrates their viability as new medicine sources; they have fewer side effects than synthetic pharmaceuticals, and natural extracts can have lower IC₅₀ values in some circumstances (Daskaya-Dikmen et al. 2017).

Peptides Outside of human cells, peptides that replicate ACE2 could be effective for containing COVID, and they offer a few advantages over tiny molecules (higher confidence) and antibodies (lower cost) (little size). Arrangements in the beneficial gaps in the COVID S-circle yielded intense inhibitors of COVID illness, which are short peptides (AK et al. 2006). Researchers are drawn to marine peptides because of their vast spectrum of healing movement, slow natural articulation in biological tissues, and affinity for targets among the taxa that have produced

these peptides are Porifera, Cnidaria, Nemertina, Crustacea, Mollusca, Echinodermata, and Craniata. The foundation for the creation of putative COVID-19 inhibitors can be using oligopeptides produced by gastrointestinal stimuli bound to the SARS-CoV-2 pine protease, in silico hydrolysis of 20 marine fish proteins was performed. Antibacterial combinations are produced by nearly every marine microorganism as the first line of defense in order to live, which has recently aroused scientists' curiosity as a possible source of peptides.

TMPRSS2 inhibitors

Surprisingly, a substantial body of research suggests that suppressing TMPRSS2 articulation or potential action is a relatively safe and successful strategy for treating viral contaminations produced by diseases like MERS-CoV, SARS-CoV, and SARS-CoV-2 are three different strains of the same virus that use TMPRSS2 for cell implantation. These analyses revealed that the destructive proclivity of the recently mentioned disorders is dependent on TMPRSS2 serine protease development. When the degree of activity of TMPRSS2 is reduced in these viral diseases, the speed of implantation, replication, dissipation, and assistant replication of the contaminations all fall significantly. Since SARS-CoV-2 is additionally one of the infections that utilize TMPRSS2 for implantation, it is proposed that inactivating TMPRSS2 with clinically proven TMPRSS2 inhibitors can be added to COVID-19 treatment.

Flavonoids, terpenes, and peptides Biologically active substances of marine origin, such as flavonoids, phlorotannins, alkaloids, terpenoids, peptides, lectins, polysaccharides, lipids, and others substances, can affect coronaviruses at the stages of penetration and entry of the viral particle into the cell, replication of the viral nucleic acid, and release of the virion from the cell; they also can act on the host's cellular targets. These natural compounds could be a vital resource in the fight against coronaviruses (Zaporozhets and Besednova 2020; Silva Antonio et al. 2020; Muhseen et al. 2020). TMPRSS2 proteases are used by SARS-CoV-2 to infect cells effectively drive the S peptide into the disease and cell film mix. Flavonoids, terpenes, peptides, and coumarins are some of the recognized frequent TMPRSS2 inhibitors. Marine life forms could also be a source of TMPRSS2 inhibitors. Terpenoids' fundamental variety allows for a wide spectrum of natural exercises; the amount of isoprene units in hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, and triterpenes makes them attractive as possible medications. Terpenoids are a kind of compound found in plants with no doubt the most often found natural chemicals in today's oceans.

Some terpenoids chemicals are inside the beginning phases of development, either in preclinical or clinical trials (Gross and König 2006). These findings reveal that peptides and proteins from the sea can assure the effectiveness of mixes designed to inhibit viral invasion, impede mixing, and destroy viral particles, as well as terpenoids and other marine components (Savant et al. 2021; Tomas et al. 2021).

Virion deproteinization

The virus's internal structures reach the cytoplasm of infected cells after cytoplasmic and viral membranes have the ability to absorb and fusion, where they undergo partial deproteinization and release of the internal nucleoprotein (Walls et al. 2019). Surface-bound proteases like TMPRSS2 deproteinize the proteins (Walls et al. 2019) and cysteine proteases in endosomes (cathepsin). Extracellular proteases when the virus departs the cell and proprotein convertases in the generating cells. As a result, the viral genome's polymerase (transcriptase) complex is used to set up transcription and replication conditions; 3CLpro, commonly known as major protease, is a chymotrypsin-like cysteine protease and is one of four proteins that aren't structural are found in CoV of SARS proteins (Mpro). In the viral life cycle, important enzymes include PL2pro, helicase, and RNA-dependent RNA polymerase, which are all papain-like proteases. The large precursor proteins PL2pro and 3CLpro after being cleaved, mature as active proteins and they play a role in the breakdown of coronavirus polypeptides that are massive. The most frequent viral protease is 3CLpro significant since it is the better of the two released. Important viral replicative proteins include RNA polymerase and helicase proteins.

3CLpro inhibitors

Due to its critical function in SARS-CoV replication, 3CLpro is being investigated as a potential target for antiviral medicines. In the last 5 years, a collection of inhibitors has been created based on the crystal structure of 3CLpro, and there are a variety of 3CLpro inhibitors available, including peptide mimics and small molecule compounds, which have been described. The HIV protease inhibitors lopinavir and ritonavir inhibit 3CLpro. In CoV in silico investigations, the compounds colistin, valrubicin, icanitabant, bepotastine, eprubicin, epoprostenol, vapreotide, aprepitant, caspofungin, and perphenazine all bind to the lopinavir/ritonavir binding site. Several research groups have identified 3CLpro as a possible candidate COVID-19 is a therapeutic target in the fight against it. Consider a worldwide group of scientists who looked into almost 10,000 pharmaceutical molecules that were currently in use or in clinical trials, as well as

a variety of other pharmacologically active chemicals and found six potential COVID-19 viral inhibitors. According to structural studies of the inhibitory enzyme found in various coronaviruses that binds to the substrate-binding cavity between domains I and II are effective against all coronaviruses. Recent reviews have looked at natural plant-derived 3CLpro inhibitors. Antiviral activity of biologically active compounds present in marine animals has been demonstrated in the fight against RNAviruses.

Phlorotannins

Polyphenolic compounds known as phlorotannins are formed up of polymerized phloroglucinol molecules (Rahman et al. 2021b). As a component that aids in fibrinolysis, *Ecklonia kurome* was found to have phlorotannin, which is a well-known example of pharmaceutical use of a known chemical. It has been examined in a number of bioassays for antibacterial, antioxidant, anticancer, antihypertensive, antidiabetic, anti-allergic, and radioprotective effects since its discovery in 1985 (Domínguez 2013). Antibacterial and antiviral properties of polyphenolic compounds found in plants from both the sea and the land are being studied (Imbs and Zvyagintseva 2018). Phlorotannins, a unique polyphenolic component discovered in brown algae, are a type of polyphenolic chemical (Imbs and Zvyagintseva 2018). The phloroglucinol monomeric unit is the basis for these chemicals. Phlorotannin's are a kind of phlorotannin that have a diverse set of biological functions, antibacterial, antioxidant, anti-inflammatory, anticancer, antidiabetic, radioprotective, antiadipogenic, antiviral, and anti-allergic characteristics. They are thought to be potential prospects for pharmacological development (Imbs and Zvyagintseva 2018). Pharmacophore consensus was utilized by Gentile and his colleagues (2020) with a high throughput modeling and molecular docking to perform a simulated screening of 14,064 chemicals; there are 164,952 conformers in the collection of marine natural products, and 17 potential SARS-CoV-2 3CLpro inhibitors have been identified. According to the results of molecular docking, the docking energy of these molecules ranged from 4.6 to 10.7 kcal/mol. Brown algae-derived phlorotannins were discovered to be the most efficient inhibitors of SARS-CoV-2 Mpro. *Sargassum spinuligerum* is a *Sargassum* species. Phlorotannins are abundant in other types of brown algae (Li et al. 2011). These are the areas where Mpro inhibitors can be found; Park et al. (2013) investigated the biological activity of *Ecklonia cava*, an edible brown alga, yielded nine phlorotannins. With the exception of phloroglucinol, all nine phlorotannins (1–9) identified inhibited SARS-CoV3CLpro dose-dependently and in a competitive manner. Dieckol with A diphenyl ether connects two eckol groups had the most significant SARS-CoV3CLpro trans/cis-cleavage inhibitory effects. Dieckol

and 6,6'-bieckol, two isolated phlorotannins from *Ecklonia cava*, a kind of brown algae that is edible, were revealed to be Mpro inhibitors. The marine compounds Mpro's active site and residues came into contact around it to produce multiple interactions between hydrogen and hydrophobic molecules. Initially alkaloids, lipids, terpenoids, and phenol are some of the chemicals present in plants that Felix et al. (2017) discovered and connected.

Lipids Marine creatures create phytoplankton, macroalgae, marine invertebrates, and sponges, to name a few, are all rich in lipids (phytoplankton, macroalgae, marine invertebrates, and sponges are all examples of marine bacteria and cyanobacteria). Saturated, monounsaturated, and diunsaturated acids; halogenated, hydroxylated, methoxylated, and non-methylene-interrupted acids; phospholipids; and glycolipids, as well as branched, halogenated, hydroxylated, methoxylated, and non-methylene-interrupted acids, are found. Two of the most polyunsaturated fatty acids that are essential are eicosapentaenoic and docosahexaenoic acids, respectively. Lipid metabolism is a critical component in viral replication that viruses take over and amplify to meet the growing demand for viral structural characteristics like the viral cell membrane because of their extensive direct or indirect biological activity involved in a variety of lipid physiological processes have gotten a lot of attention. Lipids play a role in intercellular and immunochemical activities, as well as influencing the permeability of cells and the activity of a variety of enzymes; some lipids also serve as protein regulators or signaling molecules. Previously obtained marine lipids from *Aplysiidae* sea sponges and soft corals have been found to have antimicrobial properties, according to new research (*Pterogorgia citrina*).

Terpenoids, lactone With SARS-CoV-2 Mpro, terpenoids have a better binding ability. Terpenolide is the predominant biologically active ingredient in this plant, and it has a variety of pharmacological qualities, including antioxidant, anti-inflammatory, analgesic, antibacterial, anti-migraine, and anticancer effects (CJ et al. 2005). Reverse transcriptase and protease inhibition are two antiviral methods. Up until now, protease inhibitors, notably inhibitors of human clinical trials for the treatment of coronaviruses, and HIV-1 protease was accessible. In this way, the search for natural bioactive chemicals substances derived from bio-resources with inhibitory characteristics the activity of HIV-1 protease is very important. New diterpenes identified in *Dictyota pfaffii* include protease inhibitors, a brown alga from Brazil (Mominur Rahman et al. 2021; Bhattacharya et al. 2022). Puupehedione, a terpene compound originally identified in the marine sponge *Petrosiastronglyophora*, also showed a positive interaction with the virus Mpro. After screening crude extracts and pure compounds isolated from the sea

sponge *Axinella cf. corrugata*, De Lira et al. (2007) discovered that two coumarin derivatives, esculetin-4-carboxylic acid methyl ester and esculetin-4-carboxylic acid ethyl ester, inhibit SARS-CoV3CLpro in vitro and SARS-CoV replication in Vero cells.

Alkaloids Among the most common types of second-generation metabolites detected in sponges from the sea are alkaloids. They have a diverse set of biological functions of characteristics, antiviral action, for example, and occur in a variety of heterocyclic ring derivatives (Simpf and Majik 2016). A kind of marine alkaloid metabolite identified in *Batzella* is PGAs (polycyclic guanidine alkaloids), *Crambe*, *Monanchora*, *Clathria*, *Prilocalis*, and certain starfish-like *Celerina heffernan* and *Frostmannolis*, which are all Poecilosclerida sponges (El Demerdash et al. 2018). After being found in *Aplysiidae* sponges from the sea, fistularin-3/11-epifistularin-3 was determined to have a strong connection with SARS-CoV-2 Mpro.

Flavonoids Flavonoids are a type of phytomedicine that may be used to treat a variety of ailments that is used frequently (Kasman et al. 2020b) (Fatima et al. 2021). According to an in silico analysis, the flavonoid-rich dietary components flavone, equivir, hesperetin, and myricetin bind with remarkable affinity with the ACE2 receptor's spike protein, helicase, and protease sites. COVID-19 was created by the coronavirus that causes severe acute respiratory syndrome (Kabir et al. 2021a). Flavonoids have been demonstrated to help prevent and treat a number of ailments, including viruses. Flavonoids are a form of antioxidant polyphenol, a secondary plant source component, and have also been discovered to be a viable source of 3CLpro inhibitors. Flavonoids inhibit enzymes such as phosphatases, protein phosphokinases, hydrolases, oxidoreductase, DNA synthases, RNA polymerases, phosphatases, and oxygenases. Flavonoids have the capacity to influence many components of intracellular signaling cascades, such as tyrosine kinase, mitogen-activated protein kinase (MAP kinase), and protein kinase C cascades, which are critical for their numerous actions in cells (Bhattacharya et al. 2021a)(Karthika et al. 2021a). As a consequence of the growing interest in their potential biological and pharmacological activities, flavonoids from the sea have been intensively researched in recent decades. Regardless of this, most marine flavonoids are hydroxylated and methoxylated have a unique pattern of substitution that isn't found on the ground species, including sulfate, chlorine, and amino groups which are all present. Although the bulk flavonoids are found in sea grasses and halophytes, they can also be found in mangroves, algae, mollusks, fungus, corals, and bacteria of other marine life. Antiviral action has been demonstrated in flavonoids from the sea, including those that block viral enzymes.

According to a study, flavonoids from the brown alga *Sargassum spinuligerum* bind to SARS-CoV-2 Mpro, including apigenin-7-O-neohesperidoside, luteolin-7-rutinoside, and resinoside.

Marine bioactive compounds for SARS-CoV-2

Scleractinia, an order of *Anthozoa*, is found only in the marine environment. This is the most biodiversity and active order, made up of stony corals. They can be solitary, but in colonial form, they support enormous populations of helpful microbes; the “coral halobiont” is an assembly of host coral and its extraordinary symbiotic interaction with unicellular creatures known as zooxanthellae and an assortment of microorganisms. Bacteria, fungi, and unicellular endosymbionts, such as zooxanthellae, are small photosynthetic dinoflagellate algae from the genus *Symbiodinium* that invade and then live inside coral tissue (Shah et al. 2020) (Table 2).

Zahran et al. (Zahran et al. 2020) created a small library of 15 marine-derived chemicals obtained from *Scleractinia*-associated organisms that have the potential to inhibit SARS-CoV-2. The absorption, distribution, metabolism, and excretion (ADME) analysis was used to analyze the physicochemical characteristics of the compounds that were later identified as possible inhibitors of COVID-19 targets after molecular docking investigations on naturally occurring compounds from the marine-based products library (Zahran et al. 2020). Docking was performed on five SARS-CoV-2 target sites. A major viral protease is the main target site (PDB ID 6LU7). Nsp16, a nonstructural protein (PDB ID 6W4H), is a critical protein because it forms a complex with another protein, nsp10, which results in methylation at the 2'-O site of viral RNA ribonucleotides. The virus is effectively hidden from the host immune system as a result of this change (Lin et al. 2020).

Role of marine natural products in COVID-19

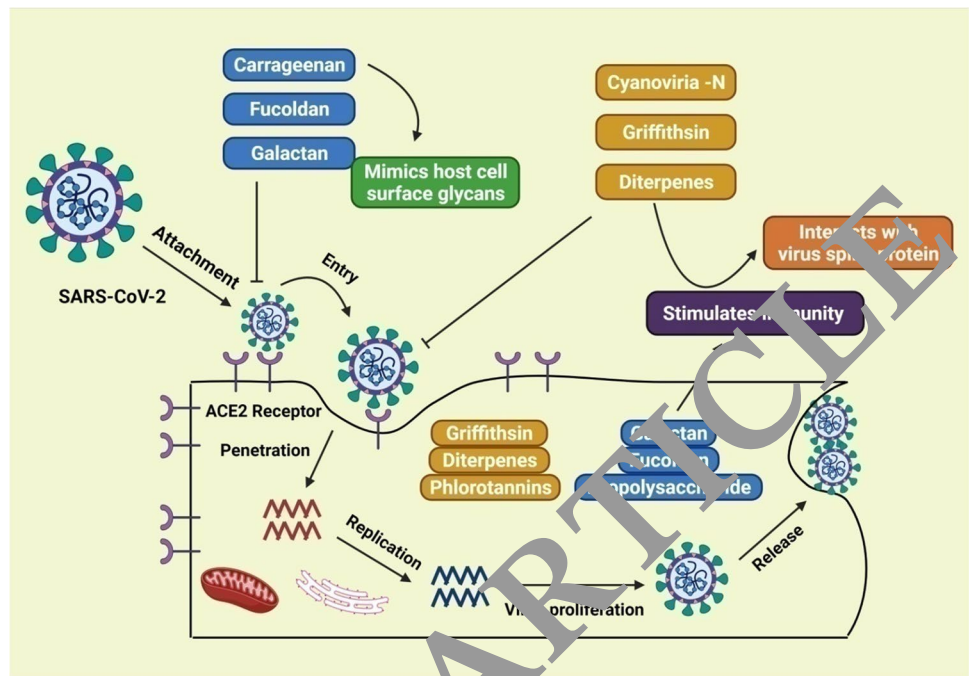
Vitamin E, B12, phycocyanin, lutein, and polysaccharides are among the bioactive compounds found in marine algae (Herrera-Calderon et al. 2020). Lambda carrageenan, in particular, is a polysaccharide isolated from marine red algae (Table 3) that has antiviral, antibacterial, anti-cancerous, and anti-coagulant properties. Both influenza virus and SARS-CoV-2 have been demonstrated to be effectively inhibited by it. A study found that the marine polysaccharide reduced viral protein expression and suppressed viral replication in a dose-dependent manner (Akter et al. 2021a). The presence of spike viral

proteins on SARS-CoV-2 and influenza A viral proteins decreased dramatically as the lambda-carrageenan dose was increased from 0 to 300 g/mL (Zahran et al. 2020). Influenza virus inhibition and SARS-CoV-2 inhibition had EC₅₀ values of 0.3–1.4 g/mL and 0.9–1.1 g/mL, respectively. At doses up to 300 g/mL, no-host cell toxicity was found. Mice challenged with the SARS-CoV-2 virus and then administered lambda-carrageenan had a 100% survival rate, indicating that the polysaccharide reduced viral entry and reproduction. These studies demonstrate lambda-antiviral carrageenan capabilities, making it a suitable marine resource for COVID-19 treatment (Fig. 2).

Although these findings are encouraging, it is crucial to note that lambda-carrageenan may have negative side effects. Previous research has found that oligosaccharides derived from the carrageenan family (kappa and lambda-carrageenan) can hinder the creation of new blood vessels, impairing blood vessel development. They were also reported to impede migration, proliferation, and tube formation of human umbilical vein endothelial cells at 200 g/mL. These findings suggest that there may be hazardous effects in humans; however, more in vitro and in vivo toxicology research is required. These data must be taken into account in the development of lambda-carrageenan as a SARS-CoV-2 inhibitor.

Sea species' medicinal potential is also seen in *Scleractinia*-associated organisms like bacteria and fungi (EM et al. 2017; URs et al. 2017; Shady et al. 2017; El-Hossary et al. 2020; Zahran et al. 2020). These organisms have been linked to inflammation and viral infection because they produce a variety of metabolites (Shady et al. 2017; El-Hossary et al. 2020; Zahran et al. 2020). *Scleractinia*-related metabolites were examined, and molecular docking was used to identify potential antiviral actions of SARS-CoV-2. Two specific microbial metabolites (Terphenyllin and Tirandamycin A) have been discovered to establish hydrogen bonds with the major protease (Mpro) and dock with great affinity (Zahran et al. 2020). These marine metabolites are regarded to be good leads for inhibiting the virus's primary protease, which is crucial to the virus's life cycle. In a similar investigation, seventeen putative Mpro inhibitors were discovered in the class phlorotannins isolated from *Sargassum spinuligerum* brown algae. The compounds connected with Mpro through substantial hydrogen bonding as well as hydrophobic interactions, with docking energies ranging from 14.6 to 10.7 kcal/mol. RNA replication and viral protein synthesis are also dependent on the SARS-CoV-2 RNA polymerase and nsp7/8. Remdesivir is a well-known inhibitor of the RNA-dependent RNA polymerase, and three *Scleractinia* metabolites have been identified to bind the polymerase in the same spot as remdesivir. This finding shows that

Fig. 2 Illustration of anti-SARS-CoV-2 drug candidates produced from marine microorganisms and their likely mechanism of action for possessing a high degree of drug-likeness for prevention and treatment of COVID-19 (Singh et al. 2021)



these marine metabolites could be useful in the treatment of COVID-19 by inhibiting viral replication.

Furthermore, a study using molecular docking studies on Mpro discovered that a number of marine chemicals have potential binding interactions (Khan et al. 2020b). Mpro was discovered to interact with five marine compounds isolated from sea sponges of the *Aplysiniidae* family and *Pterosia stronglyophora* sp., as well as the soft coral *Pterogorgia citrina*, via hydrogen and hydrophobic interactions (Khan et al. 2020b). Based on their ADME qualities, they have the potential to be used as a SARS-CoV-2 therapy (Khan et al. 2020b). One marine chemical (C1, from the *Aplysiniidae* family) was discovered to be the greatest fit for the Mpro pocket, with an affinity for all areas of Mpro and significantly stronger hydrogen and hydrophobic interactions (Khan et al. 2020b). This discovery sheds light on the compounds' spatial placement within the binding pocket, which is also characterized by hydrophobic and electrostatic interactions.

Phycocyanobilins (PCBs) are pigment chemicals found in various cyanobacteria and *Rhodophyta* algae (Nagle et al. 2020; Pendyala and Patras 2020). They've been demonstrated to have antioxidant and antiviral effects, making them suitable COVID-19 treatment candidates. Mpro and RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 are effective inhibitors of Mpro and RdRp, according to a study (Pendyala and Patras 2020). In silico screening revealed that PCBs had a higher binding affinity to RdRp than the currently available medicine remdesivir, indicating that these compounds may have anti-SARS-CoV-2 actions (Pendyala and Patras 2020). Another study indicated that PCB, along

with other phycobilin chemicals produced by *Arthrospira*, had to promise antiviral effects against SARS-CoV-2 in an in silico study. The researchers discovered that PCB interacted with the virus's spike protein's RBD via Van der Waal interactions and hydrogen bonding. PCB was discovered to have competitive binding energy of 7.2 kcal/mol, indicating that it could be used as an antiviral agent. Phycobilin compounds from *Arthrospira* were shown to exhibit minimal to no cytotoxicity in cells and to be effective at modest dosages (1–10 g/mL) in the investigation. Low mutagenicity, carcinogenicity, and nephrotoxicity have been documented for PCBs. These findings show that PCBs have potent antiviral properties and could be useful in the fight against SARS-CoV-2.

Marine organisms provide an endless supply of resources. Many compounds found in cyanobacteria, such as sulfated polysaccharides, have been shown to have antiviral effects (Chahal et al. 2021)(Nagle et al. 2020)(Akter et al. 2020), antiviral activity of sulfated polysaccharides against herpes simplex virus (HSV), hepatitis B virus, and retroviruses (Nagle et al. 2020; Kwon et al. 2020). They have been demonstrated to play a significant role in virus protection due to their anionic properties and molecular weight, both of which can have antiviral effects (Andrew and Jayaraman 2021). Polysaccharides are thought to have a lot of potential against SARS-CoV-2 because of their antiviral properties (Nagle et al. 2020; Song et al. 2020; Kwon et al. 2020). Fucoidan, a kind of sulfated polysaccharide from *Saccharina japonica*, was found to have antiviral activity against SARS-CoV-2 in a study (Kwon et al. 2020). The marine molecule was found to be more powerful than remdesivir in the trial, indicating that it could be a viable COVID-19 treatment drug (Kwon

et al. 2020). Similarly, at doses ranging from 3.9 to 500 g/mL, a study found that fucoidan from brown algae, cucumber sulfated polysaccharide, and carrageenan from red algae all have antiviral activities (Song et al. 2020). Because of its ability to bind the spike protein and block viral entrance into cells, cucumber sulfated polysaccharide was found to have the strongest inhibitory effects (Song et al. 2020). Fortunately, no cytotoxicity was reported at concentrations up to 500 g/mL, as evidenced by no significant changes in cell viability (Song et al. 2020). These findings show that sulfated polysaccharides have the potential to treat SARS-CoV-2 effectively.

Potential antiviral application of marine polysaccharide in combating COVID-19

Polysaccharides are macromolecular molecules found mostly in plants, algae, and sometimes mammals (Lee et al. 2017) (Rahman et al. 2020c) (Sharma et al. 2021) (Tagde et al. 2021b) (Chopra et al. 2021). Polysaccharide antiviral properties are determined not only by charge density and chain length but also by their precise structural features (Ghosh et al. 2009). The novel SARS-CoV-2 virus is highly lethal and poses a serious danger to human and animal health, necessitating the development of effective inhibitors (Honda-Okubo et al. 2015). Wide application possibilities exist for polysaccharides with excellent immunological control, safety, and antiviral activity, particularly in anti-coronavirus applications (Chen et al. 2021b). Coronaviruses may be significantly inhibited when carbohydrate-binding agents are present (van der Meer et al. 2007).

Many marine animals and other deepwater species have polysaccharides. According to what has already been said, chitosan is a polysaccharide repeating glucosamine and N-acetylglucosamine with a positive linear charge (Yen et al. 2009; Wang et al. 2013a), obtained from shrimp and crab shells or the cell walls of mushrooms (Kurita 2006; Salaberria et al. 2012). A number of polysaccharides, including carrageenan, fucoidan, and alginate, are found in marine algal products used in traditional Chinese herbal treatment dating back many centuries (Dutot et al. 2019). In carrageenan, the sulfated linear polysaccharides consist of repeated disaccharide units that alternately include 3- and 4-linked-D-galactopyranose or 3,6-anhydro-galactopyranose (AnGal units) (Coviello et al. 2007; Jiao et al. 2011; Necas and Bartosikova 2013), which are extracted from certain red algae containing 15–40% ester sulfate with an average molecular weight above 100 kDa (Robal et al. 2017; Sedayu et al. 2019). Iota- (ι , G4S-DA2S), kappa- (κ , G4S-DA), and lambda- (λ , G2S-D2S, 6S) carrageenan are the three commercially significant and extensively distributed carrageenan (Campo et al.

2009). It has been found that brown algae produce a polymer called fucoidan, which is an L-fucose-enriched and sulfated polymer (Wu et al. 2016a; Dutot et al. 2019). This polymer contains sulfate groups as well as minor amounts of other sugars and acids found in brown algae. These sugars and acids are found in small amounts in the various brown algae sources (Ale et al. 2011; Vishchuk et al. 2012; Wu et al. 2016a). Alginate is a highly acidic and linear polysaccharide derived from brown algae. It is composed of alternating β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues (Ikeda et al. 2000). Polyguluronate sulfate (PGS) is a sulfated brown algal polysaccharide with a low molecular weight that is formed by chemical sulfation of polyguluronate (PG) with about 1.5 sulfates per sugar residue (Zhao et al. 2007; Wu et al. 2016b).

Research on coronavirus is aided by marine polysaccharides such as carrageenan, PGS, chitosan, and its derivatives that have excellent inhibitory action against different viruses. Human rhinovirus (HRV), influenza A H1N1, and HCoV-OC43 are extremely active against iota-carrageenan-containing lozenges throughout the whole dissolving process and are a potential treatment for viral infections of the throat (Morokutti-Kurz et al. 2017). HCoV229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are all significantly inhibited by the cationically modified chitosan, N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC), and the hydrophobically modified derivative (HM-HTCC) is a potent inhibitor of the coronavirus HCoV-NL63 (Milewska et al. 2016). The common cold is caused mostly by respiratory viruses such as rhinoviruses, coronaviruses, and influenza viruses (Monto et al. 2001; Ludwig et al. 2013; Koenighofer et al. 2014). Iota-carrageenan nasal spray has been proven in clinical studies to shorten the duration of a viral common cold. Antiviral efficacy of carrageenan nasal spray has been shown against HRV, human coronavirus, and influenza A virus, with the greatest impact being seen in individuals infected with the human coronavirus. Carrageenan-treated coronavirus-infected individuals had shorter illness duration ($p < 0.01$) and fewer relapses ($p < 0.01$) than those of control patients (Koenighofer et al. 2014).

As a result of the SARS epidemic in 2003, many people who survived the disease acquired more severe cases of persistent pulmonary fibrosis. Epidermal growth factor receptor (EGFR) signaling in animal models is responsible for the development of pulmonary fibrosis, which manifests as an overactive host response to lung damage. Excessive fibrogenic responses to SARS-CoV and other respiratory viral infections may be prevented via EGFR signal inhibition (Venkataraman and Frieman 2017). The expression and activation of the EGFR pathway may be interfered with or inhibited by fucoidan and sulfated rhamnan, which may help suppress coronavirus (Wang et al. 2017b, 2018b).

Marine sponge as source of nucleoside analog inhibitors

Nucleosides are the building blocks of nucleic acid and are composed of nucleobases coupled to a sugar moiety (Seley-Radtke and Yates 2018). Nucleosides have important roles in biological processes such as the synthesis of nucleotides (Seley-Radtke and Yates 2018). Nucleoside analogs were used as a scaffold for the creation and development of nucleotide and nucleoside analog inhibitors (NIs) (Table 4). Nucleoside analogs were used to treat viral infections, particularly coronavirus infections (Pruijssers and Denison 2019). NIs are recognized as RdRp broad-spectrum inhibitors (Shannon et al. 2020). RdRp showed high structural conservation among coronaviruses and was found to have excellent structural conservation among coronaviruses (Aftab et al. 2020), making it an appealing target for the development of diverse antiviral medicines (Table 4). Mycalisine A and B are nucleoside analogs obtained from the marine sponge *Mycale* sp. in 1985 and used as scaffolds for the synthesis of NIs after structural modification by the addition of the CN group (Kato et al. 1985).

Remdesivir, a nucleotide analog containing 1-ribose and CN substitutions, has intriguing antiviral activity by inhibiting both RdRp and exonuclease proteins (Shannon et al. 2020; Zhang et al. 2021). Furthermore, 2-methyl cytosine and EIDD-2801, modified cytidine analogs, were discovered (Zandi et al. 2021) and inhibited SARS-CoV-2 replication (Shannon et al. 2020; Zandi et al. 2021) with no toxicity on Vero cells (Yosief et al. 1998). Furthermore, computer modeling of ilimaquinone (Surti et al. 2020) and its adenosine analog, asmarine B (Kim et al. 2009), revealed potential SARS-CoV-2 inhibitory efficacy (Boz et al. 2010).

Following minimal structural adjustments, the findings showed that compounds generated from marine sponges could be potential RdRp inhibitors. Changes to the sugar moiety and the addition of substituents such as cyano, fluoride, and methyl groups are examples of these alterations. Interestingly, the insertion of the cyano group in the remdesivir side chain increased the drug bioavailability and overcame the viral exonuclease resistance mechanism. Furthermore, the addition of adenosine to ilimaquinone increased its activity 100-fold above the original natural molecule. These findings suggest that, despite the potential effectiveness of the original compounds, alteration in compounds derived from the marine sponge is required for targeted targeting, increased bioavailability and activity, and resistance mechanism overcoming. Importantly, molecules with greater dual action are those that use a nucleotide or nucleoside as a scaffold in addition to sugar, such as avinosol (Diaz-Marrero et al. 2006).

Benefits of marine SPs over other natural compounds

Marine algae are excellent sources of a wide range of bioactive chemicals with a wide range of structural variations. Sulfated polysaccharides (SPs) like fucoidans in brown algae, carrageenan in red algae, and ulvan in green algae are abundant in the cell walls of marine algae. Anticancer, antiviral, antioxidant, cancer-fighting, and immunomodulating capabilities are only a few of the positive biological properties these SPs exhibit (Wijesekara et al. 2011). In addition to sulfated polysaccharide from marine algae, there are many additional natural substances that show promise in the treatment of people with COVID-19. The antiviral bioactivities of medicinal plant essential oils, flavonoids, and phenolic compounds have been described for COVID-19 in various herbal and traditional remedies (Roy and Bhattacharyya 2020). Algae- and plant-based chemicals both have anti-SARS-CoV-2 potential, but each has advantages and disadvantages. More and more scientists are looking at the potential of marine macroalgal blooms as a never-ending supply of biologically active chemicals for the development of novel and effective therapeutics. Compounds derived from algae and plants are both safe, biocompatible, and biodegradable, but since algae-based SPs are more abundant in the ocean, they have a lower manufacturing cost than plant-based natural compounds (Ruocco et al. 2016). Because marine SPs are water-soluble, they can be extracted using an aqueous extraction technique much more readily than plant-based compounds. This makes it useful in pharmaceutical businesses since its physicochemical and mechanical characteristics may be readily changed (Lee et al. 2017). Sulfated polysaccharides in pharmaceuticals haven't been linked to any known health risks, but research is needed to better understand their chemical composition, biological efficacy, bioavailability, toxicity, and other related processes.

Future direction

Oceanic species are a veritable goldmine of antiviral, antibacterial, anticancer, and other pathogen-fighting nutrients. As a result of their diverse chemical structures and distinct modes of action, these compounds are particularly useful against drug-resistant pathogens (Abdelmohsen et al. 2014; Gentile et al. 2020). Furthermore, each marine molecule has several functions that make it useful in a variety of contexts. As an example, several chemicals, such as sulfated polysaccharides, have characteristics that go beyond their ability to fight viruses and bacteria (Udayangani et al. 2020). As a result of their many unique characteristics, marine chemicals are very effective anti-SARS-CoV-2 agents. While synthetic

Table 4 Nucleotide analogs as effective antiviral agents against SARS-CoV-2

NI	Antiviral activity	Mechanism of action	Nucleoside analog	Modified sugar	IC50	References
Remdesivir	<ul style="list-style-type: none"> Antiviral with a broad spectrum of activity against a variety of virus families 	<ul style="list-style-type: none"> Chain terminator • Inhibits replication of SARS-CoV-2 Inhibits RdRp 	Adenosine analog	Cyano-modified sugar	1.0 μ M	(Brown and Pehrson 2019; Karvandi et al. 2020)
Sofosbuvir	<ul style="list-style-type: none"> It has antiviral properties against coronavirus and HIV 	<ul style="list-style-type: none"> Inhibits SARS-CoV2 RdRp enzymatic activity in vitro 	Uridine analog	2'-deoxy-2'- α -fluoro- β -C-methyl modified sugar	> 20 μ M	(Pankiewicz 2000)
Gemcitabine	<ul style="list-style-type: none"> Broad-spectrum antiviral medication SARS-CoV-2 inhibition in cell culture 	<ul style="list-style-type: none"> Inhibits pyrimidine synthesis 	Cytidine analog	The first nucleoside with a geminal difluoro-substituent sugar	1.24 μ m	
6-Azauridine	<ul style="list-style-type: none"> Immunomodulator Antiviral drug 	<ul style="list-style-type: none"> Inhibits pyrimidine de novo synthesis 	Uridine analog	Ribose sugar	0.38 μ g/ml	(Kumar et al. 2020)
Mizoribine	<ul style="list-style-type: none"> Immunomodulator Inhibits nucleotide synthesis 	<ul style="list-style-type: none"> Inhibits inosine and guanine synthesis 	Uridazole analog	D-ribofuranose sugar	(3.5 μ g/ml-16 μ g/ml)	(JP et al. 2016)
NHC	<ul style="list-style-type: none"> Potent antiviral activity 	<ul style="list-style-type: none"> RNA mutagenesis • Inhibits RdRp 	Cytidine analog	Ribose sugar	0.3 μ M	
7-Deaza-7-fluoro-purine derivatives	<ul style="list-style-type: none"> At low concentrations, inhibits SARS-CoV-2 	<ul style="list-style-type: none"> Inhibits SARS-CoV-2 replication 	Purine analog	Methyl ribose sugar	7.6 μ M	
Favipiravir	<ul style="list-style-type: none"> Antiviral activity in vivo against SARS-CoV-2; FPV; influenza A, B, and C viruses; as well as Ebola virus 	<ul style="list-style-type: none"> Inhibits RdRp 	Guanine analog	D-ribofuranosyl sugar	61.9 μ M	
EIDD-2801	<ul style="list-style-type: none"> Potential COVID-19 therapy in a phase II trial Improves pulmonary function by lowering viral load 	<ul style="list-style-type: none"> Inhibits RdRp of SARS-CoV-2 	Cytidine analog	Ribose modified ester	69.5 μ M	
Ribavirin	<ul style="list-style-type: none"> Antiviral activity against RNA viruses on a broad scale Used ribavirin in combination with interferon to treat COVID-19 	<ul style="list-style-type: none"> Inhibition of viral RNA synthesis Triphosphate leads to lethal mutagenesis Inhibit RdRp 	Guanosine analog	D-ribofuranosyl	9.2 μ M	(Jena 2020)
2'-C-Methylcytidine	<ul style="list-style-type: none"> SARS-CoV2 replication was hampered in vivo at sub-micromolar concentrations with no toxicity in Vero cells 	<ul style="list-style-type: none"> Inhibits SARS-CoV-2 replication 	Cytidine analog	Methyl ribose sugar	9.2 μ M	

chemicals usually only have a single useful characteristic, this is preferable to synthetic compounds since they are frequently used in combination treatments, increasing the risk of drug-drug interactions. Marine resources are also very cost-effective, owing to their quantity and variety. The current standard therapy remdesivir costs around \$2600 for a 5-day course of treatment, which makes them worthwhile (Dyer 2020). At effective doses of poly(*p*) (< 10 g/mL), lambda-carrageenan (< 300 g/mL), PCBs (10 g/mL), sulfated polysaccharides (< 500 g/mL), and bromotyrosines (10 μ M), no toxicity on cells was found in addition to this (Drechsel et al. 2020; Song et al. 2020; Müller et al. 2020b; Petit et al. 2021).

Marine drug development, on the other hand, faces numerous obstacles. One thing to note is that even though there are untold numbers of species living in the sea, access to the majority of these resources is extremely limited (Montaser and Luesch 2011b)(Kabir et al. 2021b)(Rahman et al. 2020c). However, despite the fact that many chemicals are readily available along the coast, other parts of the ocean may include undiscovered species and therefore novel treatments (Montaser and Luesch 2011b). Furthermore, a steady supply of promising chemicals is needed to continue preclinical and clinical studies and further develop them. Bigger output means more risk to the marine environment (Montaser and Luesch 2011b; Shinde et al. 2019). Fortunately, synthetic chemistry and biotechnology are advancing at a fast pace, and this may offer a solution (Montaser and Luesch 2011b). It's also worth noting that several putative antiviral metabolites have only been examined *in vitro* or by means of molecular docking studies. More *in vivo* research is required to explore possible side effects and medication delivery needs in greater depth. Marine species, despite the difficulties, seem to provide a bright future for pharmaceutical intervention.

Conclusion

FDA-approved drugs to prevent lethal SARS-CoV-2 infections are currently unavailable, as is a treatment protocol that meets current standards. For COVID-19 patients in the hospital, mechanical ventilation and symptom-suppressing clinical treatment are the primary forms of supportive therapy. This review focuses on the most recent findings in antiviral bioactive metabolite research using marine resources. The chemicals produced by marine creatures and species from the ocean are very useful in the treatment of COVID-19. Polyphosphates has been found to efficiently block the spike protein's RBD and, as a consequence, to reduce its capacity to bind ACE-2 on host cells. With this approach, patients with SARS-CoV-2 may avoid infection. In addition, the chemical shows promise since it may boost the immune

system and protect patients from infection as a result. As an alternative to polyphosphates, several additional compounds have been found to have antiviral properties, including PCBs, sulfated polysaccharides, and bromotyrosines, making them potential candidates for future research into COVID-19 therapies. Marine waters are rich with macro- and microorganisms that store large quantities of metabolites, many of which are yet unknown. As a result, looking into and finding new marine resources may lead to the discovery of viable medicines for treating COVID-19 patients.

To treat severe COVID-19 infection, marine bioactive substances with immunomodulatory properties could be a better choice than chemically manufactured medicines that have been extensively studied. In order to better understand marine bioactive chemicals' chemical structure, biological activity, and mechanism of action, more concentrated research is needed. By utilizing a multiomics method and bioinformatics approaches to discover the relationships between these molecules and the SARS-CoV-2 viral infection, the list of putative bioactive chemicals can be narrowed down considerably. Drug repurposing is also being investigated but has been proved to be ineffective. Additionally, the mutation rate of SARS-CoV-2 has sparked worry, as prior research has indicated that mutations in coronavirus spike proteins may be associated with medication resistance. The advancement of multiomics technologies, investigations on gene mutations, and bioinformatics techniques will all contribute to advancing the selection of suitable COVID-19 medication candidates. Overall, the marine waters are full of micro- and macroorganisms that harbor extensive amounts of metabolites, most of which have not yet been discovered. Thus, investigating and discovering novel resources that come from the sea bring promising potential therapeutics for treating patients with COVID-19.

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