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REVIEW ARTICLE

Marine bioactive compounds and their potential antiviral properties

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ABSTRACT
Many useful commercial goods come from marine species, and the rich variety of the oceans has only been partially explored. Industrial and academic cooperation may collect, isolate, and classify marine species containing bioactive substances, such as fungi, bacteria, cyanobacteria, micro-algae, macro-algae and marine invertebrates, from the world's coastlines and oceans. These organisms' pure extracts and chemicals have anti-inflammatory, anticancer, anticoagulant, antibacterial and antiviral biological properties. Since current therapies are failing, viral diseases require new drugs. Many marine organisms have yielded novel pharmacologically active compounds. Marine species' primary or secondary metabolic compounds possess antiviral properties, according to several studies. Over 40 pharmacological compounds, including potential antiviral therapies and alternatives, are available. Interest in marine-derived antiviral compounds and new marine culture and extraction technologies will speed the search for compounds with pharmacological uses in the marine environment.
Keywords: *Marine bacteria, marine bioactive compounds, secondary metabolites, antiviral activity*

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INTRODUCTION

The planet surface is covered by 70% ocean [1]. The majority of organisms were found in marine ecosystem [2]. With 300,000 identified species and many more to be studied, the tremendous chemical and biological variety of marine species can be attributed to the ocean's size and unique habitat [3]. Below 0.01%–0.1% of oceanic microbial organism is known to science, demonstrating how marine research can provide access to a wide range of marine organisms and their chemically active elements [4]. Almost every form of marine life has been studied scientifically for its natural products, including ascidians, sponges, algae, corals, bacteria and fungi [5]. According to these studies, the ocean offers significant commercial potential for agrichemicals, enzymes, nutritional supplements, and medications [6]. Marine organisms contain bioactive compounds which serve as health benefiting agents with activities like anticancer, antiasthma, antidiabetic, antiviral, anti-inflammatory etc. in humans (Figure 1). We all know that viral infections are the leading cause of death for people globally [7]. The coronavirus illness 2019 (COVID-19) and other infectious viral diseases have all been described so far, including the severe acute respiratory syndrome coronavirus-2. These viruses include influenza [8], Herpes Simplex Virus [9], Human Immunodeficiency Virus [10], Respiratory Syncytial Virus [11], Entero virus 71 [12] and Dengue Virus [13]. The primary trait of viruses is that their genomes are susceptible to mutation, which makes it challenging to manage viral infections and results in global pandemics. Meanwhile, rising migration, international travel, and urbanisation have sped up the virus's rapid spread in the absence of vaccinations and antiviral treatments [14]. There is a requirement for the development of novel compounds with anti-viral activity because existing antiviral medicines are constrained by their harmful effects and transfected viruses' potential to develop drug-resistant versions. Therefore, all viable avenues for the creation of novel antiviral medications should be explored [15]. The aquatic environment extracted compounds are possible resource for these viral inhibitions. It was discovered that natural marine agents, as a significant cause of pharmaceuticals and medication leads. These organic compounds,

which a possible resource for these inhibitors, improve survival abilities and have the potential to be used as chemical weapons against tiny or large animals, fungus, bacteria, and viruses. Many of the secondary metabolites that are the pharmaceutical sector is interested in the areas that follow generated created by marine creatures and microbes, and they have tested in therapeutic trials as potential drugs that fight viruses [16].

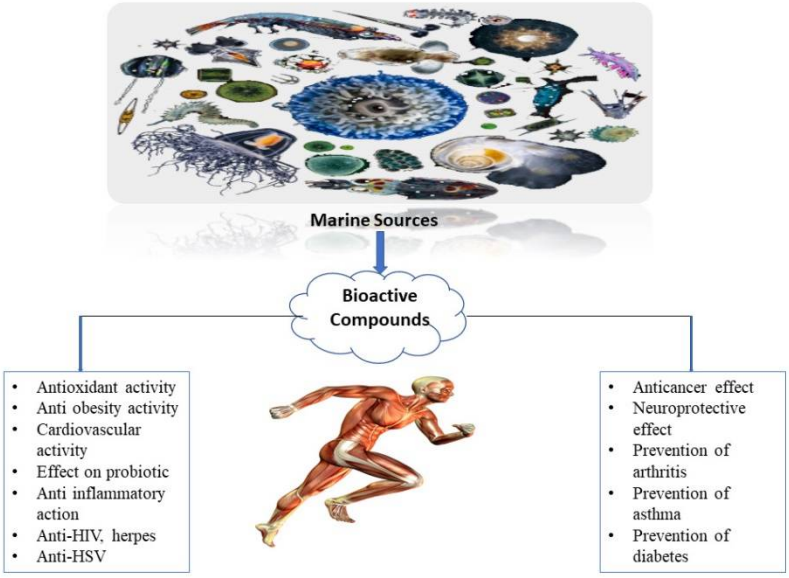

Figure 1: Biomolecules from marine sources as human health beneficial agent.

Marine organisms with antiviral properties

Throughout the previous 50 years, aquatic life have received essential substance and compounds have been proven to be beneficial for their potential industrial development, including for the manufacturing of cosmetics, dietary fine chemicals, supplements, therapeutic agents (antiviral, antibacterial, etc.,) for many different types of illnesses and agrochemicals [17]. Numerous marine sources yielded tens of thousands of unique chemicals and their metabolites, some of which are listed in figure 2 and have biological properties ranging from antiviral to anticancer [18].

Marine Bacteria

Finding the biologically active compounds obtained from aquatic bacteria that are implemented as antiviral compounds as well as agents against pathogenic micorganisms. Prokaryotes such as myxobacteria (such as *Sorangium*) and cyanobacteria (such as *Nostoc*) were used to isolate structurally and functionally varied beneficial chemicals. The majority of research targeted at discovering bioactive substances from marine organism has focused on bacteria, the order of Actinomycetales, on the generation of bacteria, exopolysaccharides, with cyanobacteria, which is thought to be eukaryotic algae [19].

Only few products of aquatic bacteria that has some viral activity, are revealed in (figure 2). Studies have showed that marine bacterial exopolysaccharides molecule is the main focus when employing sources of antiviral drugs from microorganisms as a chemical compounds [20]. Exopolysaccharides (EPS) are compounds that many marine bacteria create in order to thrive, attach to solid surfaces, and endure harsh environments. Growing interest has led to the isolation of unique marine exopolysaccharide-producing bacterium settings, especially those who remain in hostile maritime conditions with high levels of H2S and heavy metals, as well as extreme temperatures and pressures [21].

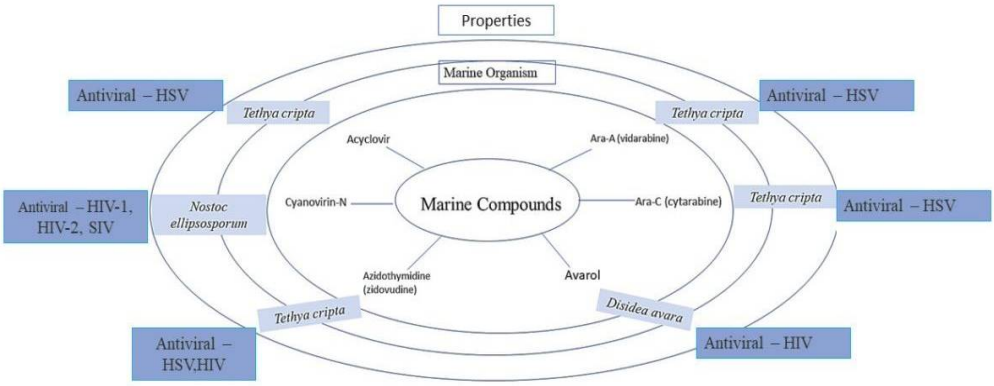

Figure 2: Marine organism with their compounds having antiviral properties

From hydrothermal vents, marine microorganisms in the deep sea including strain HYD72, *Vibrio diabolicus*, *Alteromonas infernus, Alteromonas macleodii subsp.and fijiensis* all make exopolysaccharides with unique structures which help them survive in harsh condition. Bacterial EPS generated in these conditions offers distinct chemical structures, characteristics, and innovative designs that could be used in a number of industrial fields. Thermotoga maritima and Thermococcus litoralis, two hydrothermophilic marine bacteria, have recently been identified as additional polysaccharide makers [19].

Antiviral derived from marine bacteria

Marine bacteria serve as a reservoir for antiviral compounds like exopolysaccharides and macrolactins which has been reported by many researchers to inhibit different viruses effectively.

Exopolysaccharides (EPS)

Sulphated exopolysaccharides (EPS), which can inhibit a variety of retroviral reverse transcriptases, are known to prevent viruses from adhering to and entering host cells in marine bacteria. It was discovered that the two separate microorganisms *Geobacillus thermodenitrificans* and *Bacillus licheniformis* produced unique two exopolysaccharides, exopolysaccharides (1 & 2). These two bacteria were recovered from shallow marine thermal springs on Vulcano Island. At doses below 400µg/ml, these two sets of exopolysaccharides demonstrated noncytotoxic to WISH cells and peripheral blood mononuclear cells. It was demonstrated that the antiviral actions of exopolysaccharides (1 & 2) at doses of 200µg/ml and 300µg/ml a substantial decline in HSV-2 viral titer. The expression of pro-inflammatory cytokines was shown to be increased by both EPS-1 and EPS-2, inhibiting HSV-2 multiplication in PBMCs and in particular polarising the Th1 subset [19].

Macrolactin A

Marine bacteria-derived antiviral substance produced from marine microorganisms in order to save human T-lymphoblast cells from replication of human human immunodeficiency virus. A concentration of at least 10µg/ml is required for macrolactin A, an antiviral molecule with a 24 member ring lactone that is linked to glucose -pyranosides and open chain acids [22].

Marine Algal

Microalgae and macro algae both possess natural substances with *in-vitro* anti- Human immunodeficiency virus activity [23]. There are several different types of plants known as marine algae, ranging in size from microscopic, unicellular creatures known as diatoms to seaweeds that can grow up to 40 metres long [24]. Antiviral effects can be found in marine algal polysaccharides [25]. *Spirulina platensis* a polysaccharides has shown anti-viral action to viral diversity in human cell lines, including the HIV-1, HSV-1 and mumps virus. This cyanobacterium's calcium spirulan reduced its viral proliferation by preventing its entrance into the host cell. Galactose, sulfated glucuronic acid, glucose, xylose, fructose, rhamnose, ribose and galacturonic acid are the main components of calcium spirulan. These compounds have antiviral properties because of the molecular structure they obtain from the chelation of calcium ions with sulphate groups. Animals that received calcium spirulan in their serum showed persistent antiviral effect against HIV -1 and HSV -1 [26].

Antiviral derived from marine algae

Galactan sulphate

In marine algae, polysaccharide galactan sulphate (GS), which is produced from the *Agardhiella tenera*, has shown effectiveness against HIV -1 and HIV -2. HIV -1 and HIV -2 had IC50 value 0.05µg/L and 0.5µg/L, respectively where it generated cytopathic effects in MT-4 cells. At GS concentrations is greater

than 5µg/L, the development of these virally generated syncytia in HIV -2 or HIV -1 infected HUT-78 cells were prevented, same way anti-gp120 monoclonal antibodies binds to HIV-1 gp120, Galactan sulphate from marine algae also prevents HIV-1 from attaching to cells in the same way as anti-gp120 monoclonal antibodies exhibit binding with gp120 of HIV-1. Other viruses with envelopes, such as herpes, toga, and arenaviruses, are also activated by GS [27].

A1 and A2 - Sulfated extracellular polysaccharides

Aquatic micro-algae *C.polykrikoides has*, A1 & A2 sulfated extracellular polysaccharides which was isolated and discovered. Respiratory Syncytial Virus type A & B cultured on human epithelial cells and virus type A & B were grown on Madin-Darby Canine Kidney cells both exhibit cytopathic effects that are lessened by A1 and A2. The IC50 value for A1 and A2 against human immunodeficiency virus -1 in MT-4 cell is 1.7µg/ml. A1 is active alongside Herpes simplex virus-1 in Human metapneumovirus-2 cells, whereas A2 is efficient against type 2 parainfluenza virus. When used in quantities that inhibit viruses, A1 and A2 have negligible (10%) inhibitory effects on coagulation of blood at 100µg/ml and are noncytotoxic [28].

Fucoidan

The brown seaweed *Fucus vesiculosus* produces fucoidan, a sulfated polysaccharide that is present in aquatic algae and has been proven to have some actions that prevent viral genomes like human cytomegalovirus and HSV -1 and HSV -2 from reproducing [29]. The ribonucleic acid viruses, Vesicular stomatitis virus, Sinbis, and HIV -1 are all susceptible to this substance's activity. Additionally, this substance has no effect on the poliovirus, or coxsackievirus and parainfluenza virus. Fucoidan has water soluble component, as well as non-carbohydrate component that were isolated from *Fucoidan vesiculosus* that can suppress HIV, Reverse Transcriptase *in-vitro* at a concentration 50µg/ml. The amount of human immunodeficiency virus -1 p24 antigen released can be reduced 100% by pre-incubating cell-free virus at 200µg/ml [30]. These tests reveal effects that are not the result of the targeted cells being killed. However, fucoidan has no negative effects on protein synthesis or cell growth. Target cells are truly shielded from HIV-1 virus infection by fucoidan pre-incubation. Low anticoagulant characteristics are included in the antiviral activity of fucoidan [31].

Sea algae extract

Schizymenia pacifica, an aquatic red algae were used to create citrate buffer extract. The impact of the extract on Rauscher murine leukaemia virus and avian myelblastosis virus reverse transcriptase (RT) was examined in a cell-free environment. The newly isolated RT from S. pacifica was inhibited. The substance is referred to as "sea algal extract" (SAE), and it is a polysaccharide that contains sulfonate (20%), 3, 6-anhydrogalactose (0.65%), and galactose (73%). *In-vitro* tests have shown SAE that selective HIV replication and RT inhibitor, with no unfavourable effects on growth of cells. It is believed that the sulphate compounds are essential for RT inhibition. Inducing polysaccharide activity offers support for this concept [32].

Griffithsin

The red alga Griffithsia sp. contains a protein called griffithsin that may inhibit HIV. This novel lectin has strong antiviral activity in primary isolates of HIV-1 and against several laboratory strains (IC50 = 0.043-0.63 nM). This function necessitates the monosaccharide dependent binding with viral glycoproteins (such as gp4, gp120 & gp160) [33].

Calcium spirulan

There are several species of cyanobacteria that can create sulfoglycolipids with a high anti-HIV activity [34]. Sulfoglycolipids, which are plentiful and play an important role in chloroplast membrane function, make up a portion of the membrane [35]. *Arthrospira platensis*, an aquatic blue-green algae, used to produce calcium spirulan (Ca-SP), also known as sulfated polysaccharide. In MT-4 cells, Ca-Sp has shown an effective HIV-1 antiviral drug. Ca-Sp has shown IC50 value of 2900µg/ml for cytotoxicity against MT-4 cells. This calcium spirulan is given to cell medium instantly and three hours before the infection, the viral proliferation was inhibited, with ED50 values (11.4µg/ml and 2.3µg/ml). Several viruses, including measles, mumps, Madin-Darby Canine Kidney, HEL and Vero cells, among others, are being replicated in various cell types was later found to be inhibited by Ca-SP by specifically blocking the virus' entry into host cells. These have a minimal anticoagulant effect [36].

Cyanovirin-N

Using fractionation that is guided by bioassays [37], the cyanobacterium *Nostoc ellipsosporum's* marine aqueous cellular extract is where 'Cyanovirin-N' was originally discovered [38]. Cyanovirin-N a virus-fighting peptide of 101 amino acids and mass of 11 kDa (NSC 682999; C467H737N133O164S4). SIV, as well as a number of clinical isolates and laboratory strains of HIV -1 and HIV -2, are among other retroviruses that are prevented from replicating *in-vitro* and causing cytopathic effects by low nano molar

doses of Cyanovirin-N. This Cyanovirin-N interacts with viral envelope glycoprotein to mediate antiviral activity. CN-V successfully stops the fusion of cells and the subsequent spread HIV from infected cells to healthy cells. Human immunodeficiency virus virions can be pre-treated permanently to reduce their infection potential causing no harm to the host cells. As a potential preventative viricide, the National Cancer Institute of the United States chose a novel anti- Human immunodeficiency virus drug for preclinical study. It was first thought that cyanovirin prevented Human immunodeficiency virus by combining with the gp120 surface envelope of glycoprotein. It was found that CV-N does not prevent the adherence of intact Human immunodeficiency virus-1 to a number of specific T-cell lines or the binding of sCD4 to human immunodeficiency virus-1 lysates. Therefore, they came to the conclusion that CV-N's virucidal effects come from interfering with fusion process steps after the virus initially binds to target cells [39].

Diterpenes

Recent research has focused on two diterpenes' mechanisms of action, Da-1 and AcDa-1, from the sea algae, which were isolated. *Dictyota menstrualis* and can inhibit human immunodeficiency virus-1 viral growth in cell line of PM-1 (plasma membrane). Da-1 and AcDa-1 had EC50 values of 12.7µg/ml (40 µM) and 24.1µg/ml (70µM). For Da-1 and AcDa-1, the viral production was reduced by 97% and 70%, respectively, at 100 M. Both diterpenes can prevent the viral reverse transcriptase enzyme from engaging in RNA-dependent DNA polymerase activity, but they have no effect on viral attachment or internalisation within PM-1 (plasma membrane) cells. Da-1 and AcDa-1 have IC50 values of 10M and 35M, respectively, for supressing HIV, reverse transcriptase [40].

Naviculan

A sulfated polysaccharide was discovered in the deep ocean water of Japan, in the diatom *Navicula directa*. This substance has demonstrated action that prevents HSV -1 and HSV -2 from replicating (IC50 = 7µg/ml –14µg/ml), most likely via altering viral adherence and diffusion into the host cells [41].

Marine sponges

One of the oldest multicellular invertebrate species is the marine sponge (phylum *Porifera*) [42]. Many potent natural chemicals can be found in marine sponges, some are thought to be essential lead chemicals for the development of pharmaceuticals. Antiviral chemicals of particular interest of infectious diseases brought on by viruses such as H1N1, herpes simplex virus, etc., developed into important problems for human health during recent decades. Fast evolution of virus and their capacity to acquire drug resistance need the ongoing creation of novel antiviral medications. There have been numerous successful isolations of lead antiviral compounds from marine sponges, and efforts to discover additional compounds are ongoing. The antiviral compound found in marine sponges is abundant (Table 1). High concentrations of HIV-inhibiting chemicals were found in a sponge, but this does not mean that they are more effective at preventing AIDS than they are at preventing other viral infections. A major emphasis on screening aquatic sponge for their anti- human immunodeficiency virus activity resulted to the discovery of many agents; Inhibition's basic processes remain to be poorly understood. Haplosamates A and haplosamates B, pabuamides C and pabuamides D and avarol received patent protection for its antipsoriasis medication; examples of HIV-inhibiting drugs include substances derived from several sponge [43]; [44]; [45].

Antiviral derived from marine sponges

Avarol and derivatives

One of the few substances, avarol, has an almost well-understood mechanism of action that prevents HIV infection from progressing [45]. The synthesis of Immunoglobulin M (IgM) and Immunoglobulin G (IgG) were considerably increased as they interfere with the viral infections of post transcriptional process; the *in-vitro* investigation demonstrated that avarol combines with favourable characteristics for their better humoral immune response. By preventing its naturally occurring synthesis of UAG (termination codon) suppressor glutamine transfer of tRNA, avarol protects against human immunodeficiency virus infection. Following viral infection, tRNA production increases and production of essential viral protease is required for the spreading of viruses. At low doses of merely 0.9 and 0.3 M, avarol suppresses viral release from infected cells by 80% and 50%, respectively [46].

Arabinosyl nucleoside derivatives

Since the late 1970s, Ara-A (vidarabine), which is used as a therapeutic agent against herpetic encephalitis, has been synthesised using *Tethya cripta*, a marine sponge, produced arabinosyl nucleosides that were separated and described [47]. Other alteration of semi-synthetic arabinosyl nucleoside are cytarabine, zidovudine [48] and acyclovir [49] used for clinical uses (Table 1).

Calyceramides A–C

In the search for novel neuraminidase inhibitors for influenza virus, the marine sponge *Discodermia calyx* yielded three strong sulfated calyceramides A–C. These Calyceramides A–C blocks *Clostridium perfringens*

neuraminidase having IC50 values, 0.2 µg/ml, 0.4µg/ml and 0.8µg/ml. These values have little edge in terms of potency over N-Acetylneuraminic acid with an IC50 value 1.5mg/ml. Thus, it is a matter of further investigation if these substances will exhibit a similar level of potency in inhibiting influenza virus' neuraminidase [50].

Hamigeran B and Weinbersterols

The substances from *Hamigera tarangaensis*, hamigeran B, have *in-vitro* suppression for polio virus and herpes virus [51]. From Petrosia weinbergin which has anti-mouse viral activity (corona and influenza virus) from weinbersterols (A & B), and anti-feline leukaemia virus activity *in-vitro* [52].

Anti-Human immunodeficiency virus compounds

Clathsterol, a recently identified sulfated sterol molecule, has demonstrated strong action in contradiction of HIV -1 and reverse transcriptase at 10µM concentration [53]. A depsipeptide microspinosamide were found in sea *Sidonops microspinosa*, has been discovered to inhibit HIV and effectively suppresses cytopathic result of HIV -1 infection *in-vitro* experiments employing cells having EC50 value, 0.2µg/ml [54]. However, its cytotoxicity effects on host cells having IC50 value 3µg/ml; it is the only substance that shows cytoprotective properties within a limited concentration range. Polyacetylenetriol's mode of action, which was discovered in the aquatic sponge *Petrosia sp*., has been extensively studied [46]. Polyacetylenetriol selectively inhibits retroviral RNA dependent-DNA dependent DNA polymerase action compared with cellular DNA polymerases, with IC50 values 2.6µM and 0.95µM for the former and reverse transcriptase, respectively. It shows putative hydrophobic interaction plays an essential part in suppressing HIV -1 and reverse transcriptase enzyme through a reversible non-competitive mechanism. Although polyacetylenetriol lacks sufficient specificity and is likely ineffective against HIV, modifying the chains structure of the polyacetylenic molecule could potentially yield stronger and more effective anti-acquired immunodeficiency syndrome medications [55]. The *Monanchora sp*. contains crambescidin 826, polycyclic guanidine alkaloid a novel compound. Crambescidin 826 has been shown to prevent human immunodeficiency virus-1 an envelope-mediated fusion *in-vitro* having IC50 range 1-3µM, suggesting that this type of substance may contribute to the reasonable progress of molecules of HIV -1 as fusion inhibitors. A unique compound C 22 furanoterpene called dehydrofurodendin, which exhibits activity against Human immunodeficiency virus -1, reverse transcriptase associated RNA and DNA directed DNA polymerase with an IC50 values of 3.2µM -5.6µM, was discovered in a *Madagascan Lendenfeldia* sponge [56]. *Neamphius huxleyi*, a marine sponge from Papua New Guinea, has produced a novel HIV-inhibitory depsiundecapeptide known as neamphamide A. Neamphamide A effectively suppresses cytopathic action of HIV -1 infection *in-vitro* studies using cells, having EC50 value of 28nM [57]. The Indian Sea sponge Petrosia similes contains two bis-quinolizidine alkaloids called petrosins that have been demonstrated to inhibit Human immunodeficiency virus by halting the development of massive cells (IC50, 21.2µM - 36.1µM), inhibiting recombinant RT *in-vitro* (IC50, 10.6µM - 14.8µM), and suppressing Human immunodeficiency virus-1 replication (IC50, 41.3µM -86.8µM) [58].

Marine fungi

When it comes to natural products made from aquatic microorganisms, it has been proven as a valuable and promising resource of new compounds [3]. These fungi thrive in unique and harsh environments, allowing them to produce an array of uncommon and scarce secondary metabolites. To date, researchers identified approximately 275 previously unknown compounds derived from marine fungi, and this number continues to increase [59].

Antiviral derived from marine fungi

Equsetin and phomasetin, two antiviral compounds derived from aquatic microorganism *Fusarium heterosporum* and *Phoma sp*. which exhibit suppression against Human immunodeficiency virus-1 integrase in experiments, with an IC50 values ranging from 7µM - 20µM [60]. It was discovered that virulent poxvirus molluscum contagiosum topoisomerase was inhibited by sansalvamide A (a cyclic depsipeptide discovered from an aquatic fungus named Fusarium sp). It effectively hindered DNA relaxation, the formation of covalent complexes and DNA binding with an IC50 value of 124µM. This discovery was significant as molluscum contagiosum virus which can cause significant lesions in AIDS patients and HIV infection [61]. In this case, HSV-1 and HSV-2, a novel group of linear peptides halovirus A-E, which was found in aquatic fungus *Scytidium sp*., demonstrated potential antiviral activity. ED50 values for halovirs A, B, C, D, and E were 1.1µM, 3.5µM, 2.2µM, 2.0µM, and 3.1µM, respectively. Specifically, Halovir A exhibited typical test for plaque reduction and ED50 score was 280 nM, effectively prevent the spread of both HSV-1 and HSV-2. Its precise mechanism of action is yet to be deciphered, but it is speculated that halovirs may decreases Herpes simplex virus non-infectious by potentially destabilizing the viral membrane [62]. A unique *Stachyflin* (a terpenoid), was isolated from *Stachybotrys sp*.RF-7260, demonstrated *in-vitro* viral inhibiting activity against H1N1 virus with IC50, 0.003µM,

surpassing the efficacy of antiviral-H1N1 drug like zanamivir and amantadine. Due to its pentacyclic moiety and particular cis-fused decalin, stachyflin prevents the fusing of the host cell surface and viral envelop, thus exhibiting excellent antiviral activity [63].

Antiviral derived from miscellaneous marine organisms

Researchers have conducted studies to explore the existence of compounds possessing anti-HIV properties in various marine macro-organisms.

Tachypesins and polyphemusins

It was discovered that the haemocyte waste of tachypleus tridentatus and limulus polyphemus contains large amounts of the peptides polyphemusins II and I and tachyplesins I–III these are the inhibitors of HIV-cell fusion. The above-mentioned metabolites have more than 100 synthetic peptide counterparts that have been created and tested. Strong anti-human immunodeficiency virus activity and comparatively low cytotoxicity are characteristics of Polyphemusin II's synthetic peptide T22 analogue (Limulus polyphemus) (EC50 = 2.6μM, compared to 5.2μM for AZT) [64].

Thalassiolins A–C

A new class of viral inhibitor thalassiolins A–C (sulfated flavone glycosides) were derived from marine *Testudinum* species inhibiting enzymes cDNA integrase in HIV infection. Active substance are, thalassiolin A, suppresses HIV multiplication in cell culture and targets integrase-catalyzed strand transfer (IC50 = 30 μM). While molecular modelling studies suggested that the HIV integrase's catalytic core domain was most likely the molecule's binding location, the inclusion of sulfated glucose functionality improved the molecule's efficacy against the enzyme [65].

Inhibitors of Human immunodeficiency virus-1 integrase

Didemnaketals (A & B) were shown human immunodeficiency virus -1 inhibitors having IC50 value, 2 μM and 10μM, respectively which were isolated from *ascidian Didemnum sp* [66]. Using bioassay-guided fractionation, cyclodidemniserinol trisulfate, an inhibitor of human immunodeficiency virus-1 integrase (IC50 = 60 μg/ml), which was isolated from the extracts of Palauan ascidian Didemnum guttatum [67]. In addition to inhibiting integrase, this substance also inhibited Molluscum contagiosum virus topoisomerase having IC50 = 72 μg/ml. The 20-sulfate lamellarin was extracted from ascidian [68]. Didemnid ascidians followed by *prosobranch mollusks* act as a source for *Lamellarinis*. HIV-1 integrase is inhibited by lamellarin. The integrase's strand transfer activity and terminal cleavage activity are both inhibited by this substance (IC50 = 16 μM and 22 μM, respectively).An fragrant alkaloid known as polycitone A was discovered in ascidian. Both RNA-directed DNA polymerases (IC50 = 245nM ± 15nM) and (IC50 = 470 nM ± 22 nM) are significantly inhibited by *Polycitor sp* DNA-directed DNA polymerases. The establishment of the RT-DNA complex and DNA primer extension are both hampered by polycitone A [69].

Anti- Herpes simplex virus Agents

An alkaloid derived from *Eudistoma olivaceum*, which is called as eudistomin (β-carboline) exhibits antiviral property against HSV-1 and HSV-2 actions together with other related β-carbolines [70]. Didemnins, or cyclic depsipeptides are another type of marine antiviral substance that have been identified from the tunicate species *Tridemnum.* They exhibit antiviral activity *in-vivo* and *in-vitro* against Herpes simplex virus -1 and viruses that cause yellow fever and encephalomyelitis [71].

Table 1: Marine organism having antiviral properties

Marine organism	Scientific name	Antiviral Compound	Antiviral Activity	Reference
Marine Bacteria	*Bacillus licheniformis*	EPS-1	Herpes simplex virus -2 replication	[20]
	Geobacillus thermodenitrificans	EPS-2	Replication of Herpes simplex virus -2	[19]
	Sea bacterium	Macro-lactin A	Human immunodeficiency virus replication	[22]
Marine Algae	*Cochlodinium polykrikoides*	Sulfated extracellular polysaccharides-Al	Respiratory syncytial virus (A & B)	[28]
	Cochlodinium polykrikoides	Sulfated extracellular polysaccharides-A2	Respiratory syncytial virus (A & B)	[28]
	Dictyota menstrualis	AcDa-1	Human immunodeficiency virus-1 replication	[40]
	Arthrospira platensis	Calcium spirulan	Herpes simplex virus-1 replication	[36]
	Nostoc ellipsosporum	Cyanovirin-N	Human immunodeficiency virus-1 replication	[38]
		Da-1	Reverse transcriptase for human immunodeficiency virus type 1	[40]
	Fucus vesiculosus	Fucoidan	Reverse transcriptase for human immunodeficiency virus type 1	[30]
	Agardhiella tenera	Galactan Sulfate	Human immunodeficiency virus-1 binding with the host cells	[27]
	Griffithsia	Griffithsin	Human immunodeficiency virus-1 -glycoproteins	[33]
	Navicula directa	Naviculan	Human immunodeficiency virus type 1 replication	[41]
	Schizymenia pacifca	SAE	Reverse Transcriptase of Human immunodeficiency virus	[32]
Marine sponge	*Tethya cripta*	Acyclovir	Herpes simplex virus	[49]
	Tethya cripta	Ara-A/Ara-C (vidarabine/cytarabine)	Herpes simplex virus	[47]
	Disidea avara	Avarol/Avarone	Human immunodeficiency virus -1 the blood-barrier (brain)	[45]
	Tethya cripta	Azidothymidine (zidovudine)	Human immunodeficiency virus	[48]
	Discodermia calyx	Calyceramide A-C	Influenza virus neuraminidase (NA)	[50]
	Clathria	Clathsterol	Human immunodeficiency virus-1 Reverse Transcriptase	[53]
	Monanchora	Crambescidin 826	Envelope-mediated fusion of human immunodeficiency virus-1	[55]
	Madagascan *Lendenfeldia*	Dehydrofurodendin	Reverse transcriptase-associated with RNA from human	[56]

			immunodeficiency virus type 1	
	Hamigera tarangaensis	Hamigeran B	Herpes virus	[51]
	Hippiospongia metachromia	Ilimaquinone	RNA reverse transcriptase, ribonucleases H	[71]
	Sidonops microspinosa	Microspinosamide	Human immunodeficiency virus-1 cytopathic effects	[54]
	Neamphius huxleyi	Neamphamide A	Human immunodeficiency virus-1 cytopathic effects	[57]
	Petrosia similes	Petrosin	Replication of human immunodeficiency virus type 1	[58]
	Petrosia	Polyacetylenetriol	Polymerase activity of RT (Reverse Transcriptase)	[46]
	Petrosia weinberg	Weinbersterol A, B	Mouse influenza virus	[52]
Marine Fungi	*Fusarium heterosporum*	Equisetin	Integrase from human immunodeficiency virus type 1	[60]
	Scytidium	Halovir A–E	Membrane disruption caused by Herpes simplex viruses -2 and -1	[62]
	Phoma	Phomasetin	Integrase from human immunodeficiency virus type 1	[60]
	Fusarium	Sansalvamide A	Topoisomerase-catalyzed molluscum contagiosum virus	[61]
	Stachybotrys	Stachyflin	Fusion H1N1	[63]
Miscellaneous macro organisms	*Didemnum guttatum*	Cyclodidemniserinol Trisulfate	Human immunodeficiency virus -1 integrase	[67]
	Didemnum	Didemnaketal A, Didemnaketal B	Human immunodeficiency virus -1 protease	[66]
	Trididemnum solidum	Didemnins	Herpes simplex virus -1	[72]
	Eudistoma olivaceum	Eudistomin	Herpes simplex virus -2 and Herpes simplex virus-1	[70]
	Lamellaria	Lamellarin D	Integrase from human immunodeficiency virus type 1	[68]
	Polycitor	Polycitone A (POLY A)	DNA polymerases	[73]
	Limulus polyphemus	Polyphemusin I, II	Fusion of the human immunodeficiency virus	[64]
	Tachypleus tridentatus	Tachyplesin I-III	Fusion of the human immunodeficiency virus	[74]
	Thalassia testudinum	Thalassiolin A-C	Replication of human immunodeficiency virus	[65]

CONCLUSION

Aquatic microorganisms produce pharmacological and antiviral substance, due to the possibility that they could provide limitless biological resources, which can be used for designing new therapeutic medicines finding their role in curing human viral diseases, cosmetics, enzymes, dietary supplements, and agrichemicals. They produce complex secondary metabolites over thousands of years in response to ecological stresses such space competition, predation, symbiosis, and tidal oscillations. Using bioassay-guided methods, researchers have identified over two hundred natural chemicals from aqueous or organic extracts of marine creatures that may have anti-HIV activity. Humans and other economically

important animals may one day benefit from a new generation of antiviral drugs made possible by the ongoing effort to identify and evaluate natural chemicals for their antiviral potential

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