Marine Sponge is a Promising Natural Source of Anti-SARS-CoV-2 Scaffold

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INTRODUCTION

The current pandemic caused by SARS-CoV2 and named COVID-19 urgent the need for novel lead antiviral drugs. Recently, United States Food and Drug Administration (FDA) approved the use of remdesivir as anti-SARS-CoV-2. Remdesivir is a natural product-inspired nucleoside analogue with significant broad-spectrum antiviral activity. Nucleosides analogues from marine sponge including spongouridine and spongothymidine have been used as lead for the evolutionary synthesis of various antiviral drugs such as vidarabine and cytarabine. Furthermore, the marine sponge is a rich source of compounds with unique activities. Marine sponge produces classes of compounds that can inhibit the viral cysteine protease (Mpro) such as esculetin and ilimaquinone and human serine protease (TMPRSS2) such as pseudotheonamide C and D and aeruginosin 98B. Additionally, sponge-derived compounds such as dihydrogracilin A and avarol showed immunomodulatory activity that can target the cytokines storm. Here, we reviewed the potential use of sponge-derived compounds as promising therapeutics against SARS-CoV-2. Despite the reported antiviral activity of isolated marine metabolites, structural modifications showed the importance in targeting and efficacy. On that basis, we are proposing a novel structure with bifunctional scaffolds and dual pharmacophores that can be superiorly employed in SARS-CoV-2 infection.

Keywords: COVID-19, SARS-CoV-2, marine sponge, nucleoside analogues, MPRO, immunomodulators

The current outbreak caused by the novel coronavirus (SARS-CoV-2) and designated COVID-19 by the World Health Organization (WHO), spread aggressively worldwide (Li et al., 2020). As of today, there is no safe and effective drug available for SARS-CoV-2 and the efficacy of available antiviral drugs is still controversial. Therefore, there is an urgent need for the design and development of novel treatment and therapeutic strategies to combat SARS-CoV-2 and possibly other emergent future viruses. Recently, remdesivir was approved by FDA as an anti-SARS-CoV-2. The anti-SARS-CoV-2 activity of remdesivir was proven following a randomized study at ten hospitals in Hubei, China (Wang et al., 2020). Patients receiving remdesivir showed clinical improvement when compared to placebo (Simonis et al., 2021). Remdesivir is a prodrug that is once entered the cell converted to a triphosphate nucleoside analogue with significant inhibition activity against viral RNA-dependent RNA polymerase (RdRp) (Eastman et al., 2020). Remdesivir was originally developed by Gilead Sciences in collaboration with
the United States. Centers for Disease Control and Prevention (CDC) and the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) (Eastman et al., 2020). Remdesivir is a nucleoside analogue, a class of drugs, that was only developed after being found in sea sponges. Sponges are known for the unusual nucleoside properties (Laffoley et al., 2020). FDA has also approved ocean-derived drugs for HIV, herpes, and now for COVID-19. Although over 34,000 marine natural products have been discovered with great potential to improve human life and health, this represents only 3% of the ocean’s natural sources (Laffoley et al., 2020). Therefore, the essential role of ocean-derived drugs as anti-SARS-CoV-2 are highlighted.

FIGURE 1 | Nucleotide analogues inhibitors (NIs). (A) Development of the first NIs. (B) Nucleotides analogues as potent antiviral against SARS-CoV-2.
### TABLE 1 | Nucleotides analogues as potent antiviral against SARS-CoV-2.

| NI                  | Nucleoside analogue | Modified sugar         | Antiviral activity                                                                                                           | Mechanism of action                                                                                                           | IC_{50}  |
|---------------------|---------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------|
| Ribavirin           | Guanosine analogue  | D-ribofuranosyl        | Broad-spectrum antiviral activity against RNA viruses                                                                     | Inhibition of viral RNA synthesis (Khalili et al., 2020)                                                                       | 109.5 µM|
|                     |                     |                        | Ribavirin used in combination with interferon in the treatment of COVID-19                                                   | Triphosphate leads to lethal mutagenesis                                                                                     |         |
|                     |                     |                        |                                                                           | Inhibits RdRp (Wang et al., 2021)                                                                                            | >20 µM  |
| Sofosbuvir          | Uridine analogue    | 2'-deoxy-2'-a-fluoro-β-C-methyl modified sugar | Antiviral activity against coronavirus and HIV.                                                                           | Inhibits SARS-CoV2 RdRp enzyme in vitro (Wang et al., 2021)                                                                | 7.8 µM  |
| 7-Deaza-7-fluoropurine derivatives | Purine analogue | Methyl ribose sugar | Inhibits SARS-CoV2 at low concentration                                                                                 | Inhibits SARS-CoV-2 replication                                                                                             | 9.2 µM  |
| 2'-C-Methylytidine  | Cytidine analogue   | Methyl ribose sugar    | In vivo hampered SARS-CoV2 replication in sub-micromolar concentration with no toxicity on vero cell (Zandi et al., 2020) | Inhibits SARS-CoV-2 replication (Jena, 2020)                                                                                |         |
| Favipiravir          | Guanine analogue    | Ribofuranosyl sugar    | In vivo antiviral activity against SARS-CoV-2, FPV, influenza A, B, C viruses and Ebola                                       | Inhibits RdRp (Shannon et al., 2020b)                                                                                         | 61.9 µM |
| Galidesivir         | Adenosine analogue  | 5-(hydroxymethyl)-pyrrolidin-3,4-diol | Antiviral against wide array of RNA viruses                                                                               | RNA chain terminator, thus inhibits RdRp (Wang et al., 2021)                                                                | 57.7 µM |
| BCX4430             |                     |                        |                                                                           |                                                                          |         |
| Gemcitabine         | Cytidine analogue   | The first nucleoside with a geminal fluoro-substituent sugar (Pankiewicz, 2000)                                             | Broad spectrum antiviral drug                                                                                                 | Inhibits pyrimidine synthesis (Momattin et al., 2019)                                                                         | 1.24 µM |
|                     |                     |                        |                                                                           |                                                                          |         |
| 6-Azauridine        | Uridine analogue    | Ribose sugar           | Antiviral drug                                                                                                              | Inhibits pyrimidine de novo synthesis (Iwu et al., 2020)                                                                    | 0.38 µg/ml|
|                     |                     |                        |                                                                           | Inhibits inosine and guanine synthesis (Momattin et al., 2020)                                                             | 3.5 µg/ml|
|                     |                     |                        |                                                                           | RNA mutagenesis                                                                                                             | 0.3 µg/ml|
|                     |                     |                        |                                                                           | Inhibits RdRp (Wang et al., 2021)                                                                                            |         |
| Mizonbine           | Imidazole analogue  | D-ribofuranosy sugar   | Antiviral drug                                                                                                              | Inhibits RdRp of SARS-CoV-2 (Sheahan et al., 2020)                                                                           |         |
| NHC                 | Cytidine analogue   | Ribose sugar           | Antimicrobial                                                                                                               | Decreases the viral load and improves the pulmonary function (Garcia et al., 2020)                                         |         |
| EIDD-2801           | Cytidine analogue   | Ribose modified ester  | Potential treatment for COVID 19 in phase III trial (Sheahan et al., 2020)                                                   | Inhibits RdRp of SARS-CoV-2 (Sheahan et al., 2020)                                                                           |         |
| Remdesivir          | Adenosine analogue  | Cyano-modified sugar   | Broad-spectrum antiviral against different virus families                                                                 | Chain terminator                                                                                                             | 1.0 µM  |
|                     |                     |                        |                                                                           | Inhibits replication of SARS-CoV-2 (Gordon et al., 2020)                                                                    |         |
|                     |                     |                        |                                                                           | Inhibits RdRp (Brown et al., 2019)                                                                                           |         |

**MARINE SPONGE AS SOURCE OF NUCLEOSIDES ANALOGUES INHIBITORS**

Nucleosides are the building block of nucleic acid, which consist of nucleobases linked to sugar moiety (Seley-Radtke and Yates, 2018). Nucleosides are involved in vital biological activities including the formation of nucleotides (Seley-Radtke and Yates, 2018). A variety of nucleosides analogues with unique chemical structures was isolated from marine sponge and showed significant antiviral activities (Anjum et al., 2016). The isolated nucleosides analogues were incorporated for the design and development of antiviral drugs following structural modifications in the sugar moiety and/ or the nucleobase (Chien et al., 2020). Initially, nucleosides analogues such as spongouridine and spongothermydine, isolated from Cryptotethya sponge, were investigated for antiviral activity (Bergmann and Feeney, 1951). Replacement of ribose sugar by arabinose paved the basic root for the development of FDA-approved vidarabine (ara-A) and cytarabine (ara-C) (Figure 1).

Nucleoside analogues were privileged as scaffold for the design and development of nucleotide (Table 1; Figure 1) and nucleoside analogues inhibitors (NIs) (Supplementary Figure S1; Supplementary Table S1). Nucleosides analogues were employed in the treatment of viral infections including in particular coronavirus (Pruittsers and Denison, 2019). NIs are known as broad-spectrum inhibitors of RdRp (Shannon et al., 2020a). RdRp showed high...
structural conservation among coronaviruses Aftab et al. (2020), thus considered an attractive target for the development of various antiviral drugs (Table 1; Figure 1; Supplementary Table S1; Supplementary Figure S1). Mycalisine A, and B are nucleosides analogues isolated from the marine sponge Mycale sp. 1985 and employed as scaffold for the development of NIs following structure modification by the inclusion of CN group (Kato et al., 1985; Bhakuni and Rawat, 2005). Mycalisine A inspired the synthesis of remdesivir.

Remdesivir, a nucleotide analogue with 1-ribose and CN substitution, showed interesting antiviral activity by exhibiting dual inhibition activity against RdRp and exonuclease proteins (Shannon et al., 2020a; Zhang et al., 2020a). In addition, 2-methyl cytidine and EIDD-2801, modified cytidine analogues Zandi et al. (2020), inhibited SARS-CoV-2 replication Jena (2020), Sheahan et al. (2020) with no toxicity on Vero cells (Yosief et al., 1998). Furthermore, computational modelling of ilimaquinone Surti et al. (2020) and its adenosine analogues, asmarine B (Kim et al., 2009), showed potential inhibition activity against SARS-CoV-2 (Božič et al., 2010).

The data highlighted that metabolites derived from marine sponge can be promising RdRp inhibitors following minor
TABLE 2 | Summary of compounds isolated from different marine sponges and showed immunomodulatory activity.

| Compound                     | Marine sponge                  | Immunomodulation                  | IC_{50}        | Potential Covid-19 management stage | Ref |
|------------------------------|--------------------------------|-----------------------------------|---------------|--------------------------------------|-----|
| Avarol                       | Disidea avara                  | Humoral immunostimulant           | Early infection stage | Ferández et al. (1994)             |
| Lectin                       | Pellina semitubulosa           | IL-1 and IL-2 stimulation         | Early infection stage | Engel et al. (1992)                |
| 4-α-Methyl-5 α-chol-8-en-3 β-ol and 4,5-dibromo-2-pyromelic acid | Agelas flabelliformis           | Immunosuppressive activity        | Late infection stage | Gunasekera et al. (1989)            |
| Octa-peptide hynematin 1     | Hymeniadcion sp.               | Immunosuppressive activity        | Late infection stage | Pettit et al. (1990)               |
| Contignasterol               | Petrosia contignusta           | Histamine release inhibitor and IL-6 inhibitor | 0.8 ± 0.32 μM | Late infection stage | Takei et al. (1994)              |
| Puupehedione                 | Verongia, and Hyrtios sp.      | Modulate the immune response of T-cells | 3 μg/ml | Late infection stage | Hamann et al. (1993), Nasu et al. (1998) |
| Eryloside E                  | Erylus goffrilleri             | Immunosuppressive activity        | 1.3 μg/ml     | Late infection stage | Gualitia et al. (1994)            |
| Pateamine A                  | Mycale sp.                     | IL-2 inhibitor                    | Late infection stage | Fattorusso and Tagliatela-Scatati (2000) |
| Taurodispacamide A           | Agelas oroides                 | IL-2 inhibitor                    | Late infection stage | Fattorusso and Tagliatela-Scatati (2000) |
| 3-Polyoxygenated sterols     | Disidea sp.                    | IL-8 inhibitor                    | Late infection stage | de Almeida Leone et al. (2000)     |
| Iso-iantheran A              | Ianthella quadrangulata        | Immunomodulator by activating P2Y11 receptor | 1.29 μM | Late infection stage | Greve et al. (2007)              |
| Sesquiterpene compounds      | Acremonium sp.                 | Inhibition of pro-inflammatory mediators (IL-6, NO, and TNF-α) | Late infection stage | Zhang et al. (2009)               |
| Bile acid derivatives        | Marine sponge-associated bacterium Psychrobacter sp. | IL-6 inhibitor | Late infection stage | Li et al. (2009)                  |
| Terpene dihydrogracilin A    | Dendylla membranosa            | IL-6 and 10 inhibitors           | Late infection stage | Ciaglia et al. (2017)             |

structural modifications. These modifications can include the change in the sugar moiety, and the addition of substituents such as cyano, fluoride, and methyl groups. Interestingly, the inclusion of the side chain with cyano group in the remdesivir enhanced the compound bioavailability and overcame the resistance mechanism by the viral exonuclease. Furthermore, modification of ilimaquinone by the inclusion of adenosine enhanced the activity of the original natural compound100-fold. These data indicate that modification in compounds obtained from the marine sponge is necessary for focused targeting, enhancement of bioavailability and activity, and overcome resistance mechanism, despite the potential activity of the original compounds. Importantly, compounds with superior dual activity are those sharing nucleotide or nucleoside along with sugar as scaffold such as avinosol (Díaz-Marrero et al., 2006).

MARINE SPONGE-DERIVED DRUGS AGAINST OTHER VITAL TARGETS IN SARS-COV-2 FOR POSSIBLE MULTI-TARGETING ACTIVITY

Marine Sponge as Potential Source of M^{pro} Inhibitors

M^{pro} is a critical protease required during the viral replication (Du et al., 2004). Consequently, its inhibition can stop the production of viral particles (Grum-Tokars et al., 2008). Further, M^{pro} showed no genetics homology with the human genome making it an attractive target in the development of safer antiviral drugs (Abd El-Mordy et al., 2020).

Based on several computational simulation studies in addition to molecular docking and molecular dynamics studies, variable natural marine compounds were suggested as inhibitors to SARS-CoV-2 M^{pro}. Figure 2A summarized different classes of compounds derived from the marine sponge with potential M^{pro} inhibition activity (Golda and Pyrc, 2020).

Coumarine derivatives such as esculetin-4-carboxylic acid methyl ester and esculetin-4-carboxylic acid ethyl ester isolated from the marine sponge, Axinella cf. corrugate, showed effective inhibition activity to SARS-coronavirus M^{pro} (Lira et al., 2007) at IC_{50} = 46 μM (Coelho et al., 2020). Molecular docking also indicated their effective interaction with SARS-CoV-2 M^{pro} (Vijayaraj et al., 2020). Molecular docking study also showed the potential interaction of naphthalene derivative, hamigeran-b, isolated from the marine sponge, Hamigera tarangaensis, with the M^{pro} of SARS-CoV and SARS-CoV-2 (Vijayaraj et al., 2020). Similarly, chymial alcohol (1-O-hexadecylglycerol), isolated from Desmapsamma anchorata sponge (Quijano et al., 1994), showed potential inhibition activity to SARS-CoV-2 by binding to M^{pro} (Khan et al., 2020).

Ilimaquinone is a bioactive sesquiterpene isolated from the Hippospongia metachromia sponge (Surti et al., 2020).
Computational modelling indicated the potential inhibitory activity of the compound against SARS-CoV-2 proteases (Surti et al., 2020). Virtual screening and ADMET studies indicated that terpenoid T3, isolated from the marine sponge, *Cacospongia mycofijiensis*, can exhibit potential inhibition activity against SARS CoV-2 Mpro (Sepay et al., 2020).

Several classes of compounds derived from marine sponge were proposed as potential SARS-CoV-2 Mpro inhibitors based on computational analysis; however, these data need to be further validated by both enzymatic activity and in vitro assays. On the other hand, terpenoid moiety is shared between most marine compounds proposed with Mpro inhibition activity including T3, ilimaquinone, and hamigeran-b (Figure 2A), indicating its potential involvement in the inhibition activity of Mpro.

**Marine Sponge as Source of Serine Protease Inhibitors**

TMPRSS2 is a human serine protease enzyme used by the virus for its activation and cell entry. Pseudotheonamide C and D, isolated from the *Theonella swinhoei* sponge, showed potent inhibitory activity against serine protease (Figure 2B) (Nakao et al., 1999). Similarly, aeruginosin 98B, isolated from the marine sponge *Microcystis aeruginosa*, showed inhibitory activity against serine protease (Ersmark et al., 2008). Pseudotheonamide C and D and aeruginosin 98B contain guanidino group that mimics the arginine substrate of the enzyme (Figure 2B) (Buchanan et al., 2008).

Structure-based modelling indicated that both pseudotheonamide and aeruginosin may also show potent inhibitory activity against SARS-CoV-2 Mpro (Gentile et al., 2020). However, more biological activity studies are still required. This is considered bifunctional activity since they inhibit both cysteine (Mpro) and serine (TMPRSS2) proteases.

The aforementioned data can be of great benefit to fight against SARS-CoV-2 once the biological activity of the compounds is validated.

**TARGETING THE CYTOKINE STORM BY DRUGS DERIVED FROM MARINE SPONGE: IMMUNOMODULATORS**

SARS-CoV-2 infection stimulates the host immune responses in two phases, the initial phase during the viral invasion, and the severe stage when a massive cytokine and chemokine storm takes place including the overproduction of IL-1, IL-6, IL-8, IL-17, CCL-2, TNF-α, G-CSF, IP-10, MCP-1, and MIP and exhaustion of T cells. Therefore, strategies to boost the immune system at the earlier stage (mild condition) and those to modulate or suppress the cytokine storm at a later stage (severe condition) are required to manage SARS-CoV-2 infection (Niloufar et al., 2020).

An enormous array of molecules isolated from marine sponge showed the ability to boost innate immunity at the early infection stage or to control the cytokine storm and the excessive inflammation at the late severe infection stage (Table 2; Supplementary Figure S2). Avarol produced from the *Disidea avara* sponge was reported to boost the humoral immune response upon exposure to viral infection (Müller et al., 1985). Lectin is an immuno-stimulant that was isolated from the marine sponge *Pellina semitubulosa* (Engel et al., 1992). Lectin has a hexamer polypeptide chain covalently linked via a disulfide bond that can enhance the production of IL-1 and IL-2 at 0.3 and 10.0 pg/ml.
Identification of immunosuppressive molecules from marine sponge was initially reported in the 1980s when two compounds, 4-α-methyl-α-cisolest-8-en-3 β-ol and 4,5-dibromo-2-pyryolic acid were isolated from Agelas flabelliformis Carter (Agelasidae) (Gunasekera et al., 1989). Octa-peptide hynenistatin I, isolated from Hymeniacidon sp. Sponge, demonstrated humoral and cellular immunosuppressive activity (Pettit et al., 1990). Contignasterol, produced from Petrosia contignata sponge, is a histamine-release inhibitor, which is more likely downregulating the production of IL-6 (Takie et al., 1994; Han, 2020). Puupehedione is a sesquiterpene quinone that has been isolated from several marine sponges such as Verongida sp. and Hyrtios sp. and showed the ability to modulate the immune response of T-cells (Hamann et al., 1993; Nasu et al., 1995).

Eryloside E, isolated from Erylus goffrilleri sponge, demonstrated specific immunosuppressive activity at IC50 1.3 μg/ml (Gulavita et al., 1994). Pateamine A was isolated from Mycale sp. and showed selective inhibition activity on the production of IL-2 (Romo et al., 1998; Costela-Ruiz et al., 2020). Similarly, the pyrrole-imidazole alkaloid taurodispacamide A, isolated from the marine sponge Agelas oroides, showed inhibitory activity to IL-2 production (Fattorusso and Taglialatela-Scafati, 2000). Several immunosuppressive compounds such as 3-polyoxygenated sterol were isolated from the marine sponge Disidea sp. (Supplementary Figure S3) de Almeida Leone et al. (2000) that can block the activity of IL-8, a cytokine responsible for the development of acute respiratory distress syndrome (Tang et al., 2020).

Greve et al. (2007) showed that the Ianthella quadrangulata sponge produces the polyketide iso-iantheran A, which is capable to activate the P2Y11 receptor Greve et al. (2007), a regulator of human immune responses (Ledderose et al., 2020). Terpene dihydrogracilin is a potent IL-6 inhibitor that was isolated from the sponge Dendrilla membranosa sponge (Ciaglia et al., 2017).

The data described here indicated that several metabolites derived from marine sponge showed promising immunomodulatory activity. Some of these compounds shared similar structure including the terpenoid and/or the sugar moieties (Supplementary Figure S2).

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**PROPOSED SPONGE-BASED DESIGN OF NOVEL ANTI-SARS-COV2 STRUCTURE WITH MULTI-TARGETING ACTIVITY**

The aforementioned classes of sponge-derived compounds provided an insight into pharmacophores with shared structures that can be employed in the development of novel scaffold with potent antiviral activity and improved efficacy against SARS-CoV-2. A promising strategy as indicated in Figure 3 is by designing NIs that target both SARS-CoV-2 RdRp and exonuclease (Pruijssers and Denison, 2019) as shown in remdesivir, in addition to the inclusion of other pharmacophores that target other viral proteins (Khatari et al., 2020). In that respect, marine nucleosides analogues and peptidomimetics can inhibit the viral RdRp, and Mpro, respectively, while guanine derivatives can inhibit the human TMPRSS2 (Buchanan et al., 2008). Furthermore, the addition of terpenoid moiety can be of great benefit as an immunomodulator. On that basis, we are proposing a conjugated structure as indicated in Figure 3 with bifunctional scaffolds and pharmacophore features with the ability to target essential SARS-CoV-2 proteins.

**AUTHOR CONTRIBUTIONS**

All authors involved in developing the idea, designing the manuscript, writing the draft and final version. SS supervise the data collection and writing process.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.666664/full#supplementary-material

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