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Review Article

A Review of Marine Natural Product Resources with Potential Bioactivity Against SARS-COV-2

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ABSTRACT

The emergence of new pathogenic viruses and the constant outbreak of viral diseases have created an upsurge in novel antiviral agents. Marine natural products are the most unexplored reservoir of novel, biologically active, chemically diverse compounds. A systematic literature review was conducted using PRISMA guidelines, accessing four major databases; PubMed, Science Direct, Scopus, and Google Scholar. Numerous studies supported the robust antiviral activity of marine resources against drug-resistant viruses such as SARS, Ebola, Influenza, and HIV. However, adequate research on marine resources for developing anti-covid therapy is lacking. The aim of the review was to explore the marine resources and their compounds that could lead to developing an effective antiviral drug. We also highlighted the current status of novel compounds against different species of corona family and discussed the future prospects of marine resources against COVID-19 management.

Keywords: Antiviral agent, marine resource, Covid-19, bioactive compound, SARS-CoV-2.

Introduction

Safeguarding public health has become a critical issue due to the emergence of new viral infections such as SARS Cov, MERS Cov, and COVID-19 infections, which have compromised human survival. Recently, the Covid-19 pandemic has broken out and led to 466,871 deaths till 21 June 2020.[1,2] Despite the progress made in immunization and drug development, no drug or vaccine has yet been discovered. Although, intensive studies are going around the world to find novel drugs to combat the mutant virus of the corona family. It is urgent to explore alternate antiviral therapies, including several natural products and herbal medicines, against such deadly viral infections.[3,4] The ocean provides enormous opportunities to discover new compounds as it has more than 13,000 molecules, out of which 3000 have active properties.[5,6] The ocean accounts for 75% of the world and has an enormous range of biodiversity, which are still unexplored.[7,8] Marine organisms produce unique chemical compounds that embrace polysaccharides, amino acids, glycosides, phenolic compounds, alkaloids, terpenoids, peptides, steroids, halogenated ketones, and polyketides to cope the diverse environmental condition and to protect themselves from predators.[9] Marine resources account for 50% of the earth's total diversity, with only a few (0.01%-0.1%) identified and much to investigate. This constitutes the marine organism as a valuable resource for novel compounds, and much consideration has been derived from developing new drugs to combat the SARS-CoV-2 virus.[2]

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In Asian countries, there is a long history of the extensive usage of marine macro and microalgae as functional foods and medicinal purposes. Marine resources' antiviral and antibacterial activity have been known for thousands of years. Much of the recent findings revealed the antiviral potential of marine resources against different pathogenic viruses such as human immunodeficiency virus-1 (HIV-1), herpes simplex virus-2 (HSV-2), Junin virus (JV), poliovirus (PV), severe acute respiratory syndrome (SARS) virus, measles virus, and influenza virus.[10,11] However, there are still gaps in our knowledge of their activities. Marine resources constitute a vast untapped reservoir of highly diverse and unique natural products with wide-ranging biological action. This motivated studies on *in vitro*, *in vivo*, and clinical analyses on the antiviral activity of marine resources to develop new antiviral drugs and pave the way to create new drugs against the new COVID-19 infections. This review aimed to screen the marine resources and their compounds that could lead to developing effective antiviral drugs. We highlighted the antiviral activity of novel compounds against different drug-resistant viruses and discussed the prospects of marine resources against COVID-19 management.

The exploitation of antiviral compounds from Marine Resources

Antiviral compounds from marine bacteria

One of the promising sources of therapeutic drugs is marine organisms. Research suggests that very few studies have been performed on antiviral compounds derived from marine bacteria. The marine bacterial exopolysaccharides (EPS) were the source of antiviral compounds produced by many bacteria to survive in adverse conditions, approach for growth, and attachment to solid surfaces.[12] Researchers are trying to explore new exopolysaccharides from extreme marine environment bacteria that can tolerate intense temperature, pressure, high concentrations of heavy metals, and H2S production.[13] Some deep-sea bacteria that survive in an extreme environment include strain HYD721, *Alteromonas macleodii subsp. fijiensis*, *Alteromonas infernus* and *Vibrio diabolicus*.[12] There is a diverse application of these bacterial EPS in distinct industrial fields as they possess novel chemical compositions, structures, and properties. In *Pseudomonas* sp., a bioactive compound

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named glycosaminoglycan was explored, exhibiting antiviral potential against influenza virus A and B.[14] According to Rinker and Kelly,[15] extra polysaccharides were produced by hydrothermophilic *Thermococcus litoralis* and *Thermotoga maritime*.

Exopolysaccharides

A significant number of EPSs are obtained from bacteria, and few have been reported from Archaea.[16] The polysaccharides derived from marine bacteria differ in their biological activities, and chemical composition, and some of them show immunomodulatory and antiviral activities[17,18]. In host cells, the absorption and penetration of viruses are interfered with by sulfated exopolysaccharides (EPS), inhibiting diverse retroviral reverse transcriptases. EPS-1 and EPS-2 were the new exopolysaccharides from two bacteria *Bacillus licheniformis* and *Geobacillus thermodenitrificans*, mainly found in the shallow marine hot spring of Vulcano Island, Italy.[12] Both the EPS at a concentration of ≤300 g/ml were non-toxic to PBMC's and WISH cells. There was a significant reduction in HSV-2 viral titer was observed by EPS-1 and EPS-2 at 200 and 300 g/ml concentrations showing the antiviral property of these exopolysaccharides. The cyanobacterium Arthrospira *platensis* produced polysaccharides containing spirulan-like molecules that inhibit the growth of human immunodeficiency virus type 1, human cytomegalovirus, herpes simplex virus type 1, and human herpesvirus type 6.[19]

Macrolactin A

Another antiviral compound isolated from marine bacteria is macrolactin A with a 24-member lactone ring, open chain acids connected to glucose-pyranosides. This compound protects T-lymphocyte from an HIV infection at 10 g/ml concentration and inhibits cancer cell proliferation.[20]

Antiviral compounds from Fungi

Fungi occupy essential roles in terrestrial ecosystems as decomposers, drivers of the nutrient cycle in detritus environments, and parasites and symbionts.[21] Due to their pathogenic and symbiotic roles, these organisms evolved to possess rich and promising novel bioactive natural products.[22] Several of these metabolites possess antiviral properties against different influenza viral strains (Table 1). The rich antiviral activities of marine fungi-derived compounds against the influenza virus can serve as baseline data for understanding the potential against a similar RNA virus, the SARS-CoV2 family.[23] Mangroves and corals host most of these fungal species, and the studies performed were only limited to screening, and only a few conducted experiments to establish mechanisms of action.

One of the mechanisms of action of marine fungi-derived antiviral compounds is the inactivation of viral replication. As shown in work on Enterovirus-71 (EV-71), compounds from *Stachybotrys* sp. were found to inhibit viral replication of the virus *in vitro*.[24] Another means of collapsing the viral replication is inhibiting the integrase enzyme of HIV-1.[25] Moreover, Integric acid inhibits amalgamation reactions catalyzed by pre-integration compounds from HIV-1 infected cells. The same action was also noted in emerimidine A and B, where H1N1 viral replication was inhibited in Madin-Darby Canine Kidney (MDCK) cell lines.[26]

Another mode of action is by destabilizing the viral membrane. In this way, these metabolites exert direct extracellular virucidal activity against HSV particles and thus inhibit HSV transmission.[27] In the influenza virus, a unique mechanism of action was noted from Stachyfin isolated from *Stachybotrys* sp.,[28] where the metabolite suppresses the first stage of H1N1 and H2N2 viral infection. The antiviral experiment was tested *in vivo* by oral administration of stachyfin with a solution of PEG.

Antiviral compounds from marine algae

The chemodiversity of algae offer a novel approach and can be recognized as a relevant source for developing a future natural antiviral drugs.[45,46] *In vivo* or *in vitro* antiviral activity against a broad variety of viruses such as simian and human immune deficiency viruses, herpes viruses (HCMV, HSV-1, HSV-2), paramyxoviruses (RSV), togaviruses (semliki forest virus rhabdoviruses (VSV), sindbis virus) was shown by the compounds extracted from algae. From red algae extracts, polysaccharide fractions were isolated, inhibiting the growth of HSV and other viruses.[47] The polysaccharides extracted from marine algae show antiviral effects towards influenza B and mumps virus.[48] Sulfated polysaccharides were isolated from algae and other compounds which possess antiviral activity against enveloped viruses. Thus, interest in studying antiviral compounds isolated from marine algae increased (Table 2).

Table 1: Antiviral properties of compounds derived from fungi

Class	Species	Compound	Active against	Reference
Sordariomycetes	*Fusarium heterosporum*	Equisetin	HIV-1	25
	*Stachybotrys*sp.	Stachybogrisephenone B, Grisephenone A, and 3,6,8-Trihydroxy-1-methylxanthone	EV-71	24
	*Stachybotrys*sp.	Stachyfin	H1N1 and H2N2	28
Eurotiomycetes	*Aspergillus terreus* SCSGAF0162	11a-dehydroxyisoterreulactone A, Arisugacin A, Isobutyrolactone II, and Aspernolide A	HSV	29
	Aspergillus terreus MXH-23	Butyrolactone Derivatives	H1N1	30
	Aspergillus terreus OUCMDZ-1925	Rubrolide S	H1N1	31
	Aspergillus terreus SCSGAF0162	Asperterrestide A	H1N1 and H3N2	32
	Aspergillus terreus Gwq-48	Isoaspulvinone E, Aspulvinone E, and Pulvic acid	H1N1	33
	*Aspergillus sydowii*ZSDS1-F6	Diorcinol, Cordyol C, and (*Z*)-5-(Hydroxymenthyl)-2-(6′)-methylhept-2′-en-2′-yl)-phenol	Influenza virus	34

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	Aspergillus sp. SCSIO 41501	Aspergillipeptide D	HSV-1	35
	Aspergillus sp. SCSIO XWS02F40	Asteltoxin E and F	H1N1 and H3N2	36
	Aspergillus ochraceus Jcma1F17	6,9-dihydroxy-14-*p*-nitrobenzoylcinnamolide.	H3N2 and EV-71	37
	Dichotomomyces cejpii F31-1	Scequinadoline A	Dengue virus serotype-2	38
	Emericella sp.	Emerimidine A and B	H1N1	26
	Penicillium chrysogenum PJX-17	Sorbicatechol A and B	H1N1	39
	Penicillium oxalicum 0312F1	2-(4-hydroxybenzyl) quinazolin-4(*3H*)-one and Methyl 4-hydroxyphenylacetate	Tobacco Mosaic Virus	40
	Neosartorya fischeri 1008F1	AGI-B4 and 3,4-dihydroxybenzoic acid	Tobacco Mosaic Virus	41
Leotiomycetes	*Scytalidium* sp	Halovirs A–E	HSV	27
	Phoma sp.	Phomasetin	HIV	42
	Cladosporium sp.	Oxoglyantrypine, Norquinadoline A, Deoxynortryptoquivaline, Tryptoquivaline, and Quinadoline B	Influenza virus	43
Dothideomycetes	*Alternaria* sp. ZJ-2008003	Tetrahydroaltersolanol C and Alterporriol Q	Porcine Reproductive and Respiratory Syndrome Virus	44

Fucoidan

The sulfated polysaccharide (fucoidan) was isolated from *Fucus vesiculosus*, also known as brown seaweeds, which inhibits the human cytomegalovirus (HCMV),[49] DNA virus replication and herpes viruses (HSV-1, HSV-2). In the case of RNA viruses, fucoidan was also active against HIV-1, vesicular stomatitis virus (VSV), and Sinbis virus.[50] *In-vitro* HIV RT was inhibited at a concentration of 50 g/ml by a noncarbohydrate component of fucoidan isolated from *F. vesiculosus.* [51] The target cells pre-incubated with fucoidan protect them from HIV-1 infection [51] since fucoidan holds low anticoagulation properties along with antiviral activity.[50]

Tannins, Lectins, and Polysaccharides

The anti- HIV-1 activity was shown by algal products (tannins, lectins, and polysaccharides) derived from marine macroalgae.[52]

Galactan sulfate

The polysaccharide named galactan sulfate (GS) was extracted from *Agardhiella tenera* also known as red seaweed. It indicates antiviral activity against HIV-1 and HIV-2 due to the presence of a polysaccharide called galactan sulfate (GS).[53] GS also inhibits other enveloped viruses such as arenaviruses, herpes viruses, and toga viruses by inhibiting virus adsorption and preventing expression of immediate early antigens of the virus.[53]

Calcium spirulan

Many cyanobacteria species produced the anti-HIV active sulfoglycolipids in abundant amounts as it is a part of chloroplast membrane, whereas from marine blue–green alga,[54] *Arthrospira platensis*, a sulfated polysaccharide named calcium spirulan (Ca-SP) was isolated and it has potential antiviral activity against HIV-1 in MT-4 cells.[55] Ca-SP was found to inhibit selectively the penetration of virus into host cells by retention of the molecular conformation and by chelation of calcium ions with the sulfate groups.

A1 and A2

The extracellular sulfated polysaccharides, A1 and A2, were extracted and purified from a marine microalga named *Cochlodiniumpolykrikoides*. [55] These polysaccharides A1 and A2 show cytopathic effects by inhibiting the effects of RSV types A and B grown on Hep-2 cells and influenza virus types A and B grown on MDCK cells. In the case of MT-4 cells, an IC_{50} value of 1.7g/ml was shown by A1 and A2 against HIV-1. In HMV-2 cells, the activity of A1 was against HSV-1, whereas the activity of A2 was against parainfluenza virus type 2.[55]

p-KG03

Gyrodinium impudicum is a marine microalga that produces p-KG03, a sulfated polysaccharide with glucose units conjugated to sulfated groups and uronic acid. p-KG03 interacts with viral particles and prevents tumor cell proliferation and infection caused by encephalomyocarditis virus.[56]

Diterpenes

From the marine alga *Dictyota menstrualis*, two diterpenes named Da-1 and AcDa-1 were isolated which inhibits the replication of the HIV-1 virus in the PM-1 cell line.[57] Da-1 (97%) and AcDa-1(70%) at 100M inhibit the production of viruses by inhibiting the RNA-dependent DNA polymerase activity of the viral reverse transcriptase enzyme. The proliferation and cell viability were not affected by these compounds.[57]

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Table 2: Antiviral properties of compounds derived from algae

Microalgal source	Type	Secondary metabolites	Bioactive compounds	Biological activities	References
Griffithsia sp.	Red algae	lectin	Griffithsin 12	Antiviral activity against SARS-CoV, hepatitis C Infection, HSV-2 vaginal infection	61
Porphyridium sp.	Red algae	sulfated polysaccharide (carrageenan)	xylose, glucose, galactose, and sulfate esters, hexuronic acids glucuronic acid and galacturonic acid	herpes simplex virus HSV1 and HSV-2, varicela zoster virus (VZV), retrovirus murine sarcoma virus (MuSV-124), MuSV/MuLV (murine leukemia virus), hepatitis B virus (HBV), viral haemorrhagicsepticaemia virus (VHSV), African swine fever virus (ASFV), vesicular stomatitis virus (VSV), vaccinia virus VACV and VACV-GFP and ectromelia virus (ECTV)	62
Schizymenia pacifica	Red algae	polysaccharide	sulfated galactan	Antiviral activity against herpesviruses (HSV types 1 and 2)	63
Enhalus sp.	Sea grass	-	3-amino-3-deoxy-D-glucose, a new glucanase, and cyclic acylpeptides	Antibacterial activity against *Mycobacterium tuberculosis*	64
Zosteraceae family	Sea grass	polyphenol complex	rosmarinic acid, luteolin, and luteolin disulfate	Antiviral activity against Tick-Borne Encephalitis Virus, herpes, influenza, hepatitis, yellow fever	65
Gracilaria corticata	Marine red algae	terpenoid	4-acetoxy-2 hydroxy, 2, 6, 6-trimethyl cyclohexanone	antiviral activity against herpes simplex virus types 1 and 2	66
Gracilaria lemaneiformis	Red algae	sulfated polysaccharide	-	anti-influenza virus	67
Dictiyota bartaysiana and *Turbinariade currence*	brown algae	sulphated polysaccharide	fucoidan	HIV (HIV-1 and HIV-2)	68
Sargassum vulgare.	brown seaweed	lipolytic enzymes lipid	1-lyso-2-DHA-phospholipids, CCAP 927/1 sulfoquinovosyldiacylglycerols (SQDGs)	Antiviral	69

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Ecklonia stolonifera	Brown Alga	sterols and phlorotannins	-	Influenza Virus Neuraminidase Inhibitory Activity porcine epidemic diarrhea coronavirus infection and hemagglutination acetylcholine esterase inhibitory activity	[70]
Spirulina	Blue green algae	protein	Griffithsin (GRFT)	Antiviral activity against SARS coronavirus (SARS-CoV)	[71]
Caulerpa racemosa	Green algae	sulfated polysaccharide Alkaloids Flavonoids Glycosides Phenols Saponins	Cyanovirin-N (CV-N), Calcium spirulan (Ca-SP) – Antiviral 624 polysaccharide	Antiviral activity against human immunodeficiency virus (HIV), hepatitis C virus (HCV), anti-hepatitis activity Immuno-modulating antioxidant potential	[72]
		alkaloids, phenolics, flavonoids and steroids	seaweed extracts against DENV serotypes 1–4	Antiviral activity against SARS-CoV	[73,74]

Griffithsin

A new type of lectin with potent antiviral activity named as griffithsin was extracted from red alga Griffithsia sp., which inactivates HIV and primary isolates of HIV-1 in a monosaccharide-dependent manner by binding viral glycoproteins.[58]

Sea algal extract

Schizymenia pacifica is marine algae were purified to produce a sea algal extract (SAE) compound. The composition of this compound includes 3,6-anhydrogalactose (0.65%), galactose (73%) and sulfonate (20%). Research suggests that SAE inhibits in vitro replication of HIV and HIV RT and does not show any undesirable effects on cell growth, thus producing a significant role in the inhibition of reverse transcriptase (RT).[59]

Naviculan

From deep-sea water in Toyama Bay, Japan, a diatom was collected termed *Navicula directa*, from which a sulfated polysaccharide naviculan was extracted, and this compound interferes in the early stages of viral replication by inhibiting HSV-1 and HSV-2.[60]

Antiviral compounds from Sponges

Sponges (*Phylum Porifera*) are organisms that do not possess spines and are considered the most primitive multicellular animal.[75,76] Due to the inability to move and the lack of physical defenses, they are often susceptible to marine predators. For this reason, these organisms can produce a myriad of chemical defenses to deter predators as part of their evolutionary adaptations.[7] Moreover, a growing body of evidence suggests that the antiviral compounds derived from marine sponges may come from bacterial and fungal symbionts.[77]

As shown in Table 3, a compound from *Axinella corrugata* showed effective inhibition of SARS-CoV viral replication in Vero cells, and this activity was found to be non-cytotoxic.[78] Moreover, due to the limited amount extracted from this compound, it was hypothesized that this is of microbial origin. Pseudotheonamide C and D, isolated from the sponge *Theonellaswinhoei*, were found to form covalent bonds with Cys145 residue of SARS-CoV-2 $3CL^{pro}$ through a docking study.[79] The majority of the antiviral studies done on sponge-derived compounds were on HIV. The inhibition of viral replication was believed to be the reason for their antiviral properties. Some other suggested targets of these antiviral compounds are viral adsorption and viral penetration. One example is the study performed on 4-methylaaptamine from *Aaptos aaptos* where results showed that the antiviral properties could be partially explained by the inhibition of viral penetration in live cells, while viral adsorption was rejected as a possible mechanism of action.[80] Similarly, avarol from *Dysidea avara* was noted to block the expression of p24 and p17 gag proteins, thereby inhibiting viral replication.[81] A similar mechanism of action was noted from an antiviral compound isolated from *Petromica citrina* where virus attachment and penetration to Vero cells were inhibited.[82]

Antiviral compounds from Echinoderms

Echinoderms inhabit the benthic region, which is considered useful in medical research due to its richness in species and chemical biodiversity[100,101]. One particular importance in medicine of these organisms in this region is their substantial potential lead source of antiviral compounds.[102] Although no experimental and docking study was conducted on echinoderm-derived compounds against the family of coronaviruses, rich data on antiviral activities against other viral strains can be used as a benchmark for future studies. This signifies the importance of understanding their ethnopharmacological value other than the well-established ecological significance of these species.[103] Most of the antiviral compounds extracted from echinoderms are active against HSV, as shown in Table 4.

The mechanism of action of these compounds have been theorized to be a result of the inactivation of viral particles.[104] In sea cucumbers, the mechanism believed to be due to the presence of sulfated polysaccharides that possess anti-adsorption activity against Herpes Simplex Virus Type 1 (HSV-1). This mechanism has been well documented in other marine organisms.[56,105] The action of polysaccharides against this virus was also documented in another species of sea cucumber, where an acid mucopolysaccharide showed to fight against HSV-1[106]. Similarly, virucidal effects against HSV-1 were also noted from the sulfated carbohydrate chain in a sea cucumber.[107] This further indicates that naturally occurring saponins possess inhibitory effects against HSV by interfering with the early step in the viral replicative cycle or by a direct virucidal effect. A similar mechanism of action was noted in the HIV-1 virus, where the active compound was noted to inhibit viral replication.

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Table 3: Antiviral properties of compounds derived from sponges

Class	Species	Compound	Active against	Reference
Demospongiae	*Aaptos aaptos*	4-methylaaptamine (alkaloid)	HSV-1	[80]
	Theonella sp.	Papaumides A to D (cyclic depsipeptides)	HIV-1	[83]
	Tectitethya crypta	Ara-A (Nucleoside)	HSV-1, HSV-2, and VCV	[84]
	Dysideaavara	Avarol (Sesquiterpene hydroquinone)	HIV-1 and Human T-lymphotropic retrovirus	[85]
	Xestospongia sp. and an unidentified Haplosclerida species	Haplosamates A and B (Sulfamated sterol)	HIV-1	[86]
	*Halicortex*s p.	Dragmacidin F	HIV-1	[87]
	Hamigeratarangaensis	Hamigeran B	Herpes and polio virus	[88]
	Mycale sp.	Mycalamide A and B	A59 coronavirus and HSV-1	[89]
	Siliquariaspongia mirabilis	Mirabamide A, C, and D	HIV-1	[90]
	Stylissa carteri	Oroidin	HIV-1	[91]
	Erylus discophorus	Sulfated polysaccharide	HIV-1	[92]
	Acanthostrongylophora sp.	Manadomanzamines A and B	HIV-1 and AIDS opportunistic fungal infections	[93]
	Hyrtios sp. and *Haliclona* sp.	1304KO-327 and 1304KO-328	Rotavirus	[94]
	Carteriospongia sp.	Hennoxazoles A	HSV-1	[95]
	Petromicacitrina	Halistanol sulfate C	HSV-1	[82]
		Bromopyrrole metabolites	HSV-1	[96]
	Spongia sp.	Isospongiadol	HSV-1	[97]92
	Callyspongia siphonella	Sipholenol A, Neviotine A*, Sipholenol L*	Hepatitis A virus, HSV-1	[98]
Calcarea	*Pericharaxheteroraphis*	Imidazole Alkaloids	H1N1	[99]

Table 4: Antiviral properties of compounds derived from echinoderms

Class	Species	Component	Active against	Reference
Holothuroidea	*Holothuria* sp.	Crude extract	HSV-1	[104]
	Sticophus japonicus	Acid Mucopolysaccharide	HSV-1	[106]
	Staurocucumis liouvillei	Liouvilloside A	HSV-1	[107]
	Cucumaria japonica	Cucumariaxanthins C	Eipstein-Barr Virus	[108]
	Cucumaria frondosa	Extracts from aquapharyngeal bulb	HSV-1	[109]
	Thelenota anana	Fucosylated chondroitin sulfate	HIV-1	[110]
Ophiuroidea	*Ophioplocus januarii*	Sulfated polyhydroxysteroids	HSV-1, Junín virus, respiratory syncytial virus, and polio virus	[111]
	Astrotoma agassizii	Sulfated Polyhydroxysteroids	HSV-2, Junín virus, and polio virus type 3	[112]

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Asteroidea	*Asterina pectinifera*	Polyhydroxysteroids and Asterosaponins	HSV-1	[113]
	Certonardoa semiregularis	Certonardoside A, I, and J	HSV-1*, HIV*, Coxsackievirus*, encephalomyocarditis virus*, and vesicular stomatitis virus*	[114]
	Acanthaster planci	Phospholipase A2	HIV	[115]
Echinoidea	*Tripneustes depressus*	Coelemic fluid	SHV-1 and rabies	[116]
	Sea Urchins *(i.e., Paracentrotus lividus and Psammechinus miliaris)*	Echinochrome A	HSV-1 and TBEV	[117]
Crinoidea	*Gymnocrinus richeri*	Gymnochrome B and D and Isogymnochrome D	Dengue virus	[118]

*weak antiviral activity

This mechanism is believed to be due to sulfated polysaccharides that possess anti-adsorption activity. Similarly, the action mechanism of an acid polysaccharide against the virus was also documented in another species of sea cucumber.[106,107] This highlights the inhibitory effects of naturally occurring saponins against viral strains by interfering with the early step in the viral replication or by a direct virucidal effect.

Starfish have also attracted researchers as a fascinating source of bioactive marine natural products.[119] The antiviral properties were believed to be due to sulfated sterol compounds, which possess activity against human immunodeficiency virus derived from these marine invertebrates.[120] Moreover, the antiviral properties of starfish-derived compounds were suggested to be due to the bioactivity of the hydroxyl and sulfate groups and that the sugar unit attached to the compound has a significant effect on its activity.[113] Phospholipase from *Acanthaster planci* crude venom was also found to reduce the *in vivo* HIV infection rate and HIV-specific RNA in PBMC culture by inhibiting viral replication.[115] This suggests that the antiviral properties are not only limited to the inactivation of viral particles but also by arresting RNA replication.

Similarly, brittle stars and sea urchins possess compounds with antiviral properties. This activity is believed to be due to the sulfate group, critical to inhibiting the virus.[112] This relationship between the structure of sulfate groups and their bioactivity is not surprising since a number of sulfated steroids have been reported to possess a myriad of biological activities.[121] Moreover, thermostable antiviral compounds were also isolated from sea urchins, which could be a promising source of antiviral drugs.[116]

Future Directions

The first antiviral drug "vidarabine" approved by US Food and Drug Administration (FDA), 1976 derived from the natural arabino-nucleosides. The SARS-CoV-2 main protease (M^{pro}) is identified as a pharmacological target for discovering and designing inhibitors such as SARS-CoV-2. To date, 17 potential SARS-CoV-2 M^{pro}inhibitors have been identified among marine natural products. Among them, Gentile et al.[79] found compounds **7(**8,8'-Bieckol), **10(**6,6'-Bieckol), and **11(**Dieckol) are as the most potent inhibitor against the SARS-CoV-2 due to strong affinity for main protease (M^{pro}). These compounds belong to the family of phlorotannins, isolated in the brown algae *Ecklonia cava.* Pseudotheonamide D (**12**) and pseudotheonamide C (**17**) have been isolated from the marine sponge *Theonella swinhoei* and have shown good inhibitory activity on the serine protease.[122] Currently, Khan et al.[123] investigated five marine compounds, namely C-1, C-2, C-3, C-4, and C-5 to target SARS-CoV-2 main protease (M^{pro}) (PDB ID 6MO3) and showed good binding affinity to the active site of the protease. The other docking study identified Apigenin- 7-*O*-neohesperidoside, Luteolin-7-rutinoside, and Resinoside, belonging to the class of flavonoids, exhibit high binding interaction.

Compared to synthetic compounds, the success ratio for natural compounds from marine resources is very high, and their potential in clinical trials is very promising.[124] Almost all marine organisms (e.g., bacteria, algae, sponges, fungi, corals, ascidians, etc.) contain natural products with potent biological activity that have been investigated for their antiviral activity. However, no study is available [125] on the clinical trials of such antiviral compounds extracted from marine resources specifically dedicated to COVID-19 treatment. Therefore, it is also an unexplored area for the researcher to explore the antiviral compound from marine resources and emphasize its impact on coronavirus infection. This highlights that future researches may be conducted to screen out identified compounds from marine organisms against coronavirus. Docking studies and other pharmacological and bioactive assays are important in assessing, elucidating, and identifying the mode of action, mechanism, and inactivation of viruses.

Conclusion

The previous SARS epidemic, Ebola, AIDS, and the current Covid-19 pandemic have created the task of finding a solution to counteract viral entry and pathogenesis. The marine natural products are the reservoir of largely unexplored structural and chemical diverse compounds and also have high growth rates and biomass productivity with other natural resources. In this review, we report a large number of compounds in almost all marine organisms (e.g., bacteria, algae, sponges, fungi, echinoderm, etc.) display *in vitro* and *in vivo* efficiency to discover drugs against human viruses, including SARS, Ebola, influenza, AIDS, and herpes. The marine resources have chemo diversity, which may serve as potential resources to develop new antiviral drugs and pave the way to develop new drugs against the new COVID-19 infections. Although, more in vivo and clinical studies are needed to conduct in search of a new, potential drug against SARS-CoV-2. As such, these descriptions of the mode of actions, mechanisms, pharmacology, bioactivity of different compounds isolated from marine organisms can be used in further screening for lead compounds with bioactivity against coronavirus.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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