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REVIEW ARTICLE

Promising Marine Natural Products for Tackling Viral Outbreaks: A Focus on Possible Targets and Structure-Activity Relationship

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Abstract: Recently, people worldwide have experienced several outbreaks caused by viruses that have attracted much interest globally, such as HIV, Zika, Ebola, and the one being faced, SARS-CoV-2 viruses. Unfortunately, the availability of drugs giving satisfying outcomes in curing those diseases is limited. Therefore, it is necessary to dig deeper to provide compounds that can tackle the causative viruses. Meanwhile, the efforts to explore marine natural products have been gaining great interest as the products have consistently shown several promising biological activities, including antiviral activity. This review summarizes some products extracted from marine organisms, such as seaweeds, seagrasses, sponges, and marine bacteria, reported in recent years to have potential antiviral activities tested through several methods. The mechanisms by which those compounds exert their antiviral effects are also described here, with several main mechanisms closely associated with the ability of the products to block the entry of the viruses into the host cells, inhibiting replication or transcription of the viral genetic material, and disturbing the assembly of viral components. In addition, the structure-activity relationship of the compounds is also highlighted by focusing on six groups of marine compounds, namely sulfated polysaccharides, phlorotannins, terpenoids, lectins, alkaloids, and flavonoids. In conclusion, due to their uniqueness compared to substances extracted from terrestrial sources, marine organisms provide abundant products having promising activities as antiviral agents that can be explored to tackle virus-caused outbreaks.

Keywords: HIV, Zika virus, Ebola virus, SARS-CoV-2, marine natural products, mechanism of action, structure-activity relationship.

1. INTRODUCTION

As the largest habitat on earth with approximately 70% coverage of the earth's surface, oceans are where a large number and variety of marine organisms live and interact with their environment. Given that the marine environment is different from the terrestrial condition, it is plausible that marine organisms develop various unique ways to support their adaption in such an environment [1]. At this point, the secretion of secondary metabolites is one of the critical mechanisms marine organisms develop with either supportive or protective functions.

The efforts for exploring the marine environment for the sake of the discovery of new drug candidates are increasing continuously [2, 3]. This is driven by the fact that several diseases being faced by human beings have not been cured yet because of the lack of drugs giving satisfying outcomes. Many of those diseases are related to viral infections. Several infections caused by viruses, such as human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), cannot be eradicated yet as to date since no drug of choice with better efficacy and less toxicity has been reported. This condition leads experts and related parties to intensively explore and utilize metabolites

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isolated from marine organisms to provide alternatives for curing viral-related diseases [4, 5].

However, many obstacles limit the success of bringing a marine-derived compound into the market. Consequently, to date, only thirteen marine-derived drugs have been marketed after getting approval either from Food and Drug Administration (FDA) or European Medicines Agency (EMA) [4]. Of those, only one drug, vidarabine, is used to treat viral infection caused by herpes simplex and varicella zoster viruses [4]. Recently, thirty-two compounds (either of the marine origin or as derivatives of a marine compound) have been underway in clinical trials (twenty in phase I, eight in phase II, and four compounds in phase III trials). However, none is indicated for treating viral-related infections [4].

Since the beginning of this century, several viruses have become the causative agents responsible for the viral outbreak. After the outbreak of SARS-CoV in 2002, followed by Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, some viral outbreaks remain. In 2013, a viral hemorrhagic disease caused by the Ebola virus (EBOV) affected many countries in the western part of Africa [6]. Zika virus (ZIKV) triggered another viral outbreak which was first recorded in Brazil and spread to other parts of the globe during 2015-2016 [7]. From 2019 until now, people worldwide have been facing a big viral outbreak caused by SARS-CoV-2 with its variants of concern. Data released by World Health Organization (WHO) on 14 January 2022 stated that more than 5 million people had died globally after contracting coronavirus disease 2019 (COVID-19) [8]. To make it worse, the risk of COVID-19 reinfection [9] and the emergence of omicron, a newly reported variant of SARS-CoV-2, at the end of November 2021 [10] have put global citizens under constant threat.

To date, those aforementioned outbreaks still threaten the world since no effective drug has been developed to eradicate the causative viruses. Moreover, other outbreaks caused by emerging and/or reemerging viruses might also happen. Meanwhile, the drugs developed have some limitations in their efficacy or availability. Based on these conditions, the exploration of marine resources for new antiviral drugs is important.

This review summarizes several metabolites isolated from marine organisms, such as algae, bacteria, fungi, sponges, seaweeds, seagrasses, *etc*., having activity as potential antiviral agents. The antiviral activity of those metabolites is determined by several methods, *e.g*., preclinical (*in vivo*, *in vitro*, and *in silico*) and clinical trials. Due to the space limitation, we only focus on four viruses associated with the recent outbreaks, *i.e*., HIV, ZIKV, EBOV, and SARS-CoV-2. First, we describe briefly the pathophysiological aspects of the infections caused by those viruses. Then, we list marine natural products potentially used as antiviral agents for tackling infections. We select some metabolites of choice from the list to be explained deeper regarding their mechanism of action, chemical structure, and structure-activity relationship (SAR).

2. PATHOPHYSIOLOGY

2.1. HIV Infection

Structurally, HIV is an enveloped lentivirus with two single positive strands of RNA. Although several genes have been successfully identified from the HIV genome, three major HIV genes, *gag*, *pol*, and *env*, seem to be the critical genes supporting viral replication and infectivity. The structural proteins (capsid, matrix, nucleocapsid) are encoded by a *gag*, while *pol* and *env* encode viral enzymes (integrase, protease, reverse transcriptase) and viral glycoproteins (gp120 and gp41), respectively [11]. HIV entry and membrane fusion are facilitated by glycoproteins, while the proteins encoded by *gag* and *pol* genes play pivotal roles in viral replication, assembly, budding, and maturation processes [11].

In addition to sexual transmission, HIV can also be transmitted through placental, gastrointestinal, and bloodstream routes [12]. Following exposure, HIV begins the entry process to several cell targets, *i.e*., CD4+ T helper cells, macrophages, and dendritic cells, where the former is the main target of HIV. Specifically, CD4+ cells are a critical component of the adaptive immune system and regulate both humoral and cellular immune responses. Thus, HIV infection can cause the failure of the body to produce an adequate defense mechanism system which is further associated with the emergence of opportunistic infections [11].

The entry process of HIV is initiated by gp120 binding to the CD4 receptor, which is subsequently followed by an interaction between gp120 and the chemokine coreceptors, either CCR5 or CXCR4 [13]. While CCR5 can be found in both macrophages and T cells, CXCR4 is mainly expressed by the latter [14]. Based on the interaction between gp120 and the coreceptors, two strains of HIV have been recognized, the CCR5 (R5) and CXCR4 (X4) strains. While the R5 strain (also known as the M-tropic strain) prefers to occupy CCR5 to assist the entry, the X4 strain (T-tropic strain) tends to interact with CXCR4 as its coreceptor [15]. In addition to the key contributions of CD4 as the primary receptor and coreceptors, some other components also play specific roles in facilitating HIV entry. For example, CD26 (dipeptidyl peptidase IV) can act as a cofactor for assisting the entry of HIV because of its protease activity at gp120 [16]. Overall, the dependency of HIV on CD4 coreceptors and cofactors has a plausible consequence in terms of discovering and developing anti-HIV drugs targeting these components.

Moreover, the interaction between gp120 and the corresponding coreceptors is followed by conformational changes, which are critical for supporting gp41 in initiating viral membrane fusion with the host cellular membrane [11]. Finally, the virus finds a way to release its contents into the target cell. Several drugs working as HIV fusion inhibitors have been developed, and most of those drugs block gp41 action [13].

As the contents of HIV, including single-stranded RNA, have reached the cytosol, reverse transcription processes

begin by transcribing the viral RNA into double-stranded DNA catalyzed by the reverse transcriptase enzyme, which is mostly expressed in retroviruses. Following this step, the viral DNA is transported into the nucleus and needs to be integrated into the host genome. The process of integration is catalyzed by an enzyme called integrase. It is noteworthy that the insertion of viral DNA into the host genes, referred to as HIV provirus, could bring problems in eradicating the virus because of the ability of the virus to evade the surveillance of the immune system [11]. Recently, no satisfying approach has been used to address the issue of HIV provirus latency. However, Zhu and co-workers reported the CRISPR/Cas9 system's potential role in deactivating the provirus's latency after experimenting with the latently infected Jurkat cells [17]. This finding is in line with other studies utilizing different models, *i.e*., HeLa and 293 T cells [18, 19].

The transcription, translation, and assembly phases subsequently occur following the integration phase. Transcription is a process where the integrated proviral DNA is transcribed into viral RNAs by utilizing the host RNA polymerase II enzyme [20]. Using the host machinery system, the products of transcription of proviral DNA experience spliced, transported to the cytoplasm, and translated [20]. In the splicing process, unspliced, partially spliced, and fully spliced mRNAs are generated, where each of these mRNAs encodes different products of translation. While the gag and the precursors of gag-pol proteins are encoded by unspliced RNA, env and several other proteins (*e.g*., vpr, vpu) are translated from the partially spliced RNA. The fully spliced RNA encodes several major proteins, *i.e*., tat, rev, and nef [11]. While tat is responsible for RNA elongation and modulating the transcription process, rev and nef are involved in transporting unspliced and partially spliced RNAs to the cytoplasm and evading immune surveillance [11].

Once all viral proteins and RNA are generated, they are transported to the cellular plasma membrane, where the viral assembly is carried out through a complex and intricate process. Once the assembly is completed, the budding step occurs, where the immature progenies of HIV are released from the cells. Through the action of the viral protease, these immature HIV progenies are activated and become infectious shortly after the budding process [11]. In the clinical setting, the HIV protease can be inhibited by a group of drugs called protease inhibitors (*e.g*., ritonavir, lopinavir, and indinavir) [21].

As described above, the translation of viral proteins needs the host machinery system, including the host signaling pathways. For example, it has been reported that the synthesis of gag proteins needs an mTOR signaling pathway which can be obtained by hijacking the host mTOR pathway, which is critical for regulating cellular proliferation and fighting noxious molecules [22, 23]. This signaling pathway is also involved in HIV latency. A study indicated the role of mTOR in the reactivation of latent HIV, and it has been demonstrated that the administration of Torin-1, an inhibitor of mTOR, could prevent the activation of HIV in CD4+ T cells [24, 25]. As the latency of HIV is one major problem often experienced in eradicating the virus, targeting the activated mTOR pathway should be considered as one of the therapeutic strategies. However, it is noteworthy that inhibiting this pathway may also lead to side effects for the host cells. Many questions regarding this issue remain unanswered.

Other signaling pathways are also involved in supporting the HIV life cycle or increasing its infectivity, *e.g*., toll-like receptor (TLR) [26], notch [27], wnt [28], and MAPK [29] pathways. Due to space limitations, this review will not describe the deeper role of these pathways in HIV infection. However, targeting these pathways is rational in discovering HIV treatment in the future.

Although many drugs have been used clinically as anti-HIV, efforts to discover and develop novel anti-HIV candidates are being carried on to produce more effective drugs or to anticipate cases of HIV resistance. One of the efforts is to explore biological products extracted from marine organisms, which have been known to have unique properties compared to those extracted from terrestrial organisms. The marine natural products' anti-HIV activity and chemical structures are summarized in Table **1** and Supplementary Fig. **S1**, respectively.

2.2. ZIKV Infection

ZIKV shares a similar structure with other flaviviruses, such as the dengue virus and West Nile virus. It is an enveloped single-stranded RNA virus with a positive-sense structure [56]. Its genome encodes 3 structural proteins (capsid, envelope, and precursor membrane proteins) and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [57]. Those proteins play different functions to support the ZIKV life cycle. For example, while the attachment of ZIKV to the host cell is mediated by the envelope and precursor membrane proteins, the assembly of viral particles is facilitated by the capsid proteins [56]. The development of ZIKV vaccines often targets the envelope and precursor membrane proteins [58]. Nonstructural proteins are also critical for ZIKV as they function fundamentally in several aspects, *e.g*., viral replication, ZIKV infectivity, and evasion from host immune response [59-62]. Given that these proteins are critical for ZIKV, developing anti-ZIKV drugs often targets those proteins.

Several transmission routes facilitate the exposure of ZIKV to the body with the bite of a mosquito is the most common route [63]. In addition, vertical transmission describing a transmission route in which the infected mothers transmit the virus to their fetuses, has also been reported [64]. To date, the question regarding the mechanism by which the ZIKV crosses the blood-placental barrier remains undeciphered. Sexual activities also play a certain role in transmitting ZIKV. Several reports have demonstrated that the virus could be detected in semen and vaginal samples of either humans or laboratory animals [65-68]. A study demonstrated that blood transfusion also brought a certain risk for being a mode of virus transmission [69]. Furthermore, ZIKV is also detected in urine, saliva, conjunctival fluid, and cerebrospinal fluid samples [70-73].

Table 1. Summary of the selected anti-HIV from marine sources.

Mechanism of Action	Compound	SAR	Source	IC_{50} or EC_{50}	CC_{50}	Model used	Refs.
HIV-1 Glycoprotein inhibition	CVL	-	*Chaetopterus variopedatus*	0.0043 - 0.073 µM	No cytotoxic effect was observed at any concentrations tested (0.003 - 1.67 µM)	C8166 cell line infected to HIV-1^{-}_{IIIB}. MTT assay was performed to determine its cytotoxic effect.	[30]
	Neamphamide A	Its anti-HIV activity is closely associated with the unique amino acids, *i.e.*, 3, 4-diMeGln and βOMeTyr in its structure.	*Neamphius huxleyi*	0.028 µM	0.26 µM	CEM-SS cell line infected to HIV-1_{RF}. XTT assay was performed to determine the cytotoxicity of the compounds against the host cells.	[31]
	Mirabamide A	The anti-HIV activity of this compound is related to the presence of 4-chlorohomoproline, β-methoxytyrosine 4′-O-α-L-rhamnopyranoside structures and a unique aliphatic hydroxy acid in its N-terminal.	*Siliquariaspongia mirabilis*	0.04 - 0.14 µM (neutralization assay) 0.041 µM (fusion assay)	1.8 ± 0.8 µM (TZM-bl cell line) 2.22 ± 0.4 µM (HCT-116 cell line)	IC_{50} was determined after the neutralization and fusion assays using the T-tropic and macrophage-tropic-infected TZM-bl cells and HCT-11.	[32]
	Cyanovirin-N	The presence of disulfide bonds is important in determining the antiviral activity of cyanovirin-N	*Cyanobacteria*	0.0001-0.0058 µM	No lethal effect was observed on the uninfected CEM-SS cells after exposure to either 3 µM or 9 µM of cyanovirin-N for 48-h.	CEM-SS, U937, MT-2 cell lines. Each cell line was infected with different laboratory strains of HIV-1 (*i.e.*, RF, IIIB, MN, G910-6, A17, 214, SK1, 205, G1).	[33, 34]
	Sulfated polymannuroguluronate (SPMG)	The anti-HIV activity of SPMG is closely related to the presence of sulfated groups, as these groups are important for mediating its binding to gp120. The presence and composition of saccharides are also vital. SPMG with more than 15-16 saccharides could bind to multiple gp120.	Brown algae	-	-	HIV_{IIIB}-infected CEM cell line	[35, 36]
	Galactan sulfate	Sulfate contents determine the activity of the compounds as anti-HIV. The compound having lower sulfate contents shows less anti-HIV-1 activity. Alkali modification of sulfate content in C6, but not in C2, generates lower anti-HIV-1 activity.	*Grateloupia longifolia, Grateloupia filicina*	0.002 - 0.01 µM	>7.5 µM	The model used was the human peripheral blood mononuclear cells (PBMCs) treated with several sulfated galactans.	[37]

(Table 1) contd…

Mechanism of Action	Compound	SAR	Source	IC_{50} or EC_{50}	CC_{50}	Model used	Refs.
	Fucoidans	In general, the antiviral activity of sulfated polysaccharides depends on the sulfate contents and positions [38]. However, the antiviral activity of fucoidans isolated from *Sargassum mcclurei*, *Sargassum polycystum, and Turbinara ornata* is not correlated significantly with the sulfate contents and positions [39].	*Sargassum mcclurei, Sargassum polycystum, Turbinara ornata*	0.33 - 0.7 µg/mL	No cytotoxicity at concentrations of 2 µg/mL (fucoidans from *Sargassum polycystum and Turbinara ornata)* and 20 µg/mL (fucoidans from *Sargassum mcclurei)*	U373-CD4-CXCR4 cells infected by luciferase-tagged viral X4; HEK293T cells	[39]
	Griffithsin	-	*Griffithsia sp.*	0.000043 - 0.00063 µM	No cytotoxicity effect was observed on any host cells used after being exposed to higher concentrations of griffithsin (0.0783 - 0.783 µM)	Tested on several target cells, *i.e.*, CEM-SS, human PBMC, and macrophage infected to either HIV-1 laboratory strain or HIV-primary isolates.	[40]
Interaction with CCR5/CXCR4	Penicillixanthone A	The dimer structure of polyhydroxy xanthone of penicillixanthone A may be responsible for its anti-HIV activity through a hydrophobic or electrostatic interaction with the coreceptors.	*Aspergillus fumigates*	0.36 µM (CCR5-tropic strain) 0.26 µM (CXCR4-tropic strain)	20.6 µM	The model used was the infected TZM-bl cell line. CC_{50} was determined after running the XTT assay.	[41]
Reverse transcriptase inhibition	Dolabelladienetriol	The anti-HIV activity of marine diterpenes might be correlated with (1) the presence of H-bond donors and H-bond acceptors; (2) lipophilicity. A compound with a higher cLogP and lower PSA shows no anti-HIV activity; (3) the configurations of the diterpenes. The S configuration gives a lower IC50 than the R configuration.	*Dictyota pfaffii*	6.2 µM	1, 345 - 1, 456 µM	MT-2 lymphocyte tumor cells	[42, 43]
	Dolabelladienol A			2.9 µM			
	Dolabelladienol B			4.1 µM			
	8, 4‴-dieckol	The inhibitory activity of these phlorotannins on RT may be mediated by the presence of dibenzo[1, 4]dioxin structure. However, the anti-RT activity of 8, 8'-bieckol is more powerful than its counterparts, which may be associated with the presence of a diphenyl bond in its structure.	*Ecklonia cava*	50 µM (91% inhibition ratio)	>1, 000 µM	PBMC and C8166 cells (anti-cytopathic studies); HIV-1 reverse transcriptase enzyme (RT inhibition activity); MTT assay (cytotoxicity assay)	[44]
	6, 6'-bieckol			1.07 µM 1.23 - 1.72 µM (anti-cytopathic effect)	484 µM	CEM-SS and C8166 cells (anti-cytopathic studies); HIV-1 reverse transcriptase enzyme (RT inhibition activity); MTT assay (cytotoxicity assay)	[45, 46]
	8, 8'-bieckol			0.51 µM	Not cytotoxic at any tested concentrations (6.25 - 200 µM)	HIV-1 reverse transcriptase enzyme	[47, 48]

(Table 1) contd…

Mechanism of Action	Compound	SAR	Source	IC_{50} or EC_{50}	CC_{50}	Model used	Refs.
	Oroidin	-	*Stylissa carteri*	25 µM (90% inhibition rate)	Not cytotoxic	LC5-RIC reporter cells in the EASY-HIT and MTT assay; HIV-1 reverse transcriptase enzyme.	[49]
	Clathsterol	Sulfate substitution in C-2 and C-3 may reduce the anti-HIV activity of clathsterol.	*Clathria sp.*	Active at a concentration of 10 µM	-	HIV-1 reverse transcriptase enzyme	[50]
	Aeroplysinin-1	The activity of these compounds as anti-RT is strongly related to the presence of the methoxyl moiety with two adjacent bromine atoms in their structures.	*Verongula rigida*	10 µM (percentage of inhibition 48%)	Cytotoxicity less than 45% at any tested concentrations	Cytotoxicity (U373-MAGI cell line, MTT assay); inhibition of reverse transcription (qPCR)	[51]
Integrase inhibition	Thalassiolin A	The sulfated glucopyranosyl moiety at C-7 is the critical structure in exerting their anti-integrase activity.	*Thalassia testudinum*	0.4 µM	>800 µM	Cytotoxicity (MT2 cells); integrase enzyme	[52]
	Thalassiolin B			43 µM	>800 µM		
	Thalassiolin C			28 µM	>800 µM		
	Diphlorethohydroxycarmalol	The free hydroxyl groups in its structure are responsible for its anti-integrase activity.	*Ishige okamurae*	25.2 µM	Not cytotoxic at any tested concentrations (490 - 3, 910 µM)	Cytotoxicity (HUVECs, Neutral Red assay); integrase enzyme	[53, 54]
Protease inhibition	Erythro-N-dodecanoyl-docosasphinga-(4E, 8E)-dienine	• These compounds could interact with the protease through the formation of hydrogen bonds. • Compounds having alkyl and alkenyl moieties show higher hydrogen bond scores. • The hydrophobicity of these compounds determines their activity in inhibiting HIV proteases.	*Litophyton arboreum*	4.80 ± 0.92 µM	38.17 µM (HeLa) >100 (Vero)	HIV-protease; cytotoxicity (HeLa and Vero cells)	[55]
	7β-acetoxy-24-methylcholesta-5-24(28)-diene-3, 19-diol			4.85 ± 0.18 µM	5.3 µM (HeLa) 31.3 (Vero)		
	Alismol			7.2 ± 0.7 µM	30 µM (HeLa) 49 µM (Vero)		
	8, 8'-bieckol	The presence of the hydroxyl and aryl moieties may determine the HIV protease activity.	*Ecklonia cava*	81.5 ± 9.6 µM	Not cytotoxic at any tested concentrations (6.25 - 200 µM)	Cytotoxicity (primary macrophage and RAW 264.7 cells)	[44, 47, 48]
	8, 4"'-dieckol			36.9 ± 65.4 µM	>1, 000 µM	PBMC and C8166 cells (anti-cytopathic studies); HIV-1 protease enzyme (protease inhibition activity);s MTT assay (cytotoxicity assay)	

Note. IC_{50} (half-maximal inhibitory concentration) is a concentration of a compound required to inhibit the tested virus by half; EC_{50} (half-maximal effective concentration) is a concentration of a compound required to produce its maximal effect by half; CC_{50} (half-maximal cytotoxicity concentration) is a concentration of a compound required to produce its cytotoxic effect by half.

Several receptors have been proposed as the main targets utilized by ZIKV to get into the cells, including AXL family receptors, C-type lectins, and receptors related to T cell TIM (transmembrane, immunoglobulin, and mucin) [74, 75]. These receptors can be found in various tissues or organs in humans, including nervous system, skin, reproductive system, and embryonic brain tissues, explaining the multiple symptoms manifested in ZIKV-infected patients [76]. Thrombocytopenia, Guillain-Barre Syndrome, hearing loss, visual problems, and microcephaly are several symptoms that are often monitored [76]. Nevertheless, most of the patients contracting ZIKV were reported to have either only mild symptoms or asymptomatic [76-79]. Upon the occupation of the receptors, the virus starts to perform sequential basic events, *i.e.*, viral RNA translation and replication, assembly of viral particles, and release of the virus from the host cell [74]. Although there is still a controversy regarding the exact mechanisms by which those putative receptors facilitate the entry of ZIKV, the key point is that those ZIKV entry receptors are potential targets for treating ZIKV infection.

Of those symptoms mentioned above, neurological and brain disturbances attract extensive attention. Although ZIKV can infect most cells residing in the brain, including glial cells [80, 81], microvascular endothelial cells [82], pericytes [81], and neurons [83], its ability to infect neural progenitor cells plays a pivotal role in impairing brain development which may lead to microcephaly and other neurological disruptions [84, 85].

Some signaling pathways may be involved in ZIKV infectivity *e.g.*, TLRs [85], Notch [86], JAK/STAT [87], apoptosis [88], Akt-mTOR [89], and p53 signaling pathways [90]. Modulation of these pathways by ZIKV elicits various effects, as described below. Furthermore, these pathways are potentially targeted in the case of anti-ZIKV drug development.

It has been proposed that the Toll-like receptor 3 (TLR3) signaling pathway plays a certain role in mediating the emergence of ZIKV-induced neurological symptoms [85, 91], while another group proposed the role of the Notch signaling pathway in neurogenesis dysregulation induced by ZIKV [86]. The upregulation of TLR3 has been observed in several models exposed to ZIKV, and this activation perturbs 41 genes related to neural development [85, 92-94]. In an organoid model, ZIKV-activated TLR3 is linked to the decrease of the organoid volume, which may relate to the pathogenesis of microcephaly in the clinical setting [85]. It has also been found that the viral titers determine the level of organoid volume reduction, which indicates that TLR3 activation supports ZIKV replication [85]. It is interesting that TLR3, as a part of the nonspecific immunity, enhances viral replication; the exact explanation is still unclear. These findings suggest suppressing the TLR3 signaling pathway is a potential strategy to restrain ZIKV replication. Dang and colleagues demonstrated that the inhibition of TLR3 by thiophenecarboxamidopropionate, a competitive inhibitor of TLR3, attenuated the phenotypic effects induced by ZIKV, while the exposure of the agonist of TLR3 to the brain organoid model caused brain volume reduction as seen in ZIKV-induced microcephaly [85].

Furthermore, the emergence of inflammation following the ZIKV-activated TLR3 pathway should also be monitored closely. ZIKV-induced inflammation could be detrimental as some studies reported the occurrence of cytokine storms in the models used [95-97]. Therefore, the administration of anti-inflammatory compounds should also be considered in the ZIKV drug regimen. A study reported that the administration of nonsteroidal anti-inflammatory drugs inhibited ZIKV replication, which is mediated by their action on degrading AXL [98].

The role of the Akt-mTOR signaling pathway in mediating the neuropathological effects of ZIKV infection has also been studied, which could be linked to the modulation of autophagy. A report suggested that the inhibition of the Akt-mTOR signaling pathway by ZIKV resulted in the inhibition of neurogenesis and induction of autophagy [89]. Furthermore, other groups indicated that the inhibition of autophagy led to the limitation of vertical transmission and limited ZIKV replication [99, 100]. The administration of chloroquine, 3-methyladenine, and bafilomycin A1, recognized as autophagy inhibitors, limits the replication of ZIKV [99]. Conversely, autophagy inducers, such as rapamycin and Torin 1, stimulate ZIKV replication [99]. Based on these findings, autophagy inhibition could be proposed as one of the strategies to inhibit ZIKV infection [92].

Apoptosis inhibition is another proposed strategy utilized for limiting ZIKV replication and infection. It has been demonstrated that ZIKV could induce apoptosis by upregulating caspase-3, a critical apoptosis effector protein [88, 101]. Other studies reported that p53 was involved in ZIKV-induced apoptosis, and the inhibition of this tumor suppressor protein could suppress apoptosis of neural progenitor cells induced by the virus [90, 102]. Following ZIKV-activated p53, several genes responsible for promoting apoptosis are activated, such as *bax*, *puma*, and *noxa*, while antiapoptotic genes (*e.g.*, *survivin*) are inhibited [103-105]. A recent study in neural progenitor cells found that ZIKV could interact with p53 protein in neural progenitor cells *via* its non-structural protein 5 (NS5) [106].

The endoplasmic reticulum (ER) is a pivotal organelle responsible for protein folding and maturation in eukaryotic cells. In a viral infection, as seen in ZIKV infection, ER is the main site for the assembly of viral particles, and this potentially disturbs the normal function of ER [74]. The excessive synthesis of viral proteins could lead to ER stress, a condition induced by an accumulation of misfolded proteins [107]. Following this accumulation, the unfolded protein response (UPR) signaling pathway is activated, and the signal is transmitted from the ER to the cytosol *via* UPR activators. Several key UPR activators have been identified, *e.g.*, PERK and IRE1 [92, 107]. In the case of ZIKV infection, it has been found that the UPR pathway is induced, and the use of PERK inhibitors is reported to have a beneficial effect on reversing the impaired neurogenesis caused by ZIKV [108]. Furthermore, it is also demonstrated that IRE1

Table 2. Summary of the selected anti-ZIKV from marine sources.

Mechanism of Action	Compound	SAR	Source	IC_{50} or EC_{50}	CC_{50}	Model used	Refs.
Blockage of viral target receptors	Dolabellanes Dolastanes	The *S* epimers at C-13 show more potent anti-ZIKV activity than their *R* epimers.	Brown algae and soft corals	1.2 ± 0.1 μM (compound 2) 0.92 ± 0.08 μM (compound 9) 1.2 ± 0.1 μM (compound 12) 1.8 ± 0.1 μM (compound 18)	530 μM (compound 2) 750 μM (compound 9) 580 μM (compound 12) 730 μM (compound 18)	Cytotoxicity (Vero cells, MTT assay). Anti-ZIKV activity (Vero cells infected with ZIKV)	[111]
Inhibiting ZIKV binding to the entry receptors	F-6 fraction Fac-2 fraction	The abundant contents of acetylated diterpenes in these fractions are suggested to play a pivotal role in their anti-ZIKV activity.	*Dictyota menstrualis*	2.80 μg/mL 0.81 μg/mL	592 μg/mL 482 μg/mL	Cytotoxicity (Vero cells, MTT assay). Anti-ZIKV activity (Vero cells infected with ZIKV)	[112]
Inhibition of viral replication, virus fusion and NS5 production	Destruxins	Compared to the other cyclodepsipeptides, destruxins show more potent anti-ZIKV activity. The derivatives of destruxins possessing halogen substituents have more potent activity than those having hydroxyl or carboxyl substituents.	*Beauveria felina*	At the concentration of 10 μM, ZIKV replication is inhibited significantly.	>100 μM	Cytotoxicity (A549 cells, MTT assay) Anti-ZIKV activity (virus-infected A549 cells)	[113]
	Dolastane	-	*Canistrocarpus cervicornis*	0.95 μM	935 μM	Cytotoxicity (Vero cells, MTT assay). Anti-ZIKV (virus-infected Vero cells	[111, 114]
	Indole alkaloids	The F-ring in the structure is vital for anti-ZIKV activity. The furan form of the F-ring gives the tested compounds the most potent activity. The B- and C-rings are also important for antiviral activity.	Marine-derived *Fusarium sp.*	7.5 μM (compound 2) 4.2 μM (compound 9) 5.0 μM (compound 15)	Not showing significant cytotoxicity.	A549 adenocarcinoma human alveolar basal epithelial cell line	[115]

Note. IC_{50} (half-maximal inhibitory concentration) is a concentration of a compound required to inhibit the tested virus by half; EC_{50} (half-maximal effective concentration) is a concentration of a compound required to produce its maximal effect by half; CC_{50} (half-maximal cytotoxicity concentration) is a concentration of a compound required to produce its cytotoxic effect by half.

could inhibit ZIKV replication [108]. Overall, alleviation of ER stress possesses potency as another approach for treating ZIKV infection.

When pathogens, such as viruses, reach the cytoplasm, they are sensed by pattern-recognition receptors (PRRs), followed by the activation of downstream events, including cytokine production. Several PRRs have been elucidated, *e.g.*, TLRs, nucleotide oligomerization domain (NOD)-like receptors (NLRs), and RIG-I (retinoic acid-inducible gene-I)-like receptors (RLRs) [109]. While TLRs can sense broad antigens, such as cell wall components of microbes and viral proteins, NLRs and RLRs recognize bacterial peptidoglycan and viral nucleic acids in the cytoplasm. The ability of ZIKV to evade the surveillance of the host immune system has also attracted much interest. ZIKV has developed an ability to block the PRRs. It has been reported that NS4A of ZIKV inhibits the action of the RLRs [62]. Another non-structural protein, NS5, also shows the ability to inhibit the RIG-I pathway leading to the disrupted activation of the host's innate immune responses [110].

The sustainable efforts to discover and develop new potential candidates having anti-ZIKV activity are important, although several drugs have been used to cure the infection in the clinical setting. The exploration of candidates sourced from marine organisms has been attracting interest. Compared to anti-HIV, the effort to explore potential candidates displaying anti-ZIKV action in marine is lower. The summary of marine natural products' anti-ZIKV activity and their chemical structures is shown in Table **2** and Supplementary Fig. **S2**, respectively.

2.3. EBOV Infection

Direct contact with the bodily fluids of the infected individuals is the main route of EBOV transmission, followed by viral movement through the skin or mucosal surfaces [116]. Although some varied symptoms are often observed during the initial stage of the infection, such as fever, myalgia, gastrointestinal-, and respiratory-related symptoms, the final stage of infection is signed by the emergence of massive tissue failure, increased vascular permeability, failure to activate the coagulation cascade, and hemorrhage. Finally, death occurs due to shock and multiorgan failure [116-118].

EBOV genome encodes 9 proteins, *i.e*., glycoproteins (full-length glycoprotein, soluble glycoprotein, and small soluble glycoprotein), RNA-dependent RNA polymerase, nucleoprotein, and four viral proteins (VP - VP24, VP30, VP35, and VP40) [116, 119]. Each protein is critical in supporting the pathogenicity of EBOV. While full-length glycoprotein is important for mediating EBOV binding to host cell receptors and facilitating membrane fusion, the soluble glycoprotein is secreted abundantly from the infected cells during infection [119, 120]. As to the small soluble glycoproteins, no clear function has been identified. Although nucleoprotein is needed as the structural unit of the viral nucleocapsid, it is also involved in viral replication and transcription, as the main function of the RNA-dependent RNA polymerase. The viral proteins have various main functions, *e.g*., maintenance of viral membrane integrity (VP40), formation of the viral nucleocapsid (VP24, VP30, VP35), supporting viral polymerase catalytic function (VP30, VP35), and evading host immune action (VP24, VP35) [116, 119, 121, 122]. Given that those proteins are critical for EBOV infectivity, destruction of those proteins can potentially eradicate viral replication. For example, a report from Mateo and colleagues indicated that the knockdown of VP24 of EBOV led to the failure of nucleocapsid formation, resulting in the suppression of EBOV replication [121]. Another study reported that EBOV lacking VP35 lost its virulence, and this mutant protected a non-human primate model from the wild-type EBOV [123].

Lectin family receptors are the main receptors involved in providing a site of entry for EBOV. Those are, *e.g*., asialoglycoprotein found mostly in the liver cell and macrophage C-type lectin specific for galactose/N-acetylgalactosamine found in monocytes and macrophages [116, 124-126]. Although the dendritic cell-specific, intercellular adhesion molecule 3-grabbing non-integrin receptor presented mainly in dendritic cells, macrophages, and endothelial cells, it is proposed as one of the EBOV entry receptors, the role of this receptor in facilitating the entry of the virus is still controversial. While other studies proposed that this innate immune receptor acts directly by binding to EBOV glycoprotein [127, 128], another study suggested this receptor acts indirectly by promoting EBOV attachment to the host cell [129]. Folate receptor-α is also another receptor that is critical as a cofactor for cellular entry of EBOV [130]. Upon binding between the EBOV glycoprotein and the receptor, the virus gains entry to the host cell by an endocytosis mechanism, which is then followed by the fusion of the virus and the host membrane to mediate the release of EBOV into the cytoplasm [131, 132]. Once the virus reaches the cytoplasm, it begins to perform its sequential life cycle by hijacking cellular and organelle machinery. Viral RNA translation and replication mostly occur in the cytoplasm, while the reticulum, endoplasmic, and Golgi bodies are critical for viral glycoprotein modification [116]. The assembly of viral particles occurs at the plasma membrane, which is then followed by the release of the virus from the host cell [116].

EBOV initially infected several cells, *e.g*., dendritic cells, monocytes, and macrophages. EBOV infection on dendritic cells averts T cell activation leading to dysfunctionality of the lymphocytes in producing an adequate antibody response for tackling the virus. Meanwhile, EBOV attacks on monocytes and macrophages may produce excessive pro-inflammatory factors [133, 134]. It has been known that proinflammatory factors, such as cytokines and reactive oxygen species, can induce apoptosis, which may ultimately result in T cell death [116, 135, 136]. These proinflammatory cytokines are responsible for vascular leakage and eventually lead to failure in several critical points, such as kidney, liver, and endothelial cells [116]. The effects of those cytokines are exacerbated by systemic dissemination of EBOV to those organs, resulting in the emergence of EBOV-related symptoms [137]. The key role of proinflammatory cytokines in promoting EBOV pathogenicity should be considered as a therapeutic strategy in minimizing the severe impacts caused by EBOV-induced excessive cytokine production.

In a recent study, Furuyama and colleagues reported that the action of the soluble glycoprotein mediated the pathogenicity of the Ebola virus *via* activation of the MAPK signaling pathway [119]. Hence, the administration of MAPK inhibitors should be considered a potential strategy for treating EBOV. Johnson and group have demonstrated that the administration of a MAPK inhibitor, pyridinyl imidazole, suppressed EBOV replication in macrophages and dendritic cells and blocked the entry of EBOV into dendritic cells, reduced EBOV-induced cytokine production [138]. It has been found that PI3K/Akt signaling pathway is also important for facilitating EBOV entry into host cells [139]. Thus, blockage of this signaling pathway is also potentially used for treating EBOV infection.

EBOV also activates TLRs, especially TLR4 a signaling pathway, and begins the excessive production of proinflammatory cytokines and chemokines, which is detrimental [140]. At this point, EBOV-like particles have been utilized for vaccine development. Several studies indicated that EBOV-like particles could induce the innate immune response through their activity in activating the TLR pathway [140-142]. In addition, VP35 of EBOV can antagonize the RLRs signaling pathway. Accordingly, the enhancement of RLRs activity by administering certain compounds, such as nitazoxanide and EBOV-like particles, has been explored to limit EBOV replication and increase antigen presentation to antigen-presenting cells, respectively [143, 144].

Table 3. Summary of the selected anti-EBOV from marine sources.

Mechanism of Action	Compound	SAR	Source	IC_{50} or EC_{50}	CC_{50}	Model used	Refs.
Inhibition of EBOV VP40 protein	Gymnastatin G	The presence of the hydrogen bond in their structure is important for stabilizing the interaction with the interacting amino acid residues of VP40.	Symbiont bacteria in the sponge *Cliona sp.*	-	-	In silico study using AutoDock Vina as the docking tool and matrix protein VP40 (PDB ID: 1ES6) as the target protein. Binding energy: Gymnastatin G (-5.3 kcal/mol) Sorbicillactone A (-5.9 kcal/mol) Marizomib (-5.7 kcal/mol) Daryamide C (-5.3 kcal/mol)	[147]
	Sorbicillactone A			-	-		
	Marizomib			-	-		
	Daryamide C			-	-		
Targeting EBOV glycoproteins	Cyanovirin-N	The presence of disulfide bonds is important in determining the antiviral activity of scytovirin and cyanovirin-N	*Cyanobacteria*	~ 0.1 µM	The compound shows cytotoxicity at a level of ~ 4 µM	Vero E6 cells. Cytotoxicity (neutral red assay).	[34, 148]
				0.154 µM		Vero E6 cells. Cytotoxicity (ATP-based assay)	[34, 149]
	Scytovirin			0.041 µM	10.3 µM		
Inhibition of EBOV cell entry by interrupting activity of actin filaments	Latrunculin A	The presence of the thiazolidinone group and a tetrahydropyran ring may play a critical role in interrupting actin filaments.	*Latrunculia magnifica*	1 µM inhibits ~90% viral entry & fusion	Not determined	HEK293T cells, HeLa cells, and HeLa-CD4 cells	[150-152]
	Jasplakinolide	-	*Jaspis johnstoni*	1 µM inhibits ~95% viral entry & fusion	Not determined		[151, 153, 154]
	Cytochalasin B	In cytochalasans, the hydroxyl groups at C7 and C18 play a vital role in disrupting the actin. No effect was observed when these groups were absent.	*Helmiwthosporium dematioideum*	20 µM inhibits ~90% viral entry & fusion	Not determined		[151, 154, 155]
	Cytochalasin D		*Metarrhizium anisopliae*	20 µM inhibits ~100% viral entry & fusion	Not determined		

Note. IC_{50} (half-maximal inhibitory concentration) is a concentration of a compound required to inhibit the tested virus by half; EC_{50} (half-maximal effective concentration) is a concentration of a compound required to produce its maximal effect by half; CC_{50} (half-maximal cytotoxicity concentration) is a concentration of a compound required to produce its cytotoxic effect by half.

Recently, no drugs have been approved to treat EBOV infection [145]. Thus, efforts to discover promising anti-EBOV candidates must be strengthened, given that EBOV and other filoviruses usually emerge and cause health problems periodically [146]. One alternative effort is to do an in-depth investigation on metabolites produced by marine organisms. The summary of anti-EBOV compounds extracted from marine and their chemical structures is provided in Table **3** and Supplementary Fig. **S3**, respectively.

2.4. SARS-CoV-2 Infection

SARS-CoV-2 belongs to the genus of beta coronavirus, in which SARS-CoV and MERS-CoV are also grouped. Structurally, it has four structural proteins (S = spike; E = envelope; M = membrane; and N = nucleocapsid) and sixteen nonstructural proteins have been identified recently (nsdp1 - nsp16) [156, 157]. To get into the cells, SARS-CoV-2 utilizes the host angiotensin-converting enzyme 2 (ACE2) as the main entry receptor bound to the spike glycoprotein of the virus [158]. ACE2 is expressed widely within the body, which may explain the emergence of various symptoms when someone contracts SARS-CoV-2 [159]. Gastrointestinal-related symptoms [160], respiratory-related symptoms [161], cardiovascular-related symptoms [162], and disturbances in the nervous system [163] are several symptoms often displayed by COVID-19 patients.

Following the occupation of ACE2 by the spike protein S1 subunit, the subsequent basic steps of the viral life cycle occur, including membrane fusion followed by endocytosis involving the role of S protein S2 subunit and the host proteases (*e.g.*, furin and TMPRSS2), release of the SARS-CoV-2 RNA into the host cytoplasm, translation of the viral RNA into viral proteases and replicate, RNA transcription, translation of the RNA into viral structural proteins taking place in the endoplasmic reticulum (ER) and cytoplasm, assembly, and budding steps [164, 165]. Theoretically, each of these steps of the SARS-CoV-2 life cycle could be targeted to discover promising drugs for COVID-19 treatment. Several strategies have been developed for tackling SARS-CoV-2 infection, *e.g.*, blockage of entry and fusion of SARS-CoV-2; interference with viral proteases and polymerase; and inhibition of replication, transcription and translation of viral genomic material [165].

The dysfunctionality of the ACE2 receptor by the virus plays a critical role in the pathophysiological aspects of COVID-19. This is reasonable given that ACE2 is inherently linked to the renin-angiotensin-aldosterone system (RAAS), which is an important system in the human body due to its pleiotropic effects. It has been known that ACE catalyzes the conversion of Ang I into Ang II, which is then bound to the AT1 receptor to exert its physiological effects. The excessive activity of the ACE/Ang II/AT1R axis, which can be caused by SARS-CoV-2 perturbation on the ACE2/Ang (1-7)/Mas axis, may produce detrimental effects on the body [166]. For example, the elevated level of Ang II can cause excessive vasoconstriction, which can lead to some cardiovascular disturbances (*e.g.*, hypertension and hemorrhagic stroke) [167]. Moreover, the abundance of Ang II can induce the excessive release of proinflammatory cytokines, cell proliferation, fibrosis, and thrombosis [165]. Conversely, these harmful effects may be alleviated once the level of Ang II is normalized [165, 168].

Furthermore, following the invasion of SARS-CoV-2, the immune system is then activated, and the immune cells migrate to the site of infection where the excessive amount of proinflammatory cytokines, *e.g.*, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), is released. This condition, if not controlled, could emerge as a cytokine storm [169]. At this point, anti-inflammatory drugs (*e.g.*, dexamethasone, tocilizumab, etoposide) may help COVID-19 patients prevent the fatal outcome caused by the cytokine storm [170].

Excessive production of proinflammatory cytokines is essential in inducing tissue and organ damage during COVID-19 contraction. For example, TNF-α, IL-1β, and IL-6 can induce the activity of matrix metalloproteinases (MMPs), which function to degrade the extracellular matrix (ECM) [171-173]. This would increase vascular permeability and subsequently cause extravasation of blood contents. In the context of the blood-brain barrier, ECM degradation damages the barrier integrity, resulting in increased brain vulnerability to many harmful compounds circulating in the blood. This is exacerbated by the ability of those cytokines to disturb the formation of junctional proteins, which have a critical duty for maintaining the homeostasis of the blood-brain barrier by preventing the entry of various substances *via* paracellular clefts between two adjacent endothelial cells. Voirin and colleagues indicated that the exposure of bEnd.3 endothelial cells to TNF-α and IL-6 increased the permeability of the BBB linked to the downregulation of zonula occludens-1 (ZO-1) and claudin expression, which are essential proteins in tight junction structure [174]. Other studies reported similar findings using different proinflammatory cytokines and models [175-177]. In addition to the blood-brain barrier, excessive production of proinflammatory cytokines can cause the emergence of COVID-19-related symptoms in other organs, *e.g.*, lungs [178], intestines [169], and neuromuscular organs [163, 179].

Various signaling pathways are involved in facilitating the damaging effects of SARS-CoV-2. For example, it has been demonstrated that patients' gastrointestinal symptoms are often associated with the ability of SARS-CoV-2 to indirectly inhibit the mTOR signaling pathway leading to the emergence of dysbiosis [180]. Furthermore, in the case of hemorrhagic stroke related to COVID-19, SARS-CoV-2 can indirectly inhibit PI3K/AKT signaling pathway after its occupation on ACE2 [181, 182]. Moreover, a computational study suggested that SARS-CoV-2 also targeted various signaling pathways, including NF-κB, JAK/STAT, and TGF-β [183]. Although many questions remain unanswered regarding the exact molecular mechanisms involved in the modulation of the pathways by SARS-CoV-2, these signaling pathways may become alternative targets for developing anti-COVID-19 drugs.

As the world is still fighting the pandemic caused by SARS-CoV-2, the causative coronavirus disease 2019 (COVID-19) virus, no definitive treatments have been discovered to eradicate this virus recently. In addition to the health aspect, this pandemic has affected other aspects, including economic and social aspects. For more than two years, experts around the globe have conducted many studies to find and bring potential candidates from many sources to the public that can end this pandemic, including the promising candidates extracted from marine organisms. A summary of marine natural products having potential activity in eradicating SARS-CoV-2 and in alleviating the pathological effects caused by COVID-19 contraction is shown in Table **4**. The chemical structures of these compounds are given in Supplementary Fig. **S4**.

3. MARINE NATURAL PRODUCTS OF CHOICE

This section describes the relationship between the structural aspects of several marine-derived compounds from various phytochemical groups and their promising antiviral activities. We have summarized this in Fig. (**1**).

3.1. Sulfated Polysaccharide

Sulfated polysaccharides (SPs), such as fucoidans and SPMG, are mostly found in marine algae as these compounds function as one of the important components of their cell walls [205]. In addition, SPs are also detected in other

Table 4. Summary of the selected anti-SARS-CoV-2 from marine sources.

Mechanism of Action	Compound	Source	Binding Energy (kcal.mol^{-1})	Docking Tool	Selected Target Protein	Refs.
Inhibition of viral entry	Griffithsin EC_{50} *0.61 µg/mL (SARS-CoV)* *< 0.0032 µg/mL (HCoV-NL63)* *0.16 µg/ mL (HCoV-229E)* *0.16 µg/mL (HCoV-OC43)*	*Griffithsia* sp	-	-	-	[184]
	Inorganic polyphosphates (polyP) IC_{50} *34 ± 15 µg/mL ($polyP_{40}$)* *7.8 ± 12 µg/mL (Na-$polyP_3$)*	Marine bacteria and sponges	-	-	-	[185, 186]
	Sea cucumber sulfated polysaccharide IC_{50} *9.10 µg/mL*	*Stichopus japonicus*	-	-	-	[187]
	Phycoerythrobilin	*Arthrospira*	-7.45	Autodock Vina	SARS-CoV-2 spike protein (from PDB: 6LZG)	[188]
	Phycocyanobilin		-10.35	Autodock Vina		
	Phycourobilin		-7.25	Autodock Vina		
	Scedapin C	*Scedosporium apiospermum*	-9.40	AutoDock Vina 1.1.2	Spike domain binding to GRP78	[189]
	Norquinadoline A		-8.30			
	Quinadolin B		-10.50			
	Scequinadoline A		-8.50			
	Phlorofucofuroeckol A	*Ulva clathrata*	-9.73	AutoDock Vina 4.2	ACE-2 Receptor (PDB ID: 1R42)	[190]
	Thalassodendrone	*Cymodoceaceae*	-8.65			
	Dieckol	*Ecklonia cava*	-10.23			
	Thalassioline D	*Thalassia testudinum*	-8.21			
	Prunolide A	*Synoicum prunum*	-9.16			
Main protease inhibition	15 alpha-methoxypuupehenol	*Hyrtios sp.*	-7.15	Autodock 4.2.6	Chymotrypsin-like protease complexed with GC376 (PDB ID: 7D1M)	[191]
	Macrolactin A	*Marine bacteria*	-7.60			
	Phycocyanobilin	*Arthrospira*	-7.11			
	Avarol	*Disidea avara*	-8.05			
	AcDa-1	*Dictyota menstrualis*	-7.74			
	Phlorofucofuroeckol A	*Ulva clathrata*	-9.43	AutoDock Vina 4.2	SARS-CoV-2 PLpro (PDB ID: 5TL6) and Mpro (PDB ID: 6LU7)	[190]
	Thalassodendrone	*Cymodoceaceae*	-7.91			
	Dieckol	*Ecklonia cava*	-9.77			
	Thalassioline D	*Thalassia testudinum*	-7.20			
	Prunolide A	*Synoicum prunum*	-7.73			

(Table 4) contd…

Mechanism of Action	Compound	Source	Binding Energy (kcal.mol^{-1})	Docking Tool	Selected Target Protein	Refs.
	Caulerpin	*Caulerpa racemose*	-9.28	ADT and MGL tools	SARS-CoV-2-3CL main protease (PDB ID: 6LU7) and SARS-CoV-2 main protease (PDB IDs: 2GTB and 3TNT)	[192, 193]
	Glycoglycerolipids	*Exophyllum wentii; Sargassum hornerii*	-9.25			
	Kjellmanianone	*Sargassum naozhouense*	-9.22			
	Loliolide	*Sargassum naozhouense*	-9.02			
	B-sitosterol	*Eucheuma cottonii*	-8.02			
	Saringosterols	*Sargassum muticum*	-7.55			
	Oleic acid	*Fucus sp.*	-7.24			
	Scedapin C	*Scedosporium apiospermum*	-8.60	AutoDock Vina 1.1.2	Papain-like protease (PDB ID: 6W9C) and Chymotrypsin-like protease (PDB ID: 6LU7)	[189]
	Norquinadoline A		-8.10			
	Quinadolin B		-8.30			
	Esculetin ethyl ester	*Axinella cf. corrugata*	-8.42	Autodock 4.2.6	SARS-CoV-2 main protease (PDB ID: 6LU7)	[194]
	Ilimaquinone	*Hippospongia metachromia*	-7.1	AutoDock Tools	SARS-CoV-2 papain-like protease (PDB ID: 4MM3)	[195]
	Terpenoid T3	*Cacospongia mycofijiensis*	-9.10	AutoDock 4.2.0	SARS-CoV-2 Mpro (PDB ID: 5r7y, 5r7z, 5r80, 5r81, 5r82, 5r83, 5r84, 6lu7 and 6y7m)	[196]
	Brevione F	*Penicillium sp.*	-8.4	AutoDock 4.2	SARS-CoV-2 Mpro (PDB ID: 6WWT)	[197, 198]
	Stachyflin	*Stachybotrys sp.*	-8.4			[198, 199]
	Xiamycin	*Bruguiera gymnorrhiza*	-8.4			[198]
	Strongylin	-	-8.3			
	Thyrsiferol	*Laurencia venusta*	-8.2			
	Capillobenzofuranol	-	-8.0			
	Epitaondi	-	-8.0			
	Crambescidin 786	*Poecilosclerida*	-8.05	Molecular Operating Environment	SARS-CoV-2 main protease (PDB ID: 6LU7)	[200]
	Crambescidin 826		-7.99			
RdRp inhibition	Alteramide A	*Halichondria okadai* - associated *Alteromonas sp.*	-9.0	AutoDock Vina	SARS-CoV-2 RNA-directed RNA polymerase (PDB ID: 7BV2)	[201]
	Scedapin C	*Scedosporium apiospermum*	-9.20	AutoDock Vina 1.1.2	SARS-CoV-2 RNA-dependent RNA polymerase (PDB ID: 6M71)	[189]
	Norquinadoline A		-8.50			
	Quinadolin B		-9.80			
	Scequinadoline A		-9.10			

(Table 4) contd…

Mechanism of Action	Compound	Source	Binding Energy (kcal.mol^{-1})	Docking Tool	Selected Target Protein	Refs.
	Xiamycin	*Bruguiera gymnorrhiza*	-9.3	AutoDock 4.2	SARS-CoV-2- RNA-dependent RNA polymerase (PDB ID: 7BW4)	[198, 199, 202-204]
	Thyrsiferol	*Laurencia venusta*	-9.2			
	Liouvilloside B	*Staurocucumis liouvillei*	-8.9			
	Liouvilloside A		-8.8			
	Stachyflin	*Stachybotrys sp.*	-8.7			
	Venustatriol	*Laurencia venusta*	-8.7			
	Brevione F	*Penicillium sp.*	-8.6			
	Thyrsiferyl-23-acetate	*Laurencia venusta*	-8.6			

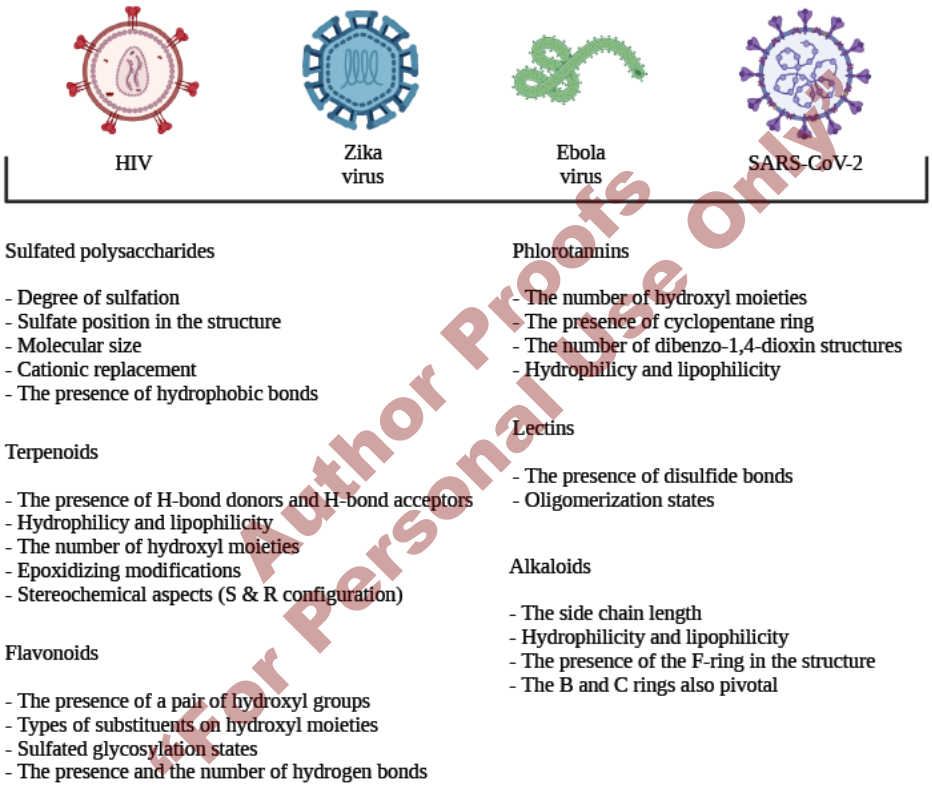

Fig. (1). The putative structural factors are important in exerting antiviral activities of several groups of marine-derived compounds (created with BioRender.com). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

sources, *e.g.*, microorganisms and marine animals, such as clams [206]. Several reports have demonstrated the biological activities of SPs, including their activity as antiviral agents. As displayed in Table **1**, fucoidans have anti-HIV activity as these SPs can interfere with viral glycoproteins (gp120 and gp41), which can lead to the entry and inhibition of HIV into the host cells [39, 207]. SPs also show good activity in inhibiting other viruses, such as herpes simplex virus and chikungunya virus. Recently, several studies have reported the potency of SPs as candidates for tackling SARS-CoV-2 [208, 209].

It has been demonstrated that the degree of sulfation plays a fundamental role in determining the antiviral activity of SPs. The SPs having more than 20% of sulfate contents tend to have antiviral activity, while the best activity is shown by those having approximately 35-60% sulfate contents compared to the total sugar groups, as seen in the SPs isolated from seaweed [38]. The interaction could mediate this activity between the anionic sulfate molecules and the cationic areas in viral glycoprotein [38]. Conversely, both carbonyl and carboxylic moieties do not support the activity of SPs as antiviral agents. This can be seen in the case of uronic acid in SPs structure. As known, uronic acid has both carbonyl and carboxylic groups in its structure. It has been reported that uronic acid at 22-42% in urunofucan isolated from *Adenocystis utricularis* shows less antiviral activity

compared to galactofucan from the same seaweed having only 4-5% of uronic acid [210].

In addition, the sulfate position also seems pivotal for SPs in exerting their antiviral activities. This could be seen in the case of 5 types of chondroitin sulfates (types A - E) which can be classified according to the sulfate groups distribution in their backbones. Of these types, chondroitin sulfate E shows relatively more potent antiviral activity than the other types, and this might be attributed to the presence of sulfate moieties at positions 4 and 6 in each disaccharide [38, 211-213].

However, a more recent study by Thuy *et al*. concluded a different result regarding the role of sulfate contents in exerting the antiviral activity of SPs. This group isolated three fucoidans from brown seaweeds (*Sargassum mcclurei*, *Sargassum polycystum*, and *Turbinara ornate*) and these fucoidans gave a potent activity as anti-HIV with IC_{50} ranging from 0.33 - 0.7 µg/mL. However, this activity is not linked closely to the sulfate contents or the positions of those sulfates in the compounds [39]. These findings indicate that other structural mechanisms might be involved in mediating fucoidans' antiviral activity.

Moreover, the molecular weight of the SPs is also important in exerting their antiviral activity. In a study, Witvrouw and De Clercq reviewed several semisynthetic SPs with various molecular weights (1 kDa - 500 kDa), and this group concluded that those with higher molecular weight gave higher antiviral activities. However, this activity is not always linearly correlated as no further increased antiviral activity was observed in the SPs with molecular weight above 100 kDa. A study by Liu and colleagues indicated that the size of sulfated polymannuroguluronate (SPMG) saccharides positively correlates with their anti-HIV activity with SPMG with more than 15-16 saccharides could bind to multiple gp120 [36].

Interestingly, the effect of molecular weight in influencing the SPs' antiviral potency seems to be more powerful than the effect of sulfate density. This could be valid in comparing chondroitin sulfate E and standard heparin in inhibiting herpes simplex virus. It is demonstrated that although heparin has a higher ratio of sulfate/disaccharide (approximately 2.7), its antiviral activity is lower than chondroitin sulfate E, having a lower ratio of sulfate/disaccharide (approximately 1.7). This might be attributed to the molecular weight difference between these compounds (chondroitin sulfate E = 70 kDa; heparin = 12.5 kDa) [38, 211]. The potent antiviral activity displayed by the SPs with larger chains might be associated with their higher possibility to interact and bind to viral entry proteins in multiple sites [38]. However, it is noteworthy that the SPs with lower molecular weight could also exert their antiviral activity through another mechanism. It has been suggested that the SPs with low molecular weight could inhibit the transmission and spread of a virus as these compounds could penetrate to infected sites, which the SPs cannot reach with higher molecular weight [214].

Other structural determinants may also affect the activity of SPs as an antivirus. These include the role of cationic replacement and the presence of hydrophobic bonds in the structural backbone of SPs. Lee and colleagues investigated the effect of cationic exposure on the structure of spirulan and an SP extracted from *Spirulina platensis*. This group found that the presence of either Cd^+ or Ag^+ in the structure would decrease the antiviral activity of spirulan against the herpes simplex virus, while the presence of Na^+ would give an opposite effect [215]. Regarding the role of hydrophobic bonds, in some cases, the presence of hydrophobic moieties could increase the antiviral activity of SPs. It is confirmed by several studies suggesting that the presence of alkyl chains increased the anti-HIV activity of the tested SP, while the introduction of hydrophilic groups decreased the activity [216, 217].

Based on the previous antiviral activity of other viruses, SPs are proposed to have potential efficacy in inhibiting or killing SARS-CoV-2. The putative mechanisms of action of these compounds in tackling the life cycle of SARS-CoV-2 are briefly described below. Four stages of the viral life cycle could be affected by the SPs. In addition to their ability to inhibit viral attachment to host receptors, *e.g*., ACE2, SPs could also block the activity of serine proteases, which could lead to the inhibition of viral penetration and fusion. Some studies linked these activities to the existence of sulfate groups in the SPs structure [205, 218, 219]. These negatively charged molecules would bind to the positively charged residues in the viral glycoproteins. Another mechanism stated that the sulfate groups could also bind to the cationic sites in the host receptor, resulting in the protection of this receptor from the occupation of the virus [218, 219].

The inhibition of viral endocytosis and uncoating processes is another mechanism by which SPs exert their antiviral effect [220]. These mechanisms cause the failure of the virus to release its genomic contents into the host cytoplasm to be inserted into the host machinery system. Finally, the SPs also attack the viral replication, transcription, translation, budding, and maturation stages [205]. These actions are mainly attributed to SPs' ability to inhibit the catalyzing effects of viral-specific enzymes, *e.g*., reverse transcriptase [221]. We provide the chemical structure of several sulfated polysaccharides in the Supplementary Figs. (**S1-S4**).

3.2. Phlorotannins

Phlorotannins are classified as polyphenols and are mainly found in brown algae, *e.g*., *Eisenia bicyclis*, *Ecklonia cava*, and *Ecklonia kurome* [222]. From those algae, several phlorotannins are identified, including phloroglucinol, eckol, phlorofucofuroeckol A, 8, 4”’-dieckol, 6, 6’-bieckol, and 8, 8’-bieckol [222, 223]. We have provided the chemical structure of several phlorotannin members in the Supplementary Figs. (**S1-S4**). In addition to their potent antiviral activity, it has been demonstrated that phlorotannins possess several other biological actions, such as antidiabetic, neuroprotective, antioxidant, and anti-inflammatory activities [47, 224, 225].

As stated above, one of the potential uses of phlorotannins is associated with their effects on tackling viral infections. Several viruses could be inhibited by phlorotannins, including HIV [47], porcine epidemic diarrhea virus [226], SARS-CoV [227], and SARS-CoV-2 [190]. The activities of phlorotannins as antiviral agents could be mediated by their ability to disturb several critical phases of the viral life cycle, *e.g.*, viral entry, transcription, replication, transcription, and viral maturation [47, 226, 228].

A study using Vero cells as the model found that the number of phloroglucinol groups correlated with the number of hydroxyl moieties in the phlorotannins structure was important for their ability to block the entry of the virus into the host cells [226]. This study indicated that single phloroglucinol produced no antiviral activity against the porcine epidemic diarrhea virus, while phlorotannins with more phloroglucinols gave lower IC_{50} values [226]. Intriguingly, although the number of phloroglucinol moieties in the dieckol structure is more than those had by phlorofucofuroeckol A, the IC_{50} of the latter is lower than that shown by the former phlorotannin indicating the superior antiviral activity of phlorofucofuroeckol A [226, 228]. This leads to another conclusion regarding the critical existence of the cyclopentane ring in mediating the antiviral activities of phlorotannins [226]. Furthermore, the activity of dieckol and phlorofucofuroeckol A in inhibiting murine norovirus exposed to RAW 264.7 cells has also been observed with both compounds giving similar activity as seen in their IC_{50} (0.9 μM) [225].

However, the superiority of phlorofucofuroeckol A over dieckol is not consistently displayed. A study investigating the role of various phlorotannins in inhibiting the main protease of SARS-CoV demonstrated that dieckol was the most potent phlorotannin with IC_{50} 2.7 μM compared to phlorofucofuroeckol A with IC_{50} 16.7 μM and other phlorotannins having less dibenzo-1, 4-dioxin moieties [227]. This indicates that the number of dibenzo-1, 4-dioxin structures in phlorotannins may play a significant role in their antiviral activity.

The presence of polyhydroxyl groups in the phlorotannin structure is noteworthy due to their hydrophilic properties. This could lead to a challenge in terms of developing them as antiviral drugs administered orally [229]. Therefore, structural modifications, such as the esterification of those hydroxyl groups, could enhance the lipophilicity of phlorotannins. However, it should be realized that this modification could impact the antiviral activity of phlorotannins, which further investigations could only confirm.

3.3. Terpenoids

Terpenes (monoterpenes, sesquiterpenes, diterpenes, and triterpenes) have various biological activities. Of those activities, the antiviral activities of terpenes have attracted much interest recently in seeking new anti-SARS-CoV-2 candidates. Due to space limitations, we only focus on the antiviral properties of marine diterpenes such as dolastane and dolabelladienetriol (see Supplementary Figs. **S1-S4** for the chemical structures of the compounds), which have been found to have potent antiviral activities. Structurally, diterpenes (C20) contain four-isoprene (2-methyl-1, 3-butadiene). They can be found naturally in terrestrial and marine sources such as various animals, plants, fungi, soft corals, and algae [114, 230].

The antiviral activities of diterpenes isolated from marine sources have been reported in some studies. For example, two fractions generated from *Dictyota menstrualis*, F-6 and Fac-2 fractions, rich in cyclic diterpenes, produce anti-ZIKV activity [112]. Another diterpene isolated from the seaweed *Canistrocarpus cervicornis*, dolastane, also gives anti-ZIKV activity, which might be related to its ability to inhibit viral replication [114]. A more recent study reported the ability of dolabellatrienone, dolabellane, and dolastane to inhibit ZIKV and chikungunya virus replications [111]. Marine diterpenes also target other viruses, including herpes, dengue, and coronavirus, which have been reviewed elsewhere [230]. The anti-HIV activity of dolabellanes and dolabelladienols isolated from the coral *Eunicea laciniata* and algae *Dictyota pfaffii*, respectively, has also been recorded [231]. These diterpenes act by binding to the allosteric sites of the reverse transcriptase leading to the dysfunctionality of this viral critical enzyme [43].

Analysis of the structure-activity relationship reveals that the anti-HIV activity of marine diterpenes might be correlated with the presence of H-bond donors and H-bond acceptors [43]. Specifically, the H-bond donor groups might be responsible for perturbing the functionality of the reverse transcriptase [43]. Related to this, lipophilicity could also affect the antiviral activity of marine diterpenes. This is represented by cLogP and polar surface (PSA) values. The study revealed that those with higher cLogP and lower PSA had no anti-HIV activity [43].

Furthermore, hydroxyl group addition also plays a certain role in increasing -anti-HIV activity. This could be seen in the case of 13- keto-1(R), 11(S)-dolabella-3(E), 7(E), 12(18)-triene isolated from the coral *Eunicea laciniata* having low anti-HIV activity. However, when this diterpene structure is modified by adding one hydroxyl group, the activity increases a hundred times [43]. Moreover, the epoxidized and epoxided forms of the 13- keto-1(R), 11(S)-dolabella-3(E), 7(E), 12(18)-triene display superior anti-HIV activity compared to their parent compound [43].

Moreover, the S and R configurations of marine diterpenes produce different influences on supporting the antiviral activity of the diterpenes. This might be seen in the case of dolabelladienol A (IC50 = 2.9 μM) and dolabelladienol B (IC50 = 4.1 μM), which display S and R configurations, respectively [42]. The S configuration gives lower IC_{50} (2.9 μM) indicating more potent activity than the R configuration (IC_{50} = 4.1 μM) [42, 43].

In addition to diterpenes, other marine terpenes also possess potency as antiviral agents. Some of them are avarol, brevione F, and stachyflin, which potentially inhibit the main protease of coronavirus [191, 198]. Others, such as

xiamycin, thyrsiferol, and liouvillosides, have activity as RNA-dependent RNA polymerase (RdRp) inhibitors [198].

3.4. Lectins

Lectins are proteins that selectively reversibly bind to carbohydrates, which are typically part of other bigger molecules. These compounds can be obtained from diverse sources, either from terrestrial or marine organisms [232]. Some studies have recorded several lectins with potent antiviral activities. Some of them are griffithsin, cyanovirin-N, and scytovirin [40, 233, 234]. It has also been reported that lectins can target various viruses potently, *e.g.*, HIV, EBOV, and coronaviruses [148, 184, 235].

Lectins exert their antiviral effects through their binding to viral glycoproteins. A study from Alexandre and co-workers reported that griffithsin, scytovirin, and cyanovirin-N could potently bind to specific mannose-rich glycans found in gp120 of HIV with IC_{50} 0.0004, 0.02 and 0.0018 μM, respectively [233]. In the case of their effect on EBOV, both cyanovirin-N and scytovirin could also interact with specific mannose residues in the EBOV envelope leading to the EBOV entry inhibition. Interestingly, these studies confirmed that scytovirin (IC_{50} = 0.041 μM) had more potent anti-EBOV activity than its counterpart (IC_{50} > 0.1 μM) [148, 149].

Mechanistically, lectins occupy glycosylation sites which are usually rich in mannose structures in the viral glycoproteins. Specifically, griffithsin is binding to M4, M7, and M9 arms of α(1, 2)mannobiose found in HIV gp120 [236]. Although oligomannose is the preferred viral carbohydrate for cyanovirin-N and scytovirin, the former prefers to bind to D1 and D3 arms, while the preferred sites for the latter are M1, M5, M8, and M9 arms [34, 237-239].

This action prevents the conformational changes of the viral glycoprotein, which are required to facilitate the virus's entry and fusion [34]. To support this action, antiviral lectins have a primary sequence containing a specific domain responsible for recognizing viral carbohydrates called the carbohydrate recognition domain [34]. The presence of disulfide bonds is observed in the structure of antiviral lectins such as scytovirin, cyanovirin-N, and actinohirin, while the other lectins do not possess this structure [34]. It is also noteworthy that, in some cases, oligomerization is important in mediating the antiviral activity of lectins. Some lectins show the ability to form oligomers (*e.g.*, cyanovirin-N and griffithsin), while others are sufficient for a monomer structure (*e.g.*, scytovirin, actinohirin, and microvirin) [34]. For lectins structure, please see Supplementary Figs. **S1-S4**.

3.5. Alkaloids

Several alkaloids extracted from marine organisms show potent activity as antivirus. Scedapin C, quinadoline B, norquinadoline A, scequinadoline A, and polycyclic guanidine alkaloids (*e.g.*, crambescidins) are some marine alkaloids displaying activity against some viruses (see Supplementary Figs. **S1-S4**), including herpes simplex virus, hepatitis C virus, influenza virus, ZIKV and SARS-CoV-2 [115, 189, 200].

Their antiviral activities could be mediated by their effects on several steps of the viral life cycle. The antiviral alkaloids have the potency to bind to viral spike glycoprotein, which could mediate the failure of the virus to get into the host cells [189]. Moreover, the alkaloids possess activity of binding to several viral enzymes (*e.g.*, papain-like protease (PLpro), chymotrypsin-like protease (3CLpro), RdRp) which are critical for the viral life cycle [189, 200]. Furthermore, their ability to disturb viral nonstructural proteins should also be considered [189].

Analysis of the structure-activity relationship reveals that the side chain length is an important determinant influencing the antiviral activity of marine alkaloids. Using polycyclic guanidine alkaloids as an example, El-Demerdash and colleagues demonstrated that alkaloids with a shorter alkyl side chain (*e.g.*, monanchoradins) gave weaker affinity to the target receptor compared to their counterparts with a longer side chain (*e.g.*, crambescidins) [200]. Intriguingly, when this group compared the lipophilicity of the tested compounds to their binding effectivity to the target receptor, they found that the compounds with more hydrophilicity gave more effective activity than those with more lipophilic properties [200].

After testing several indole alkaloids extracted from various marine sources, Guo and co-workers suggested that the presence of an F-ring is essential for exerting anti-ZIKV activity. This could be seen in the case of JBIR-03 and emindole SB having structural similarity except for the lack of F-ring in the latter compound. This group revealed that the anti-ZIKV of JBIR-03 having furan structure in its F-ring showed the most anti-ZIKV activity, while emindole SB produced no activity [115]. Although the influence is not as big as the F-ring influence, the B- and C-rings are also important for marine indole alkaloids in their antiviral activity [115].

3.6. Flavonoids

Several marine flavonoids, such as penicillixanthone A and thalassiolins (see the structure of the compounds in Supplementary Figs. **S1-S4**), display great potency as antiviral agents. These compounds exhibit activity against viruses, such as HIV, SARS-CoV, influenza A virus, and hepatitis C virus, with various putative mechanisms of action (*e.g.*, blockage of viral entry and inhibition of the critical viral enzymes) [52, 190, 240, 241].

As shown in Table **1**, thalassiolins, a group of glycosylated flavones, can inhibit integrase, a critical enzyme promoting the integration of the HIV genome into the host genome. Like other flavonoids, the presence of a pair of hydroxyl groups in the structure of thalassiolins plays an important role in facilitating the anti-HIV integrase activity of thalassiolins [242]. Furthermore, Rowley *et al*. showed that thalassiolin A (IC_{50} = 0.4 μg/mL), having two adjacent hydroxyl groups at C-3' and C-4', generated more potent activity in inhibiting integrase compared to its counterpart,

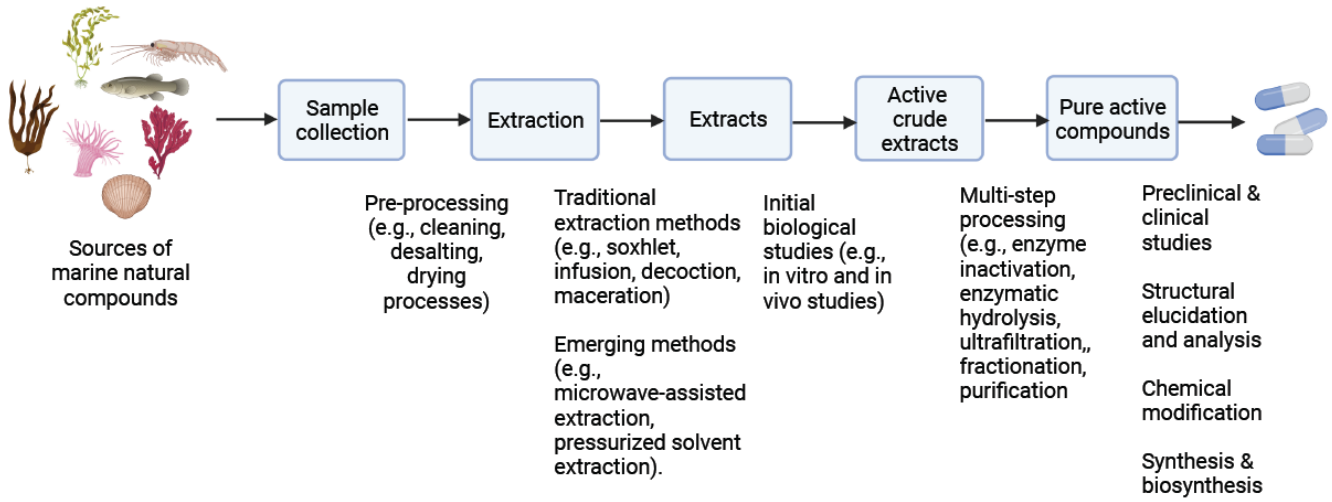

Fig. (2). General processes in developing a marine natural product (created with BioRender.com). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

thalassiolin B (IC_{50} = 43 µg/mL) and thalassiolin C (IC_{50} = 28 µg/mL) possessing only one hydroxyl group at C-4' with methoxy substituent and hydrogen atom at C-3', respectively [52].

It is also indicated that the anti-integrase activity of thalassiolins is closely linked to the presence of a sulfated glucopyranosyl group at C-7 [52]. Interestingly, flavone glycosylation is not always correlated with increased anti-integrase activity. For example, quercetin glycosylation on several sugar moieties, *e.g.*, glucose, arabinose, and rhamnose, decreases quercetin's ability to inhibit viral integrase [243]. Further studies need to be conducted to decipher the effect of glycosylation patterns on the antiviral activity of flavonoids, especially flavones.

Another flavonoid showing potent antiviral activity is penicillixanthone A. This flavonoid is obtained from *Aspergillus fumigates*, a fungus symbiont in jellyfish. A study by Tan and co-workers demonstrated the potent activity of penicillixanthone A in inhibiting the M-tropic and T-tropic strains of HIV by blocking the binding between those strains and the CCR5 and CXCR4 coreceptors, respectively [41]. This leads to the blockage of HIV entry into the host cells. A docking analysis exhibited that four hydrogen bonds mediate the interaction between penicillixanthone A and the CCR5 coreceptor, while the interaction between the compound and the CXCR4 coreceptor is mediated by three hydrogen bonds [41].

CONCLUSION

The marine products possessing activity as antivirus come from various groups of compounds, *i.e.*, polysaccharides, alkaloids, terpenes, flavonoids, tannins, and peptides. Those act as antivirus through their direct activity by inhibiting various essential steps involved in the viral life cycle, *e.g.*, viral entry and fusion, replication, transcription, translation, and viral release from the host cells. In addition, the compounds can also exert their antiviral activities by modifying the protective system of the host cell, *e.g.*, by occupying the host receptor utilized by the virus as the entrance into the cell, preventing viral binding to that receptor.

The oceans provide many natural products showing potency as antiviral agents. As the world has been facing virus-caused outbreaks and the available treatments give inconsistent satisfying outcomes to eradicate the virus, marine natural products may be a great choice to explore extensively. Supported by the availability of modern technology, the processes from sample collection from the depth of the ocean until the production of new marine-based drug entities is not as challenging as faced decades ago.

However, exploring marine natural products should strongly consider supply sustainability without harming the marine ecosystem. Compared to natural products collected from terrestrial sources, the challenges that must be experienced in the effort of collecting marine natural products are bigger because of some reasons, *i.e.*, 1) it needs sophisticated and expensive technology; 2) it requires skillful personnel to get into the depth of the ocean and collect the samples properly; 3) as natural products typically present in a minute concentration, then it needs a large number of samples to be collected from the depth where this could bring a concern for handling processes and the diversity of the marine ecosystem; 4) although most of the handling, extraction, or isolation processes of marine samples are the same as the processes undertaken for exploring product sourced from terrestrial sources, some processes need to be performed delicately given the unique characteristic of the marine samples (*e.g.*, cleaning and desalting processes, selection of the appropriate solvents, *etc.*) [3, 244, 245]. We summarize the general processes developed to extract, isolate, characterize, and purify natural marine compounds in Fig. (**2**).

To sum up, various unique metabolites extracted from marine sources are the potential to be developed as antiviral agents. As the world always fights against viral outbreaks and no satisfying outcomes are generated from the available antiviral drugs, marine natural products should be considered as the breakthrough.

LIST OF ABBREVIATIONS

???? = ????????

AUTHORS' CONTRIBUTIONS

M.S. and S.S.M did the conceptualization of the study. S.S.M. created the methodology. Y.M.E. used the software; S.S.M. and F.N. did the validation process. M.S. and S.S.M. worked on the formal analysis; M.S., S.S.M. and Y.M.E. conducted the investigation together. S.S.M. was responsible for the resources and data curation; M.S., S.S.M., Y.M.E. S.M., T.B.E., H.H., F.N., and J.S-G wrote the original draft, which S.S.M. and F.N. reviewed and edited. S.S.M. was also responsible for visualization; F.N. and J.S-G were supervising. T.B.E., F.N., and J.S-G were responsible for project administration; J.S-G made the funding acquisition. All authors have read and agreed to the published version of the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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