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REVIEW

Role of marine natural products in the development of antiviral agents against SARS-CoV-2: potential and prospects

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Abstract

A novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has surfaced and caused global concern owing to its ferocity. SARS-CoV-2 is the causative agent of coronavirus disease 2019; however, it was only discovered at the end of the year and was considered a pandemic by the World Health Organization. Therefore, the development of novel potent inhibitors against SARS-CoV-2 and future outbreaks is urgently required. Numerous naturally occurring bioactive substances have been studied in the clinical setting for diverse disorders. The intricate infection and replication mechanism of SARS-CoV-2 offers diverse therapeutic drug targets for developing antiviral medicines by employing natural products that are safer than synthetic compounds. Marine natural products (MNPs) have received increased attention in the development of novel drugs owing to their high diversity and availability. Therefore, this review article investigates the infection and replication mechanisms, including the function of the SARS-CoV-2 genome and structure. Furthermore, we highlighted anti-SARS-CoV-2 therapeutic intervention efforts utilizing MNPs and predicted SARS-CoV-2 inhibitor design.

Keywords SARS-CoV-2 · Marine natural products · Drug targets · Inhibitors

Introduction

Mankind has been attacked by three epidemics in the twenty-first century including coronaviruses that belong to the family *Coronaviridae*, which comprises a positive-sense single-stranded RNA (+ssRNA) genome. This family has a high recombination rate and genetic variability, leading to easy distribution among humans and other animals, resulting in diverse coronavirus types in human and animal populations. Coronaviruses primarily target the respiratory system and cause diseases, ranging from mild respiratory diseases to acute pneumonia and respiratory failure. Recently, there have been three severe pandemics involving respiratory diseases caused by the coronavirus. The most recent global pandemic was coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS-CoV-2), and the other two were regional epidemics, SARS-CoV and Middle East respiratory syndrome (MERS-CoV) in 2003 and 2012, respectively. The world has suffered from this pandemic and is continuing to do so. Thus, the immediate development of antiviral drugs against SARS-CoV-2 is essential. The conventional sources for treating human ailments have long been natural substances derived from plants, animals, microorganisms, and minerals. Natural product drug research has been dramatically reinvigorated by recent advancements in analytical technology, spectroscopy, and high-throughput screening with contributions from marine-based pharmaceuticals. The maritime environment is a unique resource with a vast array of biological diversity and, if properly

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investigated, has the potential to produce ground-breaking treatments. As more substances derived from marine sources enter clinical trials, the influence of this discipline on the pharmaceutical business grows (Shinde et al. 2019). Several compounds are produced by marine species for antiviral activity. More than 40 substances are commercially available in the pharmaceutical market, including prospective antiviral treatments or alternative antiviral medications. Many more are undergoing preclinical and clinical testing for potential antiviral medications (Yasuhara-Bell and Lu 2010). The current exploration of the marine environment for compounds with significant pharmacological applications will be significantly accelerated by the growing interest in marine-derived antiviral compounds, and it will continue to be a promising strategy and new trend in contemporary medicine. Thus, this study attempted to offer insights into the implications of a novel therapeutic agents against SARS-CoV-2 using marine natural products (MNPs), a treasure trove of antiviral agents. Furthermore, the structural and functional correlation in the identification of therapeutic drug targets was thoroughly discussed and can be used as a resource for developing antiviral agents against future coronavirus infections.

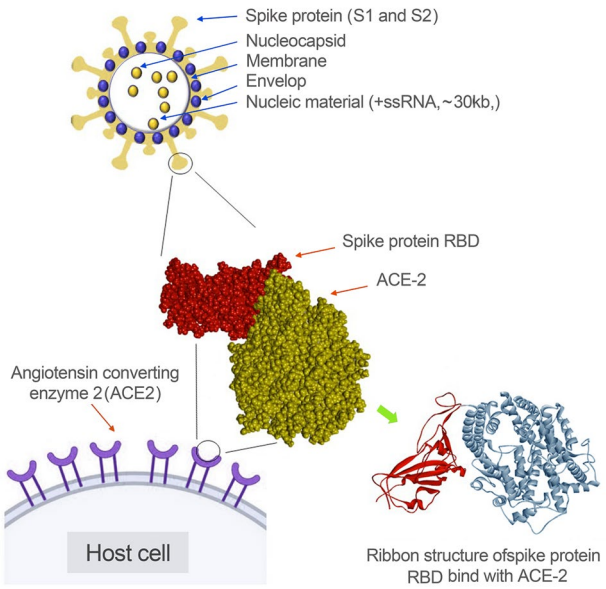

Fig. 1 Structural proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the interaction of SARS-CoV-2 spike protein with the angiotensin-converting enzyme 2 (ACE-2)

Coronavirus structure

Coronaviruses belong to the kingdom *Othornavirae*, family *Coronaviridae*, and phylum *Pisuviricota* and are a monophyletic cluster in the order *Nidovirales*. Coronavirus is an enveloped virus strain that comprises approximately 30 kb of +ssRNA genetic material (Speake et al. 2020). The subfamily *Orthocoronavirinae* comprises four coronavirus genera: α, β, γ, and δ. SARS-CoV and SARS-CoV-2 belong to the genus *Betacoronavirus*. The coronavirus virion comprises four main structural proteins, as depicted in Fig. 1. Furthermore, a coronavirus does not require these proteins to prepare a functional infectious virus. It utilizes additional proteins to prepare infectious virions (Perlman and Netland 2009; Schoeman and Fielding 2019).

Spike proteins have an extensive contribution to the determination of a variety of coronaviruses. The spike protein comprises two major protein subunits: S1 (amino-terminal) and S2 (carboxyl-terminal). The S1 subunit is the outermost part of the cell and plays a pivotal role in receptor binding. Meanwhile, the S2 subunit provides fusion between the coronavirus and the cellular membrane (Chen et al. 2020; Hasoksuz et al.2002). Collectively, these two protein subunits enable the virus to attach to the host cell receptor. The receptor-binding domain (RBD) in the spike protein S1 region is responsible for the initial attachment and varies among diverse types of coronaviruses. Mouse hepatitis virus (MHV) contains the RBD at the S1 N-terminus, and SARS-CoV and SARS-CoV-2 contain the RBD at the S1 C-terminus. The RBD of human coronavirus NL63 (HCoV-NL63), SARS-CoV, and SARS-CoV-2 forms an attachment with angiotensin-converting enzyme 2 (ACE-2) during host cell infection, and aminopeptidase is used as a receptor by several α-coronaviruses, such as transmissible gastroenteritis (TGEV) and diarrhea virus (PEDV). Dipeptidyl peptidase 4 (DPP4) is employed by MERS-CoV as a receptor for infection, and MHV is transmitted through the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) receptor (Satija et al. 2007). Receptor binding provides an avenue into the host cell and employs proteolytic cleavage (acid-dependent) of spike proteins by transmembrane protease serine 2 (TMPRSS2), cathepsin (CTSs), or other protease enzymes (Bosch et al.2003).

Membrane proteins play key roles in viral assembly. They provide a surface for factors from the virus and host to join and create new virus particles. Moreover, the Golgi apparatus is targeted by this membrane protein in MHV, feline coronavirus (FCoV), SARS-CoV-2, infectious bronchitis virus (IBV), MERS-CoV, bovine coronavirus (BCoV), and SARS-CoV. Previous studies revealed that membrane proteins combine with spike glycoproteins and viral ribonucleoproteins at the budding site for virus assembly (Neuman et al. 2011).

The enveloped protein is considered a major structural protein. Elevated expression of this protein was detected during the viral replication cycle in host cells. However, the full protein is not involved in the viral envelope (Schoeman and Fielding 2019). Previous studies have revealed that the coronavirus envelope proteins play three major roles. These are

the interactions between the membrane protein and envelope protein cytoplasmic tail, which emphasizes the participation of envelope proteins in viral assembly, the essentiality of hydrophobic transmembrane of envelope protein for releasing the assembled virion, and implications for virus pathogenicity (Satija and Lal 2007; Schoeman and Fielding 2019).

The coronavirus nucleocapsid is created by nucleocapsid proteins and its primary function is to bind to the virus's genetic material. Furthermore, it plays a major role in viral genome-related processes, such as viral RNA replication and host cellular responses to the virus. Localization of nucleocapsid proteins in the endoplasmic reticulum (ER) provides functions via assembly and budding. Moreover, a significant increase in the production of virus-like particles (VLPs) in some coronaviruses has been found to be due to nucleocapsid protein expression (Chen et al. 2020).

SARS-CoV-2 genome

The SARS-CoV-2 genome comprises +ssRNAs (Wu et al. 2020). The NCBI database contains the complete genome sequence under accession No. NC_045512.2. The genome (approximately 29.9 kb) encodes numerous open reading frames (ORFs) (13–15 ORFs), with 12 functional ORFs comprising approximately 30,000 nucleotides, including 11 protein-coding genes. Furthermore, high similarity in genetic arrangement has been reported among SARS-CoV-2, MERS-CoV, and SARS-CoV, with 89% sequence identity (Lu et al. 2015; Rota et al. 2003). The encoded proteins are predominantly divided into two groups: non-structural (NSPs) and structural proteins, which play critical roles in the entry, fusion, replication, and survival of host cells (Tong 2009). The entire SARS-CoV-2 genome encodes a polyprotein containing 7096 residues, which comprises several structural proteins and NSPs. There are two major polyproteins that can be found called pp1a and pp1ab, which are encoded by ORF1a and ORF1ab, respectively. The ribosomal frameshift mechanism of 1b was used to encode polyprotein pp1ab. The proteinases encoded by the viral genome further process these polyproteins and generate 16 proteins that are important for the viral life cycle and are conserved in coronaviruses of the same family (Fig. 2A). SARS-CoV-2 exhibits an elevated level of infection compared to SARS-CoV and MERS-CoV due to its different epidemiological dynamics and the successful utilization of other mammalian species as amplifying or intermediate hosts and acquiring mutations for efficient human transmission (Graham and Baric 2020).

NSPs play specific roles in viral replication and assembly in host cells by engaging in viral pathogenesis via gene transactivation, modulating helicase activity, countering antiviral responses, early transcription regulation, and immunomodulation (Xue et al. 2014) (EA and Jones 2019; Muller et al. 2018; Tang et al. 2020). The major functions of these NSPs are summarized in Table 1. In addition to the conserved regions, accessory genes can also be found in the SARS-CoV-2 genome, which expresses notable variability among the coronavirus groups. Nine accessory proteins were found to be encoded by at least five accessory genes (Fig. 2A).

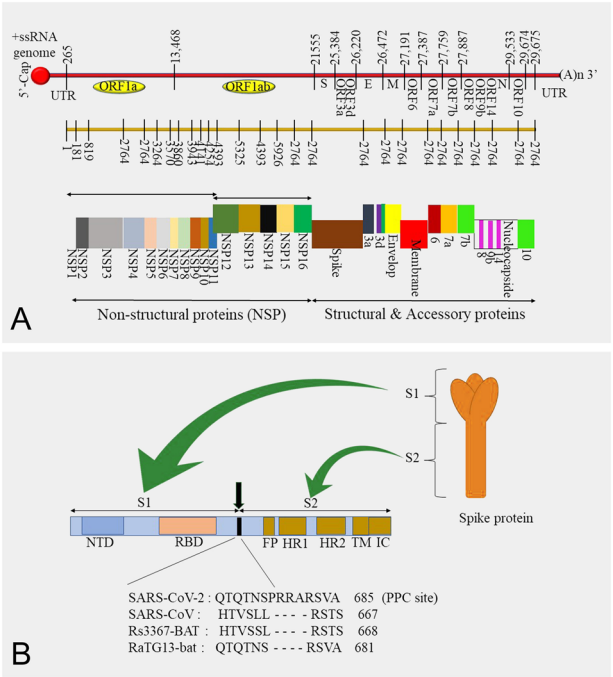

Fig. 2 The structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome and SARS-CoV-2 spike protein. **A** Order of the open reading frames (ORFs) and their expression to produce structural and non-structural proteins and **B** SARS-CoV-2 spike protein structure and the comparison of proprotein convertase sites in diverse coronaviruses

Cell entry mechanism

Determination of coronaviruses' cell entry mechanism is important for evaluating SARS-CoV-2 pathogenicity and infectivity (Li 2016; Perlman and Netland 2009). Moreover, it is a key target for intervention strategies and host immune surveillance (Du et al. 2009; Perlman and Netland 2009). The cell entry mechanism can be divided into three major phases. Initially, viral attachment is conducted by a coronavirus via binding to the cell surface receptor of the host cells, which then enters the endosome and fuses lysosomal and viral membranes (Du et al. 2009; Perlman and Netland 2009). The mature coronavirus spike protein is present as a trimer that comprises three receptor-binding S1 heads placed on top of the S2 stalk. According to previous SARS-CoV studies, ACE-2 is recognized as its

Table 1 The functions of non-structural proteins of SARS-CoV-2

No	Range	Protein name and ID	Role	Proposed function
1	1–180	Nsp1 YP_009725297.1	Nsp1 is the N-terminal product of the viral replicase	Leader protein host translation inhibitor. Mediates RNA replication and processing. Involved in mRNA degradation
2	181–818	Nsp2 YP_009725298.1	Nsp2 is a replicase product essential for proofreading viral replication	Modulation of host cell survival signaling pathway by interacting with host PHB and PHB2
3	819–2763	Nsp3 YP_009725299.1	Nsp3 is a papain-like proteinase, contains several domains	Functions as a protease to separate the translated polyprotein into its distinct proteins
4	2764–3263	Nsp4 YP_009725300.1	A membrane-spanning protein, contains transmembrane domain 2 (TM2)	Believed to anchor the viral replication–transcription complex to modified ER membranes
5	2364–3569	Nsp5 YP_009725301.1	3C-like proteinase and main proteinase	Involved in viral polyprotein processing during replication
6	3570–3859	Nsp6 YP_009725302.1	Putative transmembrane domain	Plays a role in the initial induction of autophagosomes from host endoplasmic reticulum
7	3860–3942	Nsp7 YP_009725303.1	Nsp7 is an RNA-dependent RNA polymerase	It forms a hexadecameric super-complex with nsp8 that adopts a hollow cylinder-like structure implicated in replication
8	3943–4140	Nsp8 YP_009725304.1	Multimeric RNA polymerase; replicase	It forms a hexadecameric super-complex with nsp7 that adopts a hollow cylinder-like structure implicated in replication
9	4141–4253	Nsp9 YP_009725305.1	A single-stranded RNA-binding viral protein	Participates in viral replication by acting as an ssRNA-binding protein
10	4254–4392	Nsp10 YP_009725306.1	Growth-factor-like protein contains two zinc-binding motifs	In viral transcription by stimulating both nsp14 3′–5′ exoribonuclease and nsp16 2′-*O*-methyltransferase activities. Therefore, plays an essential role in viral mRNAs cap methylation
11	4393–5324	Nsp12 YP_009725307.1	RNA-dependent RNA polymerase (Pol/RdRp)	Responsible for replication and transcription of the viral RNA genome
12	5325–5925	Nsp13 YP_009725308.1	Zinc-binding domain, NTPase/helicase domain, RNA 5′-triphosphatase	A helicase core domain that binds ATP. Zinc-binding domain is involved in replication and transcription
13	5926–6452	Nsp14 YP_009725309.1	Proofreading Exoribonuclease domain (ExoN/nsp14)	Exoribonuclease activity acting in a 3′ to 5′ direction and N7-guanine methyltransferase activity
14	6453–6798	Nsp15 YP_009725310.1	EndoRNAse; nsp15-A1 and nsp15B-NendoU	$Mn^{(2+)}$-dependent endoribonuclease activity
15	6799–7096	Nsp16 YP_009725311.1	2′-O-ribose methyltransferase	Methyltransferase that mediates mRNA cap 2′-*O*-ribose methylation to the 5′-cap structure of viral mRNAs
16	4393–4405	Nsp11 YP_009725312.1	Made of 13 amino acids (sadaqsflngfav) and identical to the first segment of nsp12	Unknown

receptor by SARS-CoV S1 RBD (Li 2015; Li et al. 2005, 2003; Walls et al. 2019). RBD follows a specific mechanism that switches regularly between standing up and lying down positions to evade the host cell's immune response (Gui et al. 2017; Yuan et al. 2017). The SARS-CoV spike protein requires proteolytic activation at the S1/S2 boundary to fuse the membranes. Here, the S1 disunites and S2 undergoes structural changes. The lysosomal proteases cathepsin and cell surface protease TMPRSS2 play major roles in activating the spike protein and cell entry mechanism (Belouzard et al. 2012; Heald-Sargent and Gallagher 2012). These specific factors of the cell entry mechanism led to severe symptoms, rapid spread, and high fatality rates in infected patients (Bolles et al.2011; Frieman and Baric 2008; Li 2013).

Recent studies have revealed that SARS-CoV-2 also recognizes ACE-2 as a receptor for cell entry, and these studies have guided the identification of critical SARS-CoV and SARS-CoV-2 functional characteristics in receptor recognition (Letko et al. 2020; Xu et al. 2020; Zhou et al. 2020). The RBD of SARS-CoV-2 expresses a significantly higher binding affinity for ACE-2 than for SARS-CoV (Shang et al. 2020a, b). However, there are conflicting reports from diverse studies on the SARS-CoV-2 RBD binding affinity to ACE-2. As mentioned above, RBD follows standing up and laying down states to evade the immune response, and

these states are associated with receptor-binding affinity. An interesting study regarding the cryo-electron microscopy structure of SARS-CoV-2 revealed that RBD was mostly in the lying down state, which demonstrates ineffective binding with ACE-2 (Walls et al. 2020; Wrapp et al. 2020). Moreover, studies have verified the role of TMPRSS-2 and lysosomal proteases as protease activators in the SARS-CoV-2 cell entry mechanism (Hoffmann et al. 2020; Ou et al. 2020).

Proprotein convertase (PPC) is a protein family responsible for activating other proteins. The PPC motif of surface glycoproteins plays a key role in the pathogenesis of viruses, such as avian influenza. However, previous studies have reported that there is no specific function of the PPC motif in enhancing SARS-CoV-2 cell entry (Letko et al. 2020). However, novel studies have emphasized the PPC motif function by investigating protease activation and receptor binding of SARS-CoV and SARS-CoV-2 as a comparison study. The results of this study revealed the important factors of the cell entry mechanism that play pivotal roles in cell infectivity, immune evasion, and virus spread in the host. The identified cleavage site is located at the boundary between S1 and S2 (Fig. 2B). Moreover, SARS-CoV does not have this cleavage site. Cell entry assays for SARS-CoV, SARS-CoV-2, and SARS-CoV-2 with a mutated cleavage site were conducted. This assay revealed that SARS-CoV-2 exhibited significantly higher cell entry than SARS-CoV and SARS-CoV-2-mutated strains. In addition, PPC inhibitors were used to evaluate the effects of PPC on SARS-CoV and SARS-CoV-2. SARS-CoV-2 cell entry was significantly downregulated by the PPC inhibitor, and there was no significant difference in SARS-CoV cell entry. These results verify that SARS-CoV-2 requires prior PPC cleavage for cell entry (Shang et al. 2020a, b).

SARS-CoV-2 replication in the host cell

Fusion of the SARS-CoV-2 spike protein with the ACE-2 receptor causes subtle conformational modifications, and the viral nucleocapsid is released into the host cell cytosol. Several host factors can be found to support these processes, including TMPRSS-2 and cathepsin-L. Immediately after releasing the nucleocapsid into the cytosol, +ssRNA acts as a functional messenger RNA (mRNA) for ORF1a and ORF1b, which encode the polyprotein pp1a (440–500 kDa) and pp1ab (740–810 kDa), respectively. Furthermore, compared to pp1ab, pp1a is expressed 1.2- to 2.2-fold more in host cells due to the high efficiency of frameshift between the ORF1 and ORF1b genes (Finkel et al. 2021). The autoproteolytic process leads to the processing of these 2 polyproteins and produces 16 NSPs, which collectively form a replication-transcription complex (RTC) for the synthesis of viral RNA. The set of sgRNAs results from this functional RTC via discontinuous transcription (V'kovski et al. 2021). RTC formation causes molecular processes in the passage guide for synthesizing numerous viral RNA copies. This negative-sense single-stranded RNA (−ssRNA) acts as an intermediate template. Simultaneously, during −ssRNA synthesis, the polymerase switches templates at short motifs called transcription-regulated sequences (TRS) to generate many 5-nested negative-sense sgRNA sets, which, in turn, are utilized as templates for the formation of 3′-nested positive-sense sgRNAs. Consequently, they interact with the host ribosomes and synthesize numerous structural and accessory proteins that build multiple viral structures (Sola et al.2015).

Free cytosolic ribosomes are responsible for the translation of nucleocapsid proteins in the host cells. Furthermore, proteins associated with spike, membrane, and envelope proteins are synthesized by ribosomes bound to the ER. Subsequently, these proteins undergo post-translational modifications (PTMs). The endoplasmic reticulum–Golgi intermediate compartment (ERGIC) is the virion assembly site. Here, scaffolding and orchestrate virion morphogenesis are provided by membrane proteins via heterotrophic interactions with other structural proteins, such as membrane spike and membrane envelope proteins provide molecular incorporation. Moreover, membrane–nucleocapsid interactions facilitate nucleocapsid condensation with the envelope along with the envelope protein (V'kovski et al. 2021). After molecular assembly, virion progenies are carried in smooth-wall vesicles and transported by secretory pathways to the plasma membrane, eventually exiting through exocytosis, upon which they spread to other parts of the body (Astuti and Ysrafil 2020; Naqvi et al. 2020; V'kovski et al. 2021).

The structure, genome, cell entry, and replication mechanisms provide many potential drug targets for inhibiting SARS-CoV-2. The traditional sources for treating human ailments have long been natural substances derived from plants, animals, microorganisms, and minerals. Natural product drug research has been dramatically reinvigorated by recent advancements in analytical technology, spectroscopy, and high-throughput screening with contributions from marine-based pharmaceuticals. The maritime environment is a unique resource with a vast array of biological diversity and, if properly investigated, has the potential to produce ground-breaking treatments. As more substances derived from marine sources enter clinical trials, the influence of this discipline on the pharmaceutical industry has grown. Herein, we discuss the potential drug targets of SARS-CoV-2 and their inhibition by MNPs.

MNPs against SARS-CoV-2

Although the development of vaccines to eliminate or limit its effects never ceases, SARS-CoV-2 continues to spread rapidly across the globe. Insufficient production to meet

the global demand, specificity with the desired viral strain, continuous SARS-CoV-2 genome mutation, and subsequent novel strains necessitate the investigation of drugs that can potentially prevent COVID-19. Furthermore, many efforts have been made to repurpose US Food and Drug Administration (FDA)-approved drugs against SARS-CoV-2. The potential drugs, antibodies, and compounds that demonstrate antiviral effects against SARS-CoV-2 are summarized in Table 2.

Natural compounds are becoming increasingly enticing in pharmaceuticals, cosmeceuticals, nutraceuticals, and functional foods because people admit that naturally occurring compounds are more secure than artificially synthesized compounds. Currently, COVID-19 control has become a global health emergency owing to the unavailability of antiviral drugs against SARS-CoV-2. Therefore, the repurposing of WHO-approved drugs, including remdesivir (Ebola), chloroquine and hydroxychloroquine (malaria), and lopinavir and ritonavir (HIV), against SARS-CoV-2 has been investigated (Kupferschmidt and Cohen 2020).

Hydroxychloroquine was approved by the FDA for treating COVID-19. The results demonstrated a significant reduction in viral load by hydroxychloroquine in infected patients as a combination treatment with azithromycin. In a further study, hydroxychloroquine was proven to be more effective in COVID-19 treatment than chloroquine (Gautret et al. 2020). However, statistical data from hospitalized COVID-19 patients revealed that there was no beneficial effect of hydroxychloroquine on the recovery rate compared to standard COVID-19 care (Therapy 2021, March 5). A study of treatments with lopinavir–ritonavir also demonstrated that there was no significant difference in standard care for COVID-19 (Cao et al. 2020). However, lopinavir–ritonavir combined with interferon β-1b and ribavirin demonstrated effective antiviral activity by alleviating and shedding symptoms in patients with mild-moderate COVID-19. Notably, interferon β-1b was not included in the control group in this study, and a placebo control group was not included in this study to compare the treatment's efficacies (Hung et al. 2020). Further studies are required to verify this.

The ocean contains many resources that yield a variety of natural products. It encompasses more than 70% of the surface of the Earth and is home to more than 300,000 identified plant and animal species (Pomponi 1999). The ocean is described as a vast treasure awaiting the discovery of numerous valuable compounds that can be used against diseases. Unique and extreme conditions, such as ecological pressure, are responsible for the evolution of these secondary metabolites with numerous biological activities (Ireland et al. 2000). The significance and use of these secondary metabolites have been extensively evaluated for many years. Experts worldwide have discovered more than 12,000 novel compounds from marine animals and plants within the last 30–40 years (König et al. 1994) and have evaluated them in diverse fields to discover useful applications, including anti-cancer, anti-inflammatory, antiviral, antibacterial, and

Table 2 Repurposed drugs against SARS-CoV-2 and their activities

No	Drug/compound/antibody	Targets of drug on SARS-CoV-2
1	Chloroquine and formoterol	Target Papain-like protease (PL^{pro}) Interferes with viral replication Chloroquine targets the terminal glycosylation of ACE-2 Interferes with the spike protein and ACE-2
2	Remdesivir (nucleotide analog)	Target RNA-dependent RNA polymerase (RdRp) Interferes with the nascent viral RNA
3	Bananin (adamantane derivative)	Targets helicase (NSP13) Interferes with viral replication
4	Pyridone-containing α-ketoamides	Targets chymotrypsin-like protease ($3CL^{pro}$) Interferes with viral replication
5	β-D-N4-Hydroxycytidine (ribonucleoside analog)	Inhibits viral replication
6	Ebselen	Reduces COVID-19 by 20.3 fold
7	Ivermectin	Targets nuclear transporter and Impα/β1 heterodimer, binds and destabilizes it. This prevents its binding with viral cargo protein and its translocation to nucleus Interferes with the suppression of antiviral responses and viral load (reduce by 5000 fold)
8	Zidovudine	Targets nucleocapsid phosphoprotein Binds with nucleocapsid phosphoprotein and provides antiviral effect
9	Camostat mesylate and bromhexine hydrochloride	Targets TMPRRS-2. Acts as a TMPRSS-2 inhibitor Interferes with viral entry
10	CR3022 (monoclonal antibody)	Targets RBD of spike protein Interferes with the cellular interaction of virus

antifungal properties (Donia and Hamann 2003; Sanjeewa et al. 2016).

An antiviral agent that can prevent SARS-CoV-2 infection remains under research and development, and repurposing of FDA-approved drugs can cause several failures and side effects, including many major handling failures, side effects, resistance, long-term treatment, and cell toxicity (Khan et al. 2021). The available vaccines against SARS-CoV-2 predominantly target structural proteins of the virus; however, regulating NSPs of SARS-CoV-2 using marine natural products may cause significant antiviral activity against SARS-COV-2. Furthermore, the complex infection and replication mechanisms of SARS-CoV-2 have provided diverse therapeutic drug targets (Table 3).

MNPSs as potent SARS-CoV-2 spike protein inhibitors

The SARS-CoV-2 spike protein plays a pivotal role in the infectivity and pathogenesis of coronaviruses (Du et al. 2009; Hofmann et al. 2004). It comprises 1273 amino acids created by 2 primary subunits: S1 and S2. These subunits undergo structural changes during viral–host membrane fusion. The RBD of S1 binds with ACE-2 via Glu394 of RBD and Lys31 of ACE-2, and these residues play an important role in viral–host interactions (Zhang et al. 2020). The RBD receptor-binding motif demonstrates high variation, which causes variations in coronavirus pathogenesis. The S2 subunit causes membrane fusion between the host and viral membranes. Therefore, S2 had three conformations. The pre-fusion native state was the initial phase. It then extends to the hairpin intermediate state and becomes a post-fusion hairpin state. Discovering this changing conformation of the spike protein has led to the establishment of therapeutic agents for alleviating SARS-CoV-2. Novel studies have revealed that the binding site of RBD on SARS-COV-2 comprises six residues (Phe486, Leu455, Gln493, Tyr505, Asn501, and Ser494), which play an important role in ACE-2 binding (Naqvi et al. 2020). The SARS-CoV-2 spike protein also comprises a homologous trimeric spike protein structure similar to SARS-CoV and MERS-CoV. This conformation comprises three chains (A, B, and C), but the N-terminus of chain B has a unique conformation compared to the other two chains (Alexandra et al. 2019; Walls et al. 2020). These similarities and alterations could be exploited as key targets in vaccine production for antiviral drug development. Vaccines are considered a major solution to control COVID-19 spread; the risk of morbidity and mortality has encouraged the development of vaccines against SARS-CoV-2. The SARS-CoV-2 spike protein is targeted by several vaccines owing to its immunogenicity. However, mutations in the spike protein may affect the efficacy of the vaccine; for example, a vaccine produced against SARS-CoV-2 isolated from Wuhan, China may not be effective against the United Kingdom variant (VUI202012/01) due to its D614G mutation in the spike protein. Therefore, the development of vaccines or drug candidates that do not depend on these mutations is vital. Thus, the interaction between the spike protein and ACE-2 RBD can be identified as an important drug target (Aatif et al. 2021).

The computational approach to evaluate MNPSs against the spike protein of the SARS-COV-2 VUI202012/01 strain provided effective drug candidates against SARS-COV-2. In this study, 1110 unique compounds with known biological activities, including anti-microbial, antiviral, anti-cancer, and anti-inflammatory activities, from the Seaweed Metabolite Database were investigated. According to these results, dieckol was identified as a successful inhibitor of the interaction between SARS-CoV-2 RBD and ACE-2. However, structural analysis of dieckol has revealed that it does not possess drug-like properties; therefore, it cannot be used as a lead inhibitor. Dieckol derivatives have been proposed as alternative 8–3-hydroxy-4-(7-hydroxynaphthalen-2-yl) oxy-phenoxy-1,4-benzodioxin-5-ol inhibitors. It successfully binds to the RBD and interferes with RBD-ACE-2 binding. However, in vitro and in vivo studies are required for further evaluation (Aatif et al. 2021).

Table 3 Potential therapeutic drug targets against SARS-CoV-2

SARS-CoV-2	Host
Spike protein	Proteases of host
Envelope protein	Proprotein convertase (PPC)
Membrane protein	Toll-like receptors (TLRs)
Nucleoprotein	High-density lipoprotein (HDL) scavenger receptor B type 1 (SR-B1)
Replicase protein	Glycosaminoglycans (GAGs) on the cell surface
Main protease (M^{pro} or $3CL^{pro}$)	
Papine-like protease	
RNA-dependent RNA polymerase	
Non-structural proteins	

Previous studies have demonstrated that the SARS-CoV-2 spike protein initially interacts with GAGs, including HS (Kim et al. 2020; Lindahl and Li 2020). Moreover, the results of these studies revealed that the SARS-CoV-2 RBD spike protein binds tightly with immobilized heparin compared to SARS-CoV and MERS-CoV. Brown seaweeds comprise sulfated polysaccharides, which have a structure similar to GAGs. These polysaccharides demonstrated strong binding abilities with SARS-COV-2 and inhibit its interaction with immobilized heparin (Kwon et al. 2020). The structure–activity relationship of the binding ability of polysaccharides with the SARS-CoV-2 spike protein was evaluated in a previous study using surface plasmon resonance. The results demonstrated that two polysaccharides, sulfated galactan and glucuronomannan, strongly inhibited the interaction between the spike protein and ACE-2 via the interaction between the SARS-CoV-2 spike protein and heparin (Jin et al. 2020).

Main protease (M^{pro}) inhibition by MNPSs

M^{pro} is one of the most attractive drug targets for SARS-CoV-2 owing to its specific role in polyprotein processing. This is the most vastly studied and well-validated drug target for SARS-CoV-2. M^{pro} is a key enzyme in the viral replication cycle. Some essential enzymes, such as RdRp for replication, require a prior proteolytic release for complete functioning [86]. M^{pro} inhibition can downregulate infectious viral particle production, which leads to the reduction of disease symptoms (Anand et al. 2003). M^{pro} studies have revealed a close structural relationship with the M^{pro} of other coronaviruses. Amino acid sequence alignment results demonstrated 99% sequence identity with BatCoV RaTG13 M^{pro}, 50% with MERS-CoV M^{pro}, and 96% with SARS-CoV M^{pro}. Sequence alignment data of M^{pro} revealed a 96% similarity between SARS-CoV and SARS-CoV-2 (Xu et al. 2020). Structural analysis of M^{pro} also demonstrated great similarity, except for the 12 amino acids in the surface proteins. Furthermore, the M^{pro} structures of SARS-CoV and SARS-CoV-2 are similar to those of cysteine proteases, which comprise a catalytic dyad (His41 and Cys145) in the active site and a stable water molecule that forms at least three hydrogen bonds with the surrounding residues instead of a third residue (Anand et al. 2003). Previous research has demonstrated that the high structural similarity of M^{pro} among SARS-CoV, SARS-CoV-2, and MERS-CoV guides drug development against SARS-CoV-2 M^{pro}, based on previously developed compounds against M^{pro} of SARS-CoV and MERS-CoV (Ullrich and Nitsche 2020).

M^{pro} belongs to the cysteine protease family of enzymes. Normally, serine and cysteine proteases contain a catalytic triad; whereas M^{pro} contains a catalytic dyad (histidine and cysteine) in its active site. The proteolytic mechanism of M^{pro} is considered a multistep mechanism. Histidine imidazole abstracts the cysteine side chain protons, and the amide bonds of the substrate are attacked by the resulting thiolate nucleophile. The proton abstraction from histidine releases N-terminal peptide products, after which the release of C-terminal products and restoration of the catalytic dyad occurs by thioester hydrolyzation (Pillaiyar et al. 2016).

The initial auto-cleavage of M^{pro} between NSP6 and NSP7 is required for polyprotein processing of pp1a and pp1ab at 11 cleavage sites (Du et al. 2004). The M^{pro} monomer is the inactive form and the primary active species is the homodimer. Two orthogonally aligned protomers can be found, and each protomer contains three domains. The domains I (residues 8–101) and II (residues 102–184) of SARS-CoV and SARS-CoV-2 contain an antiparallel β-barrel, which is similar to the trypsin-like serine protease. The domain III (residues 201–306) comprises a cluster of α-helices and is connected to domain II using a longer loop region (residues 185–200). The N-terminal fingers are used to bind protomers with each other, which involves creating a substrate-binding site located in a cleft between the domains I and II (Ullrich et al. 2020). The Ile286Ala, Thr285Ala, and Ser284Ala mutations in SARS-CoV-2 M^{pro} cause a 3.6-fold increase in catalytic activity than SARS-CoV M^{pro} (Lim et al. 2014). SARS-CoV and SARS-CoV-2 active sites were highly similar, except for the minor mutation S64A. Mutation influences the size, shape, plasticity, and flexibility of the active site, and further studies are required to use this for inhibitor design (Bzowka et al. 2020). In addition, as previously mentioned, the inactive M^{pro} monomer requires dimerization for activation. This emphasizes the need for a drug target against M^{pro} and SARS-CoV-2.

The in silico approach for evaluating inhibitors of MNPs against SARS-CoV-2 M^{pro} revealed great potential to inhibit SARS-CoV-2 (Gentile et al. 2020; Khan et al. 2021). Structural data demonstrated that the average volume of SARS-CoV-2 M^{pro} is half that of SARS-CoV M^{pro}. Furthermore, the SARS-CoV M^{pro} binding cavity is highly flexible and demonstrates significant changes in volume and shape after binding to the ligand (Anand et al. 2003). These features can also be used to design inhibitors or to convert suitable substrates into strong inhibitors. For example, the N3 inhibitor, a computer-aided designed peptide inhibitor is a successful M^{pro} inhibitor designed by mimicking natural substrates (Pillaiyar et al. 2016).

In a previous study, evaluation of phlorotannins isolated from *Ecklonia cava* as SARS-CoV M^{pro} inhibitors revealed the great potential of MNPs. Nine phlorotannins (phloroglucinol, triphloretol A, dioxinodehydroeckol, eckol, 7-phloroeckol, 2-phloroeckol, dieckol, fucodiphloroethol G, and phlorofucofuroeckol A) were evaluated. All phlorotannins, except phloroglucinol, demonstrated significant and dose-dependent inhibition against SARS-CoV M^{pro}; whereas

dieckol demonstrated the highest activity (Park et al. 2013). The structural similarity of M^{pro} between SARS-CoV and SARS-CoV-2, including its structural and functional relationship, should be exploited for further development of these compounds against SARS-CoV-2 M^{pro}.

The crystal structure of the SARS-CoV-2 M^{pro} (PDB ID. 6LU7) is available in PBD as a complex with an N3 inhibitor bound to the Cys145 residue. In a SARS-CoV-2 M^{pro} study, 14,064 compounds from the MNPs library were evaluated against SARS-COV-2 M^{pro}. All the molecules were screened in molecular docking assay, and 17 molecules (hydroxypentafuhalol A, heptafuhalol A, phlorethopentafuhalol A, pentaphlorethol A, phlorethopentafuhalol B, pentaphlorethol B, resinoside B, pseudopentafuhalol C, aeruginosin 98B, pseudotheonamide C, pseudotheonamide D, Dieckol, 6,6′-bieckol, apigenin-7-*O*-neohesperidoside, 8,8′-bieckol, luteolin-7-rutinoside, and tunichrome An2) were identified as potential SARS-CoV-2 M^{pro} inhibitors. Among these compounds, 8,8′-bieckol, 6,6′-bieckol, and dieckol were found to be the most active inhibitors; however, future in vitro and in vivo studies are required for further evaluation. On a positive note, these results emphasize another important factor that these phlorotannins, which have been used as therapeutic agents in anti-oxidant, anti-cancer, anti-inflammatory, anti-diabetic, and anti-hypertensive treatments, could potentially be used for treating COVID-19 (Gentile et al. 2020). Another study assessed five MNPs (fistularin-3/11-epi-fistularin-3 and 15-methyl-9(Z)-hexadecenoic acid isolated from sponges of the family *Aplysinidae*; (hexadecyloxy) propane,1,2-diol isolated from the soft coral *Pterogorgia citrine*; 15-α-methoxypuupehenol and puupehedione isolated from *Petrosia Strongylophora*) against SARS-CoV-2 M^{pro}. According to the results, fistularin-3/11-epi-fistularin-3 demonstrated the highest inhibitory activity. Furthermore, 15-methyl-9(Z)-hexadecenoic acid demonstrated considerable binding to the SARS-CoV-2 M^{pro} catalytic dyad. These in silico studies suggest the great potential of MNPs as SARS-COV-2 M^{pro} inhibitors. Further studies are required to evaluate these inhibitors and develop therapeutic drugs against COVID-19.

Papain-like protease (PL^{pro}) inhibition by MNPs

The SARS-CoV-2 genome encodes another protease, PL^{pro}, which is responsible for polyprotein processing. NSP1, NSP2, and NSP3 are cleavage sites used by PL^{pro} and the other 13 NSPs are processed by M^{pro}. This leads to the viral replicase complex assembly on the host cell membrane, initiating replication and viral genome transcription (Baez-Santos et al. 2015). In addition to polyprotein processing, PL^{pro} inhibits host innate immune responses, such as interferon responses, which create an antiviral state in the host cell using interferon-stimulated genes (ISGs). These responses lead to the detection of viral threats and subsequent responses (Berlin et al. 2020).

Antagonizing ubiquitin and ubiquitin-like modifications is a common mechanism for regulating innate immune responses by viral proteases (Heaton et al. 2016). Many ubiquitin chain formations encode both degradative and non-degradative functions. This results in complex protein ubiquitination (Yau and Rape 2016). Inflammatory signaling pathways use specific ubiquitin signals in human cells, including interferon-stimulated gene 15 (ISG15), a secreted protein (17kDa) encoded by ISG15. The viral infection leads to this ubiquitin-like (Ubl) ISG15 modification (Dzimianski et al. 2019). Several cellular enzymes participate in this process, enabling danger signals caused by viral infections. Viruses often use their proteases as deubiquitinases (DUBs) and deISGylases to avoid this. PL^{pro} acts as a DUB and disturbs the antiviral response of host cells by inhibiting Ubl-ISG15 modification. (Klemm et al. 2020) (Békés et al. 2015). Thus, three specific PL^{pro} substrates can be identified: antiviral ISG15 signals, degradative Lys48-polyubiquitin, and viral polyprotein. These activities are important for viral maturation, replication, and survival of the host which make PL^{pro} an excellent candidate for antiviral drug development. Thus, researchers are conducting studies to inhibit PL^{pro} and develop antiviral drugs against SARS-CoV-2. This was verified by evaluating the inhibitory activity of GRL0617 against SARS-CoV-2 PL^{pro}. According to the results, GRL0617 blocked the binding of ISG15 or ubiquitin with PL^{pro} and significantly inhibited polyprotein processing (Fu et al. 2021).

A study was conducted to evaluate PL^{pro} inhibition using ilimaquinone, a marine sponge metabolite isolated from a marine sponge called *Hippospongia metachromia*, in comparison with hydroxychloroquine, ivermectin, remdesivir, azithromycin, and favipiravir. The results demonstrated that ivermectin had the highest binding ability, followed by ilimaquinone. According to these in silico results, ilimaquinone is a promising drug candidate against SARS-CoV-2 PL^{pro} (Surti et al. 2020). Another computational simulation was conducted to identify MNPs as SARS-CoV-2 PL^{pro} inhibitors to discover potential MNPs that can significantly bind to the PL^{pro} active site and inhibit its activity. Compounds from the MNPs library were filtered using their drug-like properties, including the number of hydrogen bonds, donors, and acceptors. The results demonstrated that 14 MNPs expressed higher binding affinity than the positive controls, lopinavir and ritonavir (Kumar et al.2021).

RNA-dependent RNA polymerase (RdRp) inhibition by MNPs

NSP12, also called RdRp, contributes to the viral genome and protein synthesis, together with helicase. Furthermore,

they play an essential role in the viral lifecycle. The production of the viral genome progeny depends on RdRp, which must be synthesized to continue the process. RdRp is a common function among diverse virus genera and is the most conserved enzyme across several viral species, including influenza, hepatitis C, Zika, and coronaviruses (Venkataraman et al. 2018). The protein sequence similarity of RdRp between SARS-CoV and SARS-CoV-2 is 96% and existing structural differences can be found in catalytically inactive areas (Morse et al. 2020).

RdRp is a central enzyme used for viral replication. During viral genome synthesis, a complementary negative RNA strand is synthesized by RdRp based on +ssRNA. Based on the primer dependence, two conceivable methods are identified in genomic RNA synthesis as primer-dependent or independent (Ferrer-Orta et al.2006). Furthermore, cellular ribonucleotide triphosphates (rNTPs), CTP, ATP, UTP, and GTP afford template substrates, as observed by RdRp. The divalent metal ions manganese (Mn) and magnesium (Mg), which act as essential co-factors, promote reactions with rNTPs and catalytic aspartates are coordinated (Ogden et al. 2012).

Results from previous studies indicate that similar structures and catalytic mechanisms are shared by all RNA polymerases. In addition, this provides insights into the relationship between RdRp function and structure (Steitz 1998; Venkataraman et al. 2018). When studying the RdRp structure, a large, grooved domain resembling a cupped right hand is evident in the core RdRp structure, which is connected by "fingers," "thumb," and "palm" subdomains surrounding the active site cavity. (Fig. 3A). The catalytic process is affected by the structural motifs of RdRp, which are pitched in these domains. (Venkataraman et al. 2018). The subdomains play a role in the entry of nucleotide triphosphates, binding templates, and polymerization. The finger subdomain contains an active site and plays an important role in RNA binding and polymerization (Gao et al. 2020). Inhibition of this enzyme strongly affects the viral life cycle and activity. Therefore, the inhibition of RdRp has a promising effect on SARS-CoV-2 inhibition. *Sargassum cristaefolium*, *S. echinocarpum*, and *Padina australis* are three different brown seaweeds that are utilized to isolate MNPs. From these results, 99 compounds were evaluated and among them, 20 demonstrated a strong binding affinity with SARS-CoV-2 RdRp. Rhamnetin, a compound available in *Sargassum* spp., has the highest affinity with the RdRp finger subdomain, which is responsible for the active site (Firdaus et al. 2020). Moreover, another in silico approach revealed that compounds identified from the MNP library bind to the RdRp catalytic pocket using the same or slightly different residues as remdesivir. Among these compounds, moniloside A, isolated from *Formia monilis*, demonstrated a strong binding affinity with the RdRp active site. These

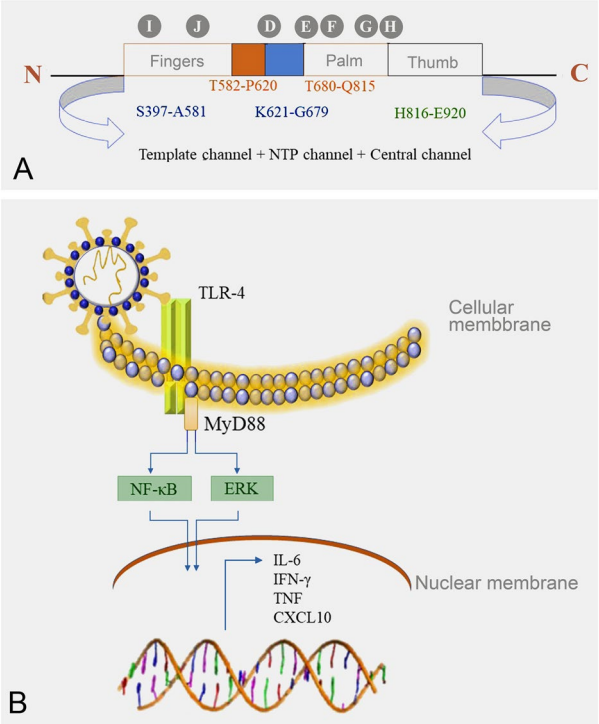

Fig. 3 RNA-dependent RNA polymerase (RdRp) structure and mechanism of SARS-CoV-2 induce cytokine storm. **A** Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase (RdRp) enzyme and **B** SARS-CoV-2-induced Toll-like receptor (TLR)-mediated inflammatory signaling pathways

studies demonstrate the potential of MNPs as promising drug candidates against SARS-CoV-2 through RdRp.

Nucleoside analogs are another approach to inhibit RdRp activity. Nucleosides are elements that make up nucleic acids and are involved in important biological activities, such as nucleotide formation (Seley-Radtke and Yates 2018). Previous studies have revealed significant antiviral activity of nucleoside analogs (Anjum et al. 2016). Spongouridine, spongothymidine, mycalisine A, and mycalisine B, isolated from marine sponges *Cryptotethya* and *Mycale* spp., respectively (Bergmann and Feeney 2002), are some examples of nucleoside analogs isolated from marine creatures that can be used against SARS-CoV-2.

Transmembrane protease serine 2 (TMPRSS-2) inhibition by MNPs

The SARS-CoV-2 cell entry mechanism strongly influences its pathogenicity and infectivity with support of host proteases. According to recent studies, TMPRSS-2 (Iwata-Yoshikawa et al. 2019) and cathepsin B and L (Simmons et al. 2005) were identified as the major host proteases

for viral cell entry and membrane fusion. The role of TPMRSS-2 in SARS-CoV-2 infection remains obscure. In humans, TMPRSS-2 is vastly expressed in epithelial tissues, including the bronchi, epithelial lining of the upper airways, and lungs (Bugge et al.2009). The similarity in the TMPRSS-2 protein sequence between humans and mice was 78%. Moreover, a previous study on mouse embryos and adults revealed that TMPRSS-2 was expressed in the respiratory tract (bronchi and bronchioles), epithelial lining of the gastrointestinal tract, and urogenital system, but not in the alveolar epithelium (Vaarala et al. 2001). Furthermore, mice with depleted TMPRSS-2 demonstrated no abnormalities in organ histology, function, development, or survival (Kim et al.2006). The in vivo results of a previous study using TMPRSS-2 knockout mice and wild-type mice revealed that TMPRSS-2-depleted mice had less pronounced coronavirus replication in the lungs, especially in bronchioles (Iwata-Yoshikawa et al. 2019). The physiological function of TMPRSS-2 was not 100% revealed. However, the involvement of TMPRSS-2 in sodium current regulation by proteolytic cleavage of the epithelial sodium channel in lung epithelial cells has been described in earlier studies (Donaldson et al. 2002). The coronavirus cell entry mechanism predominantly involves two distinct pathways: entering the cell via either the cell surface (TMPRSS-2) or the endosome (Cathepsin-L). According to previous studies, TMPRSS-2 (serine proteases) facilitates SARS-CoV spread more than cathepsin-L (cysteine protease) (Zhou et al. 2015). Overall, the role of host proteases on the spike proteins is crucial for cell entry. Thus, inhibition of this priming process could be an effective way to regulate infectivity, emphasizing the potential of host proteases as drug targets against SARS-CoV-2. This was further verified by studies conducted with a serine protease inhibitor, camostat mesylate, which partially inhibited TMPRSS-2 and SARS-CoV-2 cell entry. The cell entry mechanism was fully inhibited by the addition of camostat mesylate together with E-64d, a cathepsin B/L inhibitor.

A previous study investigated the inhibitory activities of pseudotheonamide C and D and aeruginosin 98B isolated from the marine sponges *Theonella swinhoei* and *Microcystis aeruginosa*, respectively, on TPMRSS-2 (Nakao et al. 1999) (Ersmark et al. 2008). In addition, both compounds contain a guanidine group that mimics the arginine substrate of the enzyme (Buchanan et al. 2008). This result reveals an interesting factor in serine protease inhibition. Compounds that contain a guanidine group that can mimic the arginine substrate may be potential SARS-CoV-2 cell entry inhibitors. Another study revealed that gallinamide A, a selective inhibitor of human cathepsin-L isolated from marine cyanobacteria (*Schizothrix* spp.), can bind to the active site of this cysteine protease and block its activity (Miller et al. 2014). This would be useful for inhibiting SARS-CoV-2 cell entry.

Glycosaminoglycans (GAGs) on the cell surface inhibition by MNPs

GAGs are a linear polysaccharide family found on the cell surface that comprises repeating disaccharide units containing hexosamine, sulfated galactose residues, or uronic acid. GAGs are involved in several important biological processes, including pathogenesis, immunity, and cellular signaling (Lindahl et al.2015). According to a novel study, the binding kinetic results between both monomeric and trimetric spike proteins of SARS-CoV-2 and GAGs revealed that the GAG binding motif of spike proteins significantly binds with heparin sulfate (HS). According to the results, virions initially land on the surface of airway epithelial cells by binding to HS using a spike protein. The proteoglycans on the cell surface wrap the trimeric spike protein using their long HS chains. This leads to an interaction between the SARS-CoV-2 spike protein and ACE-2 (Kim et al. 2020). Therefore, inhibition of these processes strongly disturbs the entry of SARS-CoV-2 into the cell. The positive charge of the SARS-CoV-2 spike protein preferentially binds with long structures that are heavily sulfated (Kim et al. 2020). Fucoidan, a polysaccharide primarily obtained from brown seaweed, contains significant quantities of L-fucose and sulfate ester groups. These polysaccharides exhibit a vast range of biological activities, including anti-inflammation, immunomodulatory, and anti-oxidant activities (Jayawardena et al. 2022, 2020; Wang et al. 2020). Furthermore, these polysaccharides demonstrated remarkable antiviral potential against various envelope proteins, including herpes simplex, dengue, and respiratory syncytial viruses. The production cost, availability, and low toxicity of fucoidan are additional advantages. Fucose serves as the primary monomeric module in polymers, known as fucoidans. Monomeric monomers are linked together by either alpha-(1–2) or alpha-(1–3). Other potential sugar residues include galactose, mannose, xylose, and glucuronic acid. The polymer also contained acetyl groups. L-Fucopyranosyl residues often have the sulfate component substituted at the C2 or C4 and occasionally at the C3 position (Damonte et al. 2004). Thus, they have the potential to interfere with the interaction between spike protein and host cell receptors by mimicking GAGs. Several studies have verified the antiviral potential of sulfated polysaccharides against SARS-CoV-2 (Jin et al. 2020; Kwon et al. 2020; Song et al. 2020). This was further verified in a study conducted using a polysaccharide series isolated from *Saccharina japonica*. According to the results, sulfated galactofucan and glucuronomannan demonstrated significantly high inhibition, which directly interfered with the interaction between the spike protein and SARS-CoV-2 RBD (Jin et al. 2020). The specific role and significance of GAGs in SARS-CoV-2 cell entry make GAGs a potential drug target for SARS-CoV-2.2

Host cell translational mechanism inhibition by MNPs

Numerous host proteins play central roles in the SARS-CoV-2 life cycle. Some host proteins are essential for viral translation and replication. Viruses are entirely dependent on host translational mechanisms and cell pathways, which are essential for viral replication. Thus, these pathways are considered alternative antiviral approaches (Wong and Damania 2021). The binding of the 43S pre-initiation complex with the 5′ cap on mRNA initiates the translational process, and this complex begins the mRNA scanning from the start codon and recruits the 60S ribosomal subunit. This leads to ribosome assembly and initiates elongation. Viruses exploit host translational mechanisms by mimicking host mRNAs (Jaafar and Kieft 2019). Ribosomal entry of mRNA is blocked by NSP1 of SARS-CoV-2, which prevents its translation. Furthermore, a reporter gene that encodes the 5′ untranslated region (UTR) of SARS-CoV-2 mRNA exhibits a fivefold upregulation of gene expression compared to the host cell 5′ untranslated region (UTR) (Schubert et al. 2020). This revealed that SARS-CoV-2 hijacks the host translational process and depends on it for producing viral proteins. Plitidepsin, a chemical compound isolated from the sea squirt *Aplidium albicans,* which targets eukaryotic translation elongation factor 1a (eEF1A) of the host, has antiviral activity against SARS-CoV-2. Plitidepsin treatment in mice resulted in a significant reduction in viral titer in the lungs compared to remdesivir. Furthermore, the viral nucleocapsid protein expression was also significantly lower in plitidepsin-treated cells than in remdesivir-treated cells, despite the same amount of nucleocapsid sgRNA in both cells. This verified the inhibitory effect of plitidepsin on viral nucleocapsid protein translation (White et al. 2021). The safety profile of plitidepsin has also been verified in multiple cancer clinical trials (Wong and Damania. 2021). These findings suggest that translational inhibitors are promising antiviral drugs against SARS-COV-2.

Future perspectives to inhibit SARS-CoV-2 using MNPs

As mentioned under the "Cell entry mechanism" section, the SARS-CoV-2 cell entry mechanism depends on serine and cysteine proteases and requires spike protein cleavage by PPC. Furin activity and type of PPC are essential for SARS-CoV-2 cell entry, and the furin cleavage site does not exist in other β-coronavirus subtypes. Furin is present in the trans-Golgi network and is activated under acidic conditions. Precursor proteins with a specific PPC motif are cleaved and activated by furin. Sequence alignment of spike protein S1 and S2 sites among diverse coronaviruses demonstrates that the SARS-CoV-2 spike cleavage site contains a specific redundant amino acid sequence "PRRA" that is not expressed in other coronaviruses. This is a furin cleavage site. The higher infectivity of SARS-COV-2 compared to that of SARS-CoV and BAT-CoVRaTG13 is mediated by furin cleavage, and furin inhibition may significantly decrease infectivity (Devi et al. 2022). This hypothesis suggests that furin activity is predominant in the virus infection cycle and could be an effective drug target against SARS-CoV-2. According to previous studies, several furin inhibitors were discovered, such as α1-antitrypsin Portland inhibiting the HIV, D-Arg-based peptides (Anderson et al. 1993), and decanoyl-Arg-Val-Lys-Arg-chloromethylketone. Presently, pure peptides, peptide mimics, and non-peptide compounds are used as furin inhibitors. However, these peptides have numerous obstacles, including degradation by proteases, low stability without additional modifications, opsonization, and agglutination (Bruno et al. 2013). The chloromethyl ketone-derived molecule, dec-RVKR-cmk, is a vastly used furin inhibitor that inhibits catalytic site binding. Chemical modification elevates the inhibitory activity of these compounds, such as the C-terminal modification of dek-RVKS-cmk with dicarboxylated arginine mimetics (Imran et al. 2019). Recently published data revealed that a synthetic peptide mimetic named MI-1851 inhibits the use of furin to regulate SARS-CoV-2 infection. Furthermore, MI-1851 combined with the TMPRSS-2 inhibitor T-ex5 PPMO demonstrated remarkable SARS-CoV-2 inhibition (Bestle et al. 2020). Based on these results, several important factors regarding furin behavior were identified, such as the amino acid side chains in the active site that play a pivotal role in cleavage. An Arg residue in the P1 and P2 positions, at least two residues, either Lys or Arg in the P4 and P6 positions, and the P1 position should be free from hydrophobic or aliphatic amino acids. These facts provide insights into the design of inhibitors against furin, for example, α1-PDX/hf (Dufour et al. 2001; Jean et al. 1998). Marine organisms, including vertebrates and invertebrates, exhibit a significant diversity. The peptides or proteins isolated from them also demonstrated highly diverse biological activities depending on the organism and body part. Furthermore, peptides derived from marine organisms are more stable against gastrointestinal proteases than peptides from other sources (Pavlicevic et al. 2020). Thus, peptides isolated from marine organisms have elevated potential for use against SARS-CoV-2.

SARS-CoV-2 is associated with immune-mediated pathology via inappropriately regulated cytokine responses in the lungs and other tissues (Merad and Martin 2020). The activation mechanism and upstream signaling pathways of this hyperactive cytokine response are yet to be completely elucidated. This hyperinflammatory response is known as a cytokine storm and is responsible for severe complications and death. The MYD88 adaptor protein plays a crucial role

in TLR-mediated downstream signaling pathways for inflammatory cytokines production (Fig. 3B) (Sariol and Perlman 2021). A novel study revealed the involvement of TLR-4 in this hyperinflammatory condition. Therefore, TLR-4 modulators can successfully control COVID-19 complications, revealing their potential as drug targets against SARS-CoV-2 (Kaushik et al. 2021). The anti-inflammatory activity of secondary metabolites isolated from marine organisms has been vastly studied (Mayer et al. 2011; Nagahawatta et al. 2022a, b, c). Many compounds and peptides isolated from marine organisms attenuate TLR-mediated NF-κB and MAPK signaling pathways, which inhibit the production of inflammatory mediators, such as iNOS and COX-2, and inflammatory cytokines, such as TNF-α, IL-6, and IL-1β (Gonzalez et al. 2013; Ko et al. 2016; Sanjeewa et al. 2020). As reported by recent studies, Eastern Asian countries that have commonly consumed seaweed-rich diets demonstrated fewer disasters caused by SARS-CoV-2 than Western countries (Pereira and Critchley 2020; Tamama 2020). Thus, compounds isolated from Phaeophyta, such as polyphenolic compounds, can be a great source for regulating the cytokine storm caused by SARS-CoV-2 infection.

SR-B1 is a high-density lipoprotein (HDL) receptor located on the cell surface that is responsible for the selective uptake of cholesterol esterase and other lipid components (Shen et al. 2018a, b). This transportation system can be found in isolated hepatocytes, adipocytes, fibroblasts, macrophages, ovarian cells, testicular Leydig cells, and adrenal cells (Shen et al. 2018a, b). Furthermore, SR-B1 is expressed in alveolar II cells and is responsible for the uptake of vitamin E preferentially from HDL (Kaushik et al. 2021). According to a novel study, the SARS-CoV-2 spike protein comprises six putative amino acid consensus motifs responsible for cholesterol recognition. Furthermore, the results of this study revealed that SARS-CoV-2 S1 binds to cholesterol and interacts with HDL or its components, but SARS-CoV-2 S2 does not. One motif was present in the spike protein RBD. SR-B1 cannot directly bind to the SARS-CoV-2 spike protein, but HDL attachment to the spike protein and SARS-CoV-2 entry are both significantly enhanced by SR-B1 expression. Moreover, SR-B1 co-expression with ACE-2 significantly increases the susceptibility of cells to SARS-CoV-2. These findings revealed that SR-B1 facilitates cellular attachment of SARS-CoV-2. This observation further verified that SR-B1 silencing inhibits SARS-CoV-2 entry (Wei et al. 2020). SR-B1 acts as a cofactor for SARS-CoV-2 via a cell entry mechanism. This emphasizes the potential of SR-B1 as a therapeutic target for SARS-CoV-2 infection. As reported by Wen-Jun et al. (2018), some structural characteristics are crucial for its functionality. For typical receptor oligomerization and lipid transportation of SR-B1, the N-terminal transmembrane glycine (Gly) dimerization motif (Gly15, Gly18, and GLY25l) is essential (Shen et al. 2018a, b). Dante et al. provided a structural framework for this protein family through the crystal structure of LIMP-2 which is homologous to SR-B1 (Neculai et al. 2013). Nearly seven cysteine residues are conserved in mammals, including mice, hamsters, pigs, cows, and humans. Furthermore, four SR-B1 cysteines (Cys280, Cys321, Cys323, and Cys324) participate in binding to HDL (Shen et al. 2018a, b). These results provide insights into the development of inhibitors using MNPs through in silico evaluations.

Many researchers have discovered or are attempting to discover drug agents against diverse therapeutic targets for SARS-CoV-2. Herein, we considered the potential of a drug agent with a multi-target approach against different SARS-CoV-2 drug targets. If any drug agent has this multi-target potential, it will be able to inhibit SARS-CoV-2 by multiple approaches. Based on this hypothesis, we recently conducted a study that developed inhibitors against two drug targets, including $3CL^{pro}$ and PL^{pro} of SARS-CoV-2. In this study, authors evaluated 16 compounds isolated from marine seaweeds using molecular docking and conducted further evaluations. According to the study results, four polyphenolic compounds isolated from brown seaweeds were identified: ishophloroglucin A, diphlorethohydroxycarmalol, dieckol, and eckmaxol, which significantly inhibit $3CL^{pro}$ and PL^{pro} proteolytic activity and have the potential to develop into inhibitors with a multi-target approach against SARS-CoV-2 (Nagahawatta et al. 2022a, b, c, d). We are currently observing the inhibitory potential of these compounds against the interaction between SARS-CoV-2 ACE-2 and spike protein.

The results of these studies have revealed the potential of these compounds as therapeutic SARS-CoV-2 inhibitors. The natural marine compounds, structures, source of origin, and method of inhibition are summarized in Supplementary Table 1.

Conclusion

The coronavirus disease (COVID-19) pandemic has caused major global health concerns. Communities and scientists have a social and ethical responsibility to work collectively to defeat SARS-CoV-2. Vaccination is the major tool used to combat SARS-CoV-2 infection. Furthermore, several studies have been conducted to repurpose FDA-approved drugs. The discussion on the limitations of these attempts highlights the need for alternative therapeutic drugs against SARS-CoV-2. The authors described the structural and functional relationships in complex infections and replication of SARS-CoV-2 and revealed the potential of MNPs as inhibitors of diverse drug targets. Moreover, this analysis identified the potential of MNPs in developing promising therapeutic drugs against

SARS-CoV-2 and offered extensive information to researchers for future COVID-19-related studies.

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Data availability The data that support the findings of this study are included in this published article (and its supplementary information files).

Declarations

Conflict of interest The authors declare no conflict of interest. Author You-Jin Jeon is one of the Editorial Board Members, but he was not involved in the journal's review of, or decision related to, this manuscript.

Animal and human rights statement This article does not contain any studies with human participants or animals performed by the authors.

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