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REVIEW ARTICLE

Exploring the therapeutic potential of marine-derived bioactive compounds against COVID-19

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Abstract

The ocean is the most biodiverse habitat of various organisms. The organisms surviving in the harsh conditions of the ocean consist of several spectacular properties and produce bioactive compounds of pharmacological importance. These compounds are effective even in small quantities with various immunomodulatory qualities such as antioxidant and anti-inflammatory properties. Though the vaccines for COVID-19 are developed, and drug development is also in progress, but till now no effective drug is available for this deadly virus. Researchers are mining the huge data of bioactive compounds to develop the specific drug for COVID-19. The use of the repurposed drugs is challenging against the rapidly mutating virus with variable symptoms and mode of transmission. This review is an attempt to compile all the spattered data of marine-derived bioactive compounds with antiviral properties and to explore their therapeutic potential against COVID-19.

Keywords Bioactive compounds · Marine-derived · COVID-19 · Antiviral · Halobiont · Sponge · The therapeutic potential

Introduction

SARS-CoV-2 emerged as an outbreak in Wuhan, China, and soon it spread to all parts of the world. Contamination is speeded by infected individuals who traveled the country; furthermore, lack of awareness about this new virus which has symptoms similar to common flu also enhances the spread. The spread of COVID-19 was so rapid that it infected nearly 1 million people within 3 months, and 50,000 deaths have been reported. Very soon, the infection rate increased tenfold with 10 million people reported and more than 500,000 deaths. Studies suggest that the transmission by asymptomatic people is the major factor of the high infection rate of COVID-19, and that was estimated up to 40% (http://www.niaid.nih.gov/diseases-conditions/covid-19). Another disturbing fact about this virus is that different mutants of the virus are emerging; the changes in invariants were observed basically in the spike protein of the coronavirus. New variants are spreading quickly leading to new cases with more pace.

This disease has drawn the attention of scientists throughout the world, and various studies have been initiated to understand the virus and how to control its spread and manage the virus. Researchers are investigating approaches to treat SARS-CoV-2 diseases by attempting to produce drugs, therapeutics, and vaccines. Some of the repurposed drugs can stop the entry of the virus to cells, some can slow down the immune response, and some prevent the replication process of the virus. Considering the progressing COVID-19 pandemic brought by it, assigned as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), sources are being made for creating productive treatment alternatives to handle the infection.

The SARS-CoV-2 has been distinguished as an enveloped, single-stranded, positive-sense RNA virus that belongs to the group Betacoronavirus of family Coronovirdae. Other genera of the family are alpha coronavirus, delta coronavirus, and gamma coronavirus) (Behl et al. 2020; Gorblimey et al. 2020, Singh et al. 2021, Woo et al. 2010). It is essentially known to infect the upper respiratory tract and digestive tract (Zhu et al. 2020). Further, this virus consists of different underlying proteins, spike glycoprotein, non-structural proteins

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such as helicase, protease, protease, and RNA-subordinate RNA polymerase, and some extra proteins are also encoded by the SARS-CoV-2 genome. Structure analysis showed that the spike glycoprotein is crown-shaped which leads to the origin of the name "the corona" (derived from the Latin word for crown). While spike protein is present on the exterior surface (membrane) of the virus, viral capsid and single-stranded RNA genome are present inside the virus. The entry of a virus inside the host cell initiates when the glycoprotein present on the surface of the virus binds to the receptor present in the cell. The virus enters the hearts and kidneys by binding with the blood vessels and in the lungs by binding with the epithelial cells and intestine (Xu et al. 2020). This glycoprotein is responsible for the interaction of viruses and receptors, present on the host cell. Since this spike glycoprotein is a basic necessity for the passage of this virus into the host cells, several new investigations are centered around this primary protein. It has been additionally reasoned that the previously stated five proteins also emerged as appealing focuses for antiviral examinations against previous infections, i.e., SARS and MERS (Middle East respiratory syndrome) (Zumla et al. 2016).

The SARS-CoV-2 pandemic created an emergency crisis circumstance that makes it crucial to discover new treatments and activities targeted at diminishing the virus spread followed by infection and discovering new remedial applications for existing and affirmed drugs that permit its fast treatment of new infection. Similarly, given the progressively better information on the viral mechanism in human cells, it is vital to look for new compounds and consolidate treatments that might be useful in the prophylaxis and therapeutics of COVID-19.

Marine-derived bioactive compounds could be a decent choice/alternative against SARS-CoV-2. The utilization of marine organisms to prevent or treat various infections has been done for a long time and is still being done in treating various complex diseases such as cancer, various viral diseases, and malaria. These compounds have the potential of having pharmacological activities such as anti-tumor, antiviral, antioxidant, anti-microbial, and anti-coagulant (Bhatt et al. 2020) (Fig. 1).

Marine-derived antiviral compounds

As the antiviral compounds derived from marine sources have gained attention, the advancement and innovation in techniques used in the marine ecosystem and extraction will facilitate the investigation of the marine bioactive derivatives that have huge applications in pharmacology, and the potential to be developed as a future drug. In the past 30 years, the marine sources and their biological activities are explored well, and a large number of unique compounds and their metabolites have been identified, and some have been utilized as anticancer and antiviral, etc. (Arif et al. 2004) (Table 1).

In the marine ecosystem, many bacteria striving in habitats with extreme pressure and temperature, along with high H_2S and heavy metal concentrations, yield exopolysaccharides as an approach for growth and attachment to solid surfaces and their survival in extreme conditions (Vincent et al. 1994). Marine fungi and their metabolites are perceived for their promising bioactive compounds in the last few years. A portion of these metabolites gives marine fungi the advantage to survive extreme conditions, substrate competence, and avert dangers (Gallo et al. 2004). Since, most of the fungi live in symbiotic association with other marine microbes such as algae, sponges, and other invertebrates (Duarte et al. 2012), fungi metabolites are also affected by the source from where they are being isolated. Various studies revealed the association of marine-derived bioactive compounds with different biological functions such as anticancer, antiviral, anti-plasmodial, and anti-diabetic properties along with other pharmaceutical activities like inhibition of cell cycle, inhibition of kinase and phosphatase, antioxidant, neuritogenic, and anti-inflammatory (Hart 1999; Abdel-Lateff et al. 2003; Daferner et al. 2002; Gautschi et al. 2004; Tziveleka et al. 2003).

The marine corals and sponges are considered an important library of potential future drugs. In the 1950s, nucleosides, spongothymidine, and spongouridine were discovered from the marine sponge *Cryptotethia crypta* (Bergmann and Feeney 1950, 1951); since then, approximately 15,000 marine products were isolated from sponges which later on reported for the discovery of 5300 different other products. The extraction of new compounds is continued which are originated from marine sponges. Because of their huge biodiversity, sponges are considered as "gold mine" (Sipkema et al. 2005) (Fig. 2).

Marine bioactive compounds for SARS-CoV-2

The order *Scleractinia* of class *Anthozoa* is found exclusively in the marine ecosystem. This order comprising stony corals is the most biodiverse and dynamic. They can be solitary, but in the colonial form they harbor vast communities of beneficial microbes; this assemblage of host coral and its remarkable symbiotic relationship with unicellular organisms known as zooxanthellae and an array of microorganisms form the "coral halobiont". Associated organisms can be bacteria, fungi, complemented by unicellular endosymbionts, zooxanthellae, which are microscopic photosynthetic dinoflagellate algae belonging to the genus *Symbiodinium* invading and then residing inside of coral tissue (Table 2).

Zahran et al. (2020) worked on a small library of 15 marine-derived compounds that were isolated from Scleractinia-associated organisms, which have shown the

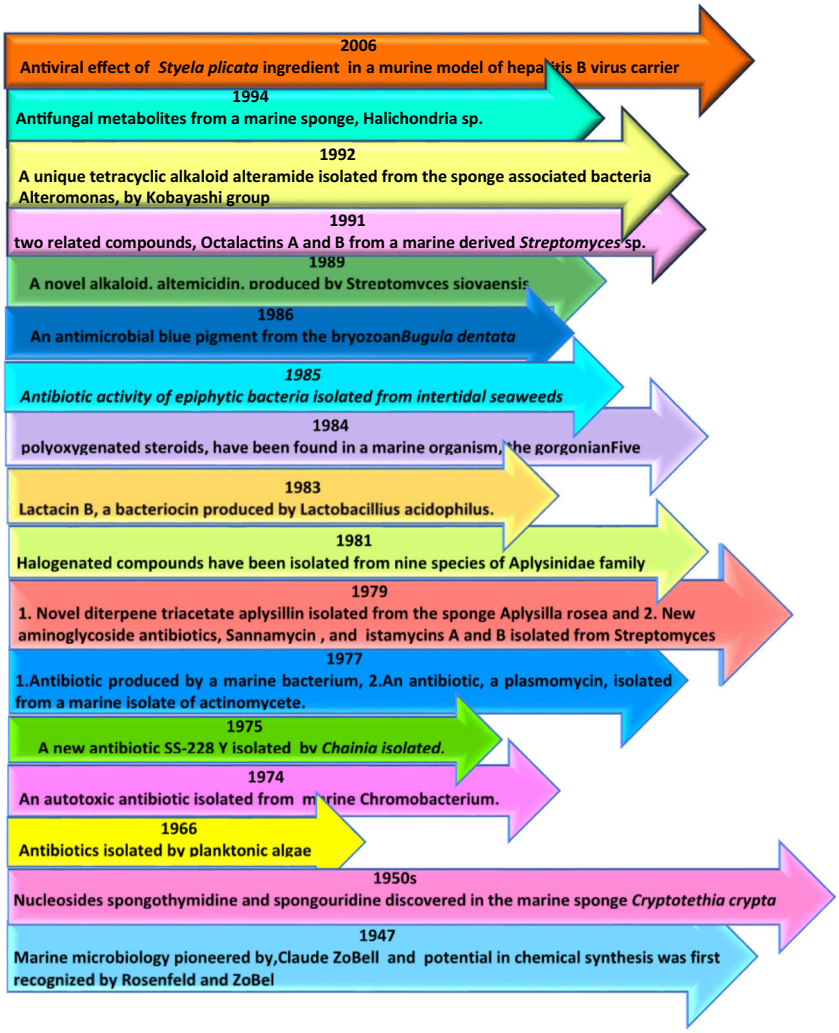

Fig. 1 Certain significant events in the history of marine-derived bioactive compounds

potential of inhibitory actions towards SARS-CoV-2. The selection of naturally occurring compounds from the marine-based products library was based on the ADME analysis to evaluate their physio-chemical properties of the compounds which were later, after molecular docking studies, reported as potential inhibitors of COVID-19 targets (Zahran et al. 2020). Docking was carried out on five target sites of SARS-CoV-2. The first target site is a viral main protease (PDB ID 6LU7). Viral methyltransferase, Nsp16 a nonstructural protein (PDB ID 6W4H), is a crucial protein because it forms a complex with different protein nsp10 which leads to methylation at the 2'-O position of viral RNA ribose. With this modification, the virus successfully conceals itself from the host immune system (Lin et al. 2020).

Viral RNA-dependent RNA polymerase (nsp12) (RdRp) is an enzyme that has a crucial function in replication during the viral replication cycle inside the host by forming a complex with nsp7 and nsp8. This class of enzyme is inhibited by Remdesivir in its triphosphate form (PDB ID 7BV2) (Yin et al. 2020).

Another target site, viral spike protein (PDB ID 6M0J), which binds to the receptors present on host cells, assists the entry of the virus into host machinery, and human ACE2, which is the viral recognition protein (PDB ID 6VW1), but these two sites were not able to give good docking scores with selected compounds. Among the selected compounds, Isotirandamycin B, Tirandamycin B, and Tirandamycin A are found to be potential inhibitors against SARS-CoV-2 methyltransferase nsp16/10 and Alteramide A showed inhibition against RdRp (nsp12) (Delgado et al. 2020).

The potential of a small library of 5 marine bioactive compounds inhibitory action against SARS-CoV2 main protease (M^{PRO}) has been investigated. The data was retrieved for the apo form of M^{pro} from protein data bank (PDB ID 6M03) and marine-derived bioactive compounds from PubChem; the compounds include 2 MNPs from *Petrosia,* a species of sponges, from the family Aplysinidae, and one coral species *Pterogorgia citrina.* The compounds were docked, and those with good docking energy were later on examined by molecular dynamics and simulation studies to check the stability,

Table 1 Antiviral agents are derived from marine organisms

Organism	Species	Compound	Biological activity against viruses	Reference
Sponges	Tethya cripta	Acyclovir	HSV	Elion et al. 1977
Sponges	Tethya cripta	Ara-A (vidarabine)	HSV	Pde Garilhe et al. 1964
Sponges	Tethya cripta	Ara-C (cytarabine)	HSV	Muller et al. 1985
Sponges	Disidea avara	Avarol	HSV	Muller et al. 1987, Horwitz et al. 1964
Sponges	Tethya cripta	Azidothymidine (zidovudine)	HSV, HIV	Horwitz et al. 1964
Bacteria	Bacillus licheiformis	EPS-1	HSV-2	Arena et al. 2006
Bacteria	Geobacillusthermodenitrificans	EPS-2	HSV-2	Arena et al. 2009
Bacteria	Deepsea bacteria	Macrolactin A	HIV, HSV	Gustafson et al. 1989b
Cyanobacteria	Nostoc ellipsosporum	Cyanovirin-N	HIV-1, HIV-2	Boyd et al. 1996
Fungi	Fusarium heterosporum	Equistein	HIV-1	Singh et al. 1998
Fungi	Scytidium sp.	Halovir A-E	HSV-1 and HSV-2 (destabilization of membrane)	Rowley et al. 2003
Fungi	Phoma sp.	Phomasetin	HIV-1 integrase	Singh et al. 1998
Fungi	Fusarium sp.	Sansalvamide A	MCV relaxation of DNA it is binding, and complex formation by topoisomerase	Hwang et al. 1999
Fungi	Stachybotrys sp.	Stachyflin RF-7260	H1N1	Minagawa et al. 2002a, 2002b
Fungi	Aspergillus terreus	Rubrolide S	H1N1	Zhu et al. 2014
Fungi	Penicillium chrysogenum	sorbicatechols A	H1N1	Peng et al. 2014
	Cladosporium sp	Cladosporisteroid B	Anti-H_3N_2	Pang et al. 2018
Fungi	Penicillium sp.	Trypilepyrazinol	HIV and HCV	Li et al. 2019b
Fungi	Penicillium raistrickii	Raistrickindole A and raistrickin	Anti-HCV	Li et al. 2019a
Fungi	Aspergillus versicolor	Quinones (anthraquinones)	anti-HSV-1	Huang et al. 2017
Fungi	Neosartorya udagawae	Neosartoryadins A and B	H1N1	Yu et al. 2015
Fungi	Streptomyces koyangensis SCSIO 5802	Novel Butenolide derivative	Anti-HSV-1	Huang et al. 2019
Fungi	Simplicillium obclavatum	Simplicilliumtide J and Verlamelins A and B	HSV-1	Liang et al. 2017
Fungi	Aspergillus versicolor	Aspergilols H, I and Coccoquinone A	HSV-1	Huang et al. 2017
Fungi	Acremonium persicinum SCSIO 115	Acremonpeptides A and Acremonpeptide D	HSV-1	Luo et al. 2019
Fungi	Penicillium sp. IMB17-046	Trypilepyrazinol	Anti-HIV and HCV	Li et al. 2019b
Fungi	Cladosporium sp	Pregnane	Anti -RSV	Yu et al. 2018
Sponges	Discodermia calyx	Calceramide A-C	Influenza	Nakao et al. 2001
Sponges	Clathria sp..	Clathsterol	HIV-1	Rudi et al. 2001
Sponges	Sidonops microspinosa	Microspinosamide	HIV-1	Rashid et al. 2001
Sponges	Monanchora sp.	Crambescidin	HIV-1	Chang et al. 2003
Sponges	Hamigera tarangaensis	Hamigeran B	Herpes and poliovirus	Wellington et al. 2000
Sponges	Hippiospongia metachromatic	Ilimaquinone	RNase H function of the reverse transcriptase	Loya and Hizi 1993
Sponges	Neamphius huxleyi	Nemphamide A	HIV-1 CPE	Oku et al. 2004
Sponges	Truncatella angustata	Truncateols O and P	Anti -HIV	Zhao et al. 2018

flexibility, and average distance between the compounds and target site for 100 ns root mean square deviation (RMSD), root mean square fluctuation (RMSF) along with the calculation of a distance matrix. Among them, the (11R)-11-epi-Fistularin-3 belonging to the Family Aplysinidae of molecular formula $C_{31}H_{30}Br_6N_4O_{11}$ (PubChem ID 11170714) concluded as a

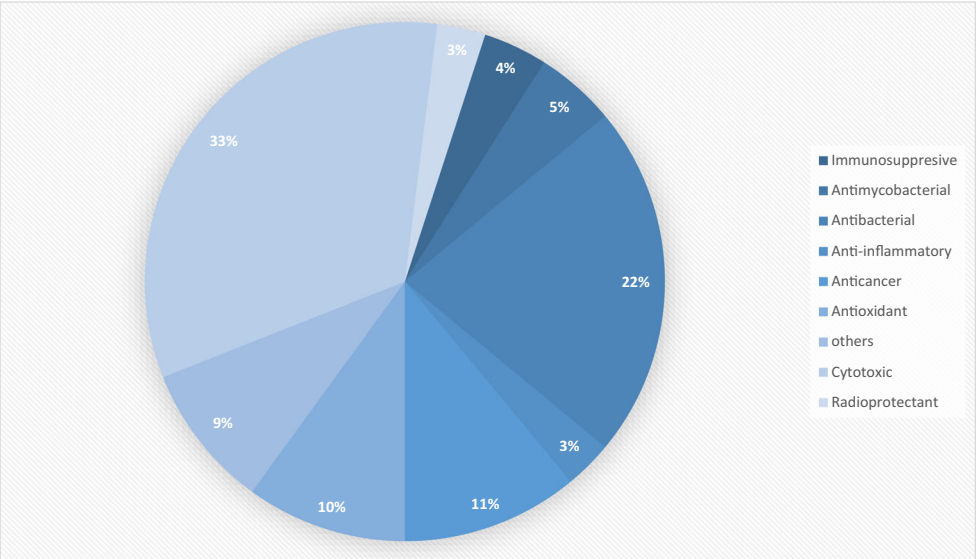

Fig. 2 The spectrum of biological activity of stony coral-associated organisms

promising inhibitor of COVID-19, exhibiting a good docking score and its interaction with active site forming many hydrophobic interactions and hydrogen bonds (Khan et al. 2020).

Further, Gentile et al. (2020) selected 17 inhibitory molecules against SARS-CoV-2 by performing the virtual screening from the MNP library of 14,064 molecules. The docking and molecular dynamics simulation studies were conducted on the potential inhibitory compounds (Gentile et al. 2020). The selected library of marine natural products contains an enormous number of conformers (164,952 conformers) which are generated from the 14,064 molecules, but only 770 conformers meet the criteria of pharmacophore filter, which is a binding-site derived model. Final filtering was done concerning the co-crystallized N3 ligand which has an RMSD value lower than 2 Å which decreases the library to 197 molecules, molecular docking, and molecular dynamics (MD) simulation studies procedure performed on 180 residual molecules.

The compounds belonging to the chemical category phlorotannins, phloroglucinol (1,3,5-trihydroxy benzene), isolated from brown alga *Sargassum* frequently found in the species *Sargassum spinuligerum* found to be more promising inhibitors. The complete process for the isolation of marine microorganisms, characterization of secondary metabolites/biomolecules, screening of biomolecules, and their potential use by in silico approach and in vitro process and further development of a drug is shown in Fig. 3.

SARS-CoV-2 inhibitors from marine macroalgae

Marine macroalgae have been investigated by numerous experts as a superb chance to turn into a boundless medium of biologically functional compounds to provide potential therapeutic drugs (Table 3). Both algae and plant-derived active compounds are biodegradable, biocompatible, and safe, yet the creation cost of sulfated polysaccharides produced from algae is lower than the plant-derived bioactive (Ruocco et al. 2016).

Marine-derived sulfated polysaccharides are water soluble and could be separated without much of a stretch utilizing a watery extraction strategy, unlike plant-based extracts that utilize harmful organic compounds. The physio-chemical and mechanical properties of sulfated polysaccharides can effectively be adjusted, which builds its utilization in drug ventures (Lee et al. 2017). The antiviral activity of polysaccharides is well studied and contemplated as one of the most promising choices for the prevention and control of COVID-19 (Mohammed et al. 2021).

Polysaccharides isolated from marine organisms are the most significant and prevalent biological macromolecules available in diverse structures. Despite being a potential source of natural compounds for drug discovery, they are not being utilized well.

The biological activity of sulfated polysaccharides includes inhibition of the viral replication cycle inside the host cell. The mechanism involves hindering the transcription and translation processes of the virus cycle or adjusting the host cell immune response. Although potential inhibition against COVID-19 is shown by both, green growth-based and plant-based mixtures, the two of them have their advantages and disadvantages.

Sulfated polysaccharides, present in the cell walls of marine microbes, are naturally occurring complex polymers. It includes carrageenan and agar isolated from macroalgae, fucoidan, and laminarian produced by brown macroalgae and ulvan from green macroalgae (Wijesekara et al. 2011).

Table 2 Marine-derived bioactive compounds against SARS-CoV-2 extracted from coral halobiont

Compound name	Biological activity	Chemical category	Source (microorganism)	Reference
Alteramide A	Cytotoxic and antifungal	Tetracyclic alkaloid	Pseudoalteromonas sp	Shigemori et al. 1992, Moree et al. 2014
1E-Pitiamide B	Antiproliferative	Fatty acid amide	Phormidium corallyticum	Cai et al. 2016
Pitiamide A	Antiproliferative	Fatty acid amide	Phormidium corallyticum	Cai et al. 2016
Aspetritone A	Cytotoxic antibacterial	Anthraquinone derivative	Aspergillus tritici SP2-8-1	Wang et al. 2017
Tirandamycin B	Antibacterial	Tirandamycin derivative.	Streptomyces sp	Cong et al. 2019
Tirandamycin A	Antibacterial	Tirandamycin derivative	Streptomyces sp	Cong et al. 2019
Isotirandamycin B	Bacteriostatic	Tirandamycin analog.	Streptomyces sp	Cong et al. 2019
F-11334A1	Cytotoxic antitubercular	Hydroquinone derivative	Gliomastix sp.	Chen, et al. 2020
(2E, 4E)-4′- Dihydrophaseic acid	Not mentioned	Sesquiterpene	Scopulariopsis sp.	Song et al. 2020
Aspetritone B	Cytotoxic antibacterial	Anthraquinone derivative	Aspergillus tritici SP2-8-1	Wang et al. 2017
Violaceol II	Cytotoxic and antioxidant	Phenyl ether derivative	Scopulariopsis sp.	Elnaggar et al. 2016 Liu et al. 2017
Violaceol I	Cytotoxic and antioxidant	Phenyl ether derivative	Scopulariopsis sp.	Elnaggar et al. 2016 Liu et al. 2017
13-O-acetylsydowinin B	Antioxidant	Xanthone. Stylophora sp.	Scopulariopsis sp	Elnaggar et al. 2016 Liu et al. 2017
3-Prenylterphenyllin	Cytotoxic antibacterial	Terphenyllin derivative G	Aspergillus tritici SP2-8-1	Wang et al. 2017
AGI-B4	Cytotoxic	Xanthone	Scopulariopsis sp.	Elnaggar et al. 2016

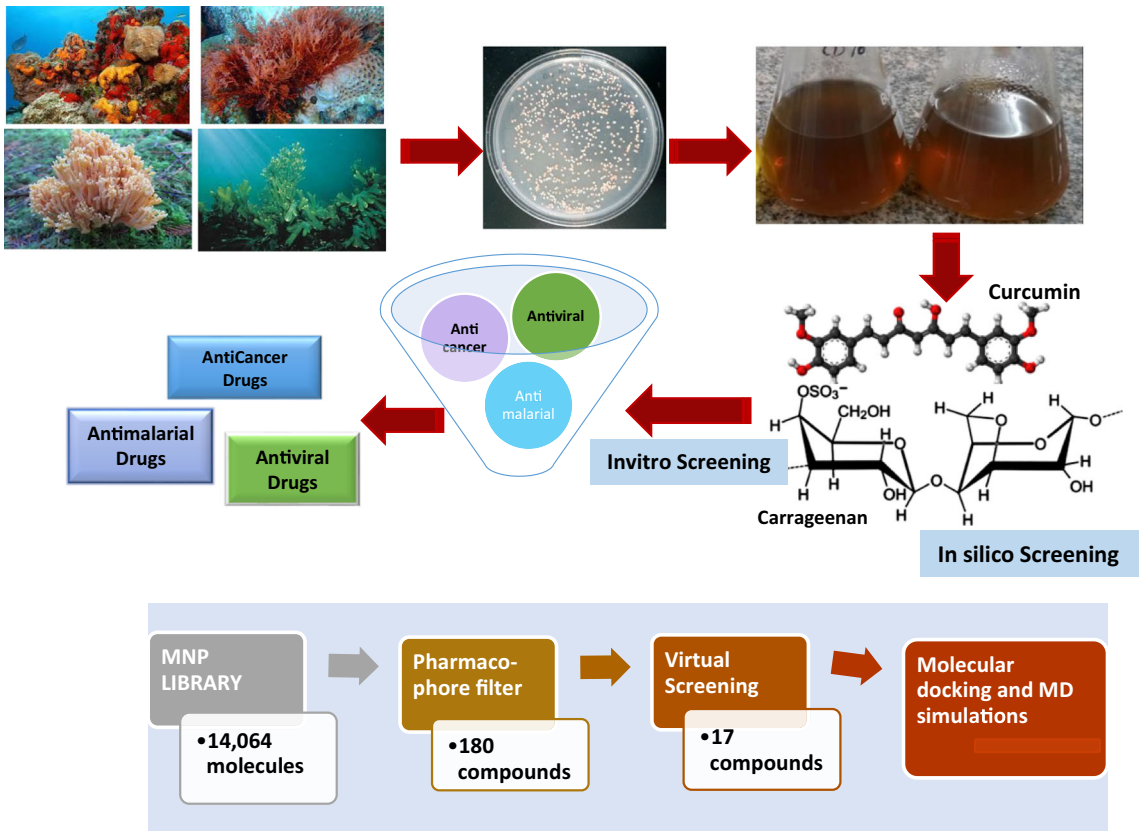

Fig. 3 Schematic representation of the process for isolation of marine microorganisms, characterization of secondary metabolites/biomolecules, screening of biomolecules, and their potential use by in silico approach and in vitro process and further development of drug

Table 3 Marine-derived sulfated polysaccharides having inhibitory properties against SAR-CoV-2

Compound name	Mechanism of action	References
Iota-carrageenan derived nasal spray	In-vitro inhibition of COVID-19	Bansal et al. 2020
Carrageenan-derived nasal spray	2.5% decrease in recurring symptoms	Koenighofer et al. 2014
Carrageenan and fucoidan	Binds with s-glycoprotein of virus	Song et al. 2020
Iota-carrageenan derived lozenges	S-glycoprotein denaturation	Morokutti-Kurz et al. 2017
Iota-carrageenan and fucoidan kappa carrageenan	Prevention of respiratory tract infections	Grassauer et al. 2008
Iota-carrageenan-derived nasal spray	Upper respiratory tract nasal congestion	Graf et al. 2018
Iota-carrageenan	The increased recovery rate from COVID-19 infection by 2.4-fold	Hemilia et al., 2020
Lambda-carrageenan	Prevents viral attachment to receptors of cell surface	Jang et al. 2020
Fucoidan	Binding of sulfated polysaccharides with s-glycoprotein	Kwon et al. 2020

The antiviral property of sulfated polysaccharides and their uses against the SARS-CoV-2 especially as vaccine adjuvants, nanomaterial, and drug delivery applications have been explored. This study proposed the strategy for polysaccharide capped gold particle vaccine loaded with S or N protein, for the therapeutic of SARS-CoV-2 (Chen et al. 2020).

Wang et al., in 2012, suggested that sulfated polysaccharides deter the various stages of the infection cycle of SARS-CoV-2 and can provide future drugs against SARS-CoV-2 (Wang et al. 2012). Sulfated polysaccharides were previously reported to prevent infection against other notorious diseases. The sulfated polysaccharides of seaweeds antagonistic nature towards the herpes simplex virus (HSV) (Gomaa and Elshoubaky 2016). Their antiviral activity against HIV-1 (Besednova et al. 2019) and inhibitory action against the chikungunya virus was also demonstrated (Cirne-Santos et al. 2019). Inspired by various researches, the mechanism of action of marine-derived biomolecules against COVID-19 is depicted in Fig. 4.

Sulfated galactans, the major polysaccharide of red algae, consists of linear polymers, and the chain consists of alternating units with 3-linked β-D-galactopyranose and 4-linked α-D-galactopyranose. In the sulfated galactan, two major instances were found: carrageenans, which consist of a 4-linked α-galactose fraction with dextro-rotatory (D-) arrangement. Whereas agarans consist of the 4-linked α-galactose constituent with levorotatory (L-). The antiviral properties of carrageenan have also been demonstrated with

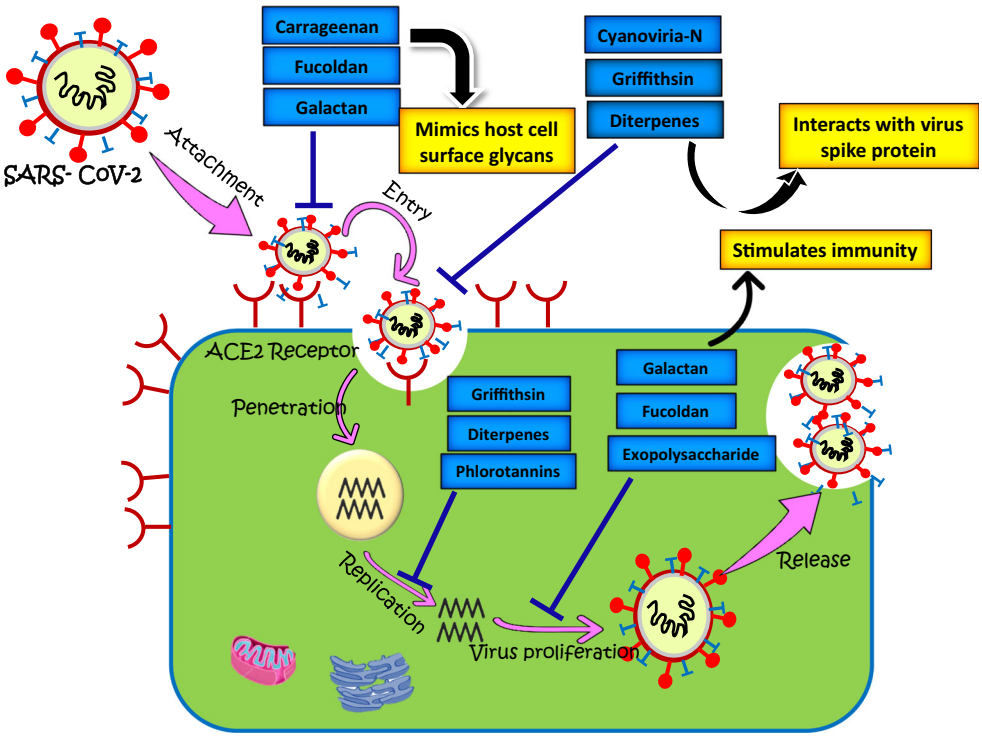

Fig. 4 Schematic diagram indicating a collection of efficacious anti-SARS-CoV-2 drug; potential candidates derived from marine microorganisms and their possible mode of action for possession of high degree drug-likeness for prevention and treatment of COVID-19

the potential to prevent various viral infections. It can significantly disrupt the association of virus and host cell receptors, hence obstruct the entry of viral particles inside of the cell (Al-Alawi et al. 2011).

Grassauer et al. (2008) explored the impact of carrageenan on the restraint of the cell death due to COVID-19, in *Feline* kidney cells. Iota-carrageenan, a sulfated polysaccharide derived from seaweed, shows critical resistance at low concentrations (4 μg/ml); however, kappa and lambda-carrageenan were not found adequate. They revealed that the host cell pretreated with the elevated concentration of carrageenan, i.e., 400 μg/ml showed just 35% suppression. The outcome showed that pre-treatment is not adequate to shield cells from SAR-CoV-2 infection. They proposed carrageenan as an antiviral agent, ought to be available with virus interacting with the host cell at the time of infection. Moreover, it proposes that carrageenan could be covered or inseminated to the strong surface of cleanliness or sterile things like a cotton swab, facial masks, gloves, and tissue paper, etc. (Grassauer et al. 2008; Morokutti-Kurz et al. 2021).

An iota-carrageenan-based nasal spray was also developed, which was found to be efficacious in patients with a common cold, one of the common symptoms of human coronavirus 229E (alpha) and human Covid OC43 (beta). Its administration has shown a decrease of 2.5-fold in reoccurring symptoms and enhanced viral eviction in comparison to the patients treated under placebo control (Hemilia and Chalker 2020; Koenighofer et al. 2014).

Graf et al., in 2018, developed a nasal spray involving xylometazoline hydrochloride (0.05%) and carrageenan (0.12%). This combination of these two has been accounted for to assuage nasal blockage in the upper respiratory tract, and at the same time, respiratory mucosa was found to be protected against the virus (Graf et al. 2018).

The lozenges using iota-carrageenan (10 mg) as active drug constituents were developed to treat throat problems brought about by a human Covid OC43. The studies indicated that virus surface protein, glycoproteins, were inactivated at the effective time of lozenge inside the mouth. Due to the low pH of the mouth, carrageenan-produced lozenges faced the morphological changes of glycoproteins. Denaturation of glycoproteins prompts hindering of viral effects on the host (Morokutti-Kurz et al. 2017). Further, in 2021, the same group reported that the admission of the COVID-19 spike pseudotyped lentivirus can successfully be prevented by the use of iota-carrageenan in a dose-dependent manner. The experiment revealed that 2.6 μg/ml of iota-carrageenan can efficiently neutralize the SARS-CoV-2 spike pseudotyped lentivirus with an IC_{50} value. The work was supported by similar results against several rhinoviruses and endemic coronaviruses when used as iota-carrageenan containing nasal spray. The overall study suggests that the application of iota-carrageenan may be used as a potent and safe preventive treatment against COVID-19 (Morokutti-Kurz et al. 2021).

Infection of SARS-CoV-2 exerts release of reactive oxygen species release (ROS) due to which the adjoining cells become vulnerable to the virus infection. In such a case, the drugs with antioxidant activity would be a good candidate against SARS-CoV-2 infection to maintain redox homeostasis (Morshedul 2019). Some marine algae-derived bioactive compounds have been reported to have strong antioxidant properties. Hence, they may act as shielding against oxidative stress-induced damage. Fucoxanthin, a carotenoid extracted from Sargassum siliquastrum, impeded H_2O_2-induced DNA damage by protecting with increased production of GSH level, as well as higher expression of SOD gene (Pangestuti et al. 2013).

The effect of fucosterol was tested on experimental model rats, and it was observed that it was able to increase cellular antioxidant enzymes, such as CAT, SOD, and GPx (Lee et al. 2003). It has also been observed that fucosterol was efficient to inhibit ROS production in tert-butyl hydroperoxide (t-BHP)-stimulated RAW264.7 cells (Jung et al. 2013). Apart from this, fucosterol showed protection from oxidative stress-induced damage of human hepatic cells, HepG2 cells, by enhancing the level of an intracellular antioxidant, GSH (Choi et al. 2015).

Consideration and challenges

COVID-19 is an unusual global health threat, and there is no effective drug available to date to deal with the pandemic situation and to reduce the infection rate (Mishra et al. 2020; Alam et al. 2020). In the current pandemic situation, it is of utmost importance to ensure that rigorous and adequate clinical trials have been performed to evaluate the new antiviral drugs to avoid the ineffective and unsafe usage of drugs (Lai et al. 2020). The marine-derived secondary metabolites with diverse new chemical structures have already represented its potential in a variety of fascinating biological activities and immense prospective for the discovery of new therapeutic compounds for drug development to deal with the emerging mutants of COVID-19. The potential feature of novel marine bioactive compounds as anti-inflammatory and antioxidant activity could be used against COVID-19 as these are very potent, efficiently modulates several cell signaling pathways to reduce cytokine release, and activates antioxidant response pathways.

Extensive investigation and the deep analysis of the structural activity of marine bioactive compounds, which have immunomodulatory activities, would prove to be a good option in the treatment of severe COVID-19 infection as compared to chemically synthesized drugs. More confined and focused studies are required to understand the chemical composition

and structure, biological activity, and mechanisms of action of marine bioactive compounds in pharmaceutical sectors.

Though we have an advanced multi-omics approach that can be used to narrow down the choice of potential bioactive compounds and bioinformatics tools that can help to find the interaction of these molecules with SARS-CoV-2 virus infection (Singh et al. 2021). Through repurposing of drugs is also being studied, but it has shown ineffectiveness. Moreover, the mutation rate of SARS-CoV-2 has raised the concern because previous studies have suggested that mutations in the target proteins of the coronaviruses can be associated with drug resistance (Deng et al. 2014).

The world is still facing the uncertainty of COVID-19 spread and protection against it. The advancement in multi-omics technology, studies on gene mutations as well as bioinformatic tools will help to put one step forward in the selection of potential drug candidate to the threat of COVID-19.

Author contribution All authors contributed to the article and approved the submitted version. RS was involved in the designing, conception, and revising of the manuscript critically for intellectual content. NC was involved in drafting the manuscript. MK was involved in critically examining the manuscript and incorporation of important relevant information.

Data Availability NA.

Declarations

Ethics approval and consent to participate NA.

Consent for publication NA (as no image has been copied).

Conflict of interest The authors declare no competing interests.

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