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Review article

Antiviral potential of natural products from marine microbes

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ABSTRACT

Humans have been suffered from viral infections over the centuries, such as influenza, HSV, and HIV, which have killed millions of people worldwide. However, the availability of effective treatments for infectious diseases remains limited until now, as most of the viral pathogens resisted to many medical treatments. Marine microbes are currently one of the most copious sources of pharmacologically active natural products, which have constantly provided promising antivirus agents. To date, a large number of marine microbial secondary metabolites with antiviral activities have been widely reported. In this review, we have summarized the potential antivirus compounds from marine microorganisms over the last decade. In addition, the structures, bioactivities, and origins of these compounds were discussed as well.

Contents

1. Introduction

As we all know, viral infections are the main reasons for human death worldwide [1]. Several infectious viral diseases occurred so far have been reported, which involve viruses such as influenza [2], Herpes Simplex Virus (HSV) [3], Human Immunodeficiency Virus (HIV) [4], Respiratory Syncytial Virus (RSV) [5], Enterovirus 71 (EV71) [6], Dengue Virus (DENV) [7], Ebola Virus [8], as well as the recently emerging coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [9]. The main characteristic of viruses is that their genomes are easily mutated, making it difficult to control viral infections and causing pandemics worldwide. Meanwhile, in the absence of vaccines and antiviral therapies, the rapid spread of the virus has been accelerated by increased migration, global travel and urbanization [10]. However, most antiviral drugs today have adverse drug reactions and develop viral resistance to treatments. The threat of drug resistance not only results in huge challenges to the clinical

Abbreviations: HSV, Herpes simplex; HIV, Human immunodeficiency virus; HCV, Hepatitis C virus; RSV, Respiratory syncytial virus; EV71, Enterovirus 71; DENV, Dengue virus; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; CHIKV, Chikungunya virus; WEEV, Western equine encephalitis virus; CPE, Cythopathic effect.

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management of viral infections, but also places a heavy burden on the global economy [11]. Although considerable progress has been made in the development of antiviral drugs since acyclovir, a nucleoside analogue, was invented in 1960, novel drugs that can work through different mechanisms to combat resistance are still desperately in need [12]. In recent years, with the development of virology, many virus-specific processes or proteins have been identified as targets for chemotherapy [13]. Viral replication cycle includes viral adsorption, viral cell fusion, reverse transcription, integration, translation and other steps, which can be used as targets for antiviral drugs [14]. In addition, specific viral enzymes which involve the synthesis of viral DNA, RNA and glycoproteins are also potential targets [15]. For example, acyclovir disturbs some key herpes virus enzymes that have an affinity for nucleotide analogues [16]. Despite the successful understanding of viral proliferation cycle and comprehensive studies for suitable vaccines and treatments against viral infections over the past half of century, still several infections such as HIV afflict a substantial proportion of the world populations in all generations [17]. There is no definite vaccine against numerous prevalent viral infections, including most respiratory-tract viruses, HSV-1 and HSV-2 or DEVN [18]. Moreover, drug resistance to available antiviral agents by different viruses such as the HIV type 1 or HSV-1 has always been a serious impediment to treatment of viral infections, stimulating the search for new efficient molecules [16,17].

Recently, the ocean has arisen great attention from scholars and practitioners, as many marine derived secondary metabolites with evidently anti-inflammatory, antitumor, antimicrobial, antiviral, antimalarial, and antioxidant activities have been discovered [19,20]. According to the MarinLit database, annually more than 1200 novel natural products were reported from a variety of marine sources, such as algae, corals, sponges, and especially microorganisms [19]. Moreover, these antivirus natural compounds even have entered the advanced stages of clinical trials, several of which are commercially available. For example, vidarabine is currently used for the treatment of HSV infection, whose lead structure, spongouridine, was originally isolated from the marine sponge [21]. Marine microbes have become a promising reservoir of new antivirus secondary metabolites [22]. There are about 1 million microorganisms in 1 mL of seawater, including some cyanobacteria, actinomyces, bacteria, and fungi, which have great potential in the pharmaceutical research [23]. In addition, some of marine microorganisms rely on the symbiosis with marine animals and plants to acquire nutrition, but due to fierce competition, they have metabolized some specific molecules to obtain extremely limited resources [24]. These secondary metabolites can chemically be divided into alkaloids, peptides, polyketides, terpenoids, etc, which contained diverse biological functions such as antibacterial, antiviral and antitumor activities. Excitingly, cyanobacterial-derived cyanovirin N has been utilized as anti-HIV compound in preclinical development [25]. However, only limited natural compounds discovered from marine microbes have been used in clinical research, reflecting the lack of understanding and development of marine microbial resources [26].

This review provided a comprehensive overview of 79 natural products derived from marine microbes over the last decade, presenting various antiviral activities, including anti-influenza (48%) anti-HSV (33%), and others (19%) (Fig. 1). These secondary metabolites were mainly isolated from marine microbes *Aspergillus*, *Penicillium* and *Streptomyces* discovered from the marine environment of different countries (Figs. 2 and 3). Most of antiviral molecules (Fig. 3) were obtained from marine microbes sampled in China. 18 secondary metabolites, such as truncateol O (**16**) and *R*-wailupemycin K (**18**), displayed significant antiviral activities even more effective than those of the positive drugs [27,28]. Table 1, Table 2 and Table 3 listed the name, isolation source (marine microbes) and the antiviral activities of these compounds.

2. Potential anti-virus agents from marine microbes

2.1. Anti-influenza virus compounds

Among human influenza viruses, influenza A virus is the most susceptible to mutations causing worldwide pandemics many times, such as 1918 Spanish flu pandemic [29]. Influenza viruses contain two functional surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA) [30]. NA has become a major target for drug design against influenza virus as it acts as a significant role in influenza virus replication and has highly protected active site [31,32]. Rubrolide S (**1**, Fig. 4), a new rubrolide, was first discovered in the fermentation broth of the marine-derived fungus *Aspergillus terreus* OUCMDZ-1925 that was isolated in viscera of the barracuda (*Chelon haematocheilus*) grown in the Yellow River [33]. This compound displayed significant inhibitory activity toward H_1N_1 virus with IC_{50} value of 87.1 μM (ribavirin as positive control, IC_{50} = 118.8 μM) [33]. Chemical study of marine-derived *Streptomyces youssoufiensis* OUC6819 discovered that heterologous expression of the type III polyketide synthase (PKS) gene vioA resulted in production of four novel violapyrones (VLPs), VLPs Q–T (**2**–**5**, Fig. 4) [34]. Using ribavirin as a positive control, anti-influenza A [H_1N_1 (A/Virginia/ATCC1/2009) and H_3N_2 (A/Aichi/2/1968)] virus activity of VLPs were evaluated [34]. The results showed that these VLPs exhibited considerable anti-H_1N_1 and anti-H_3N_2 activities with IC_{50} values of 30.6–68.4 μM and 45.3–95.0 μM, respectively (ribavirin as positive control, IC_{50} = 66.7 and 99.6 μM, respectively) [34]. The strain *Cladosporium sphaerospermum* 2005-01-E3, isolated from sediments collected in the Pacific Ocean, resulted in the isolation of a new hybrid polyketide, cladosin C (**6**, Fig. 4) [35]. Compound **6** exhibited anti-influenza A H_1N_1 virus activity with IC_{50} value of 276 μM (ribavirin as positive control, IC_{50} = 131 μM) [35]. Another marine fungus *Penicillium chrysogenum* PJX-17 was derived from a soft coral collected at Terra Nova bay, Antarctica. Chemical investigation of the fungus *P. chrysogenum* PJX-17 afforded two novel sorbicillinoids combining a bicycle [2.2.2] octane with a 2-methoxyphenol moiety, named sorbicatechols A (**7**, Fig. 4) and B (**8**, Fig. 4) [36]. These compounds showed inhibitory activities against H_1N_1 virus, with IC_{50} values of 85 and 113 μM, respectively (ribavirin as a positive control, IC_{50} = 84 μM) [36].

A new diketopiperazine derivative (3*Z*,6*Z*)-3-(4-hydroxybenzylidene)-6-isobutylidenepiperazine-2,5-dione (**9**, Fig. 5), two known analogues, (3*Z*,6*S*)-3-benzylidene-6-isobutylpiperazine-2,5-dione (**10**, Fig. 5) and albonoursin (**11**, Fig. 5) were separated from the extract of marine-derived *Streptomyces* sp. FXJ7.328 collected from coastal sediment at Huanghai beach [37]. Compound **9** showed anti-H_1N_1 virus with IC_{50} value of 41.5 ± 4.5 μM. In addition, compound **10** and **11** showed potent activity against influenza A (H_1N_1) virus with IC_{50} values of 28.9 ± 2.2 and 6.8 ± 1.5 μM, respectively (ribavirin as a positive control, IC_{50} = 38.8 ± 1.5 μM [37]. The strain identified as *Aspergillus terreus* Gwq-48, which was isolated from a mangrove rhizosphere soil sample collected in the coast of Fujian province resulted in the discovery of a new butenolide isoaspulvinone E (**12**, Fig. 5), together with two known butenolides aspulvinone E (**13**, Fig. 5) and pulvic acid (**14**, Fig. 5) [38]. These compounds displayed significant inhibitory activities against H_1N_1 virus, with IC_{50} values of 32.3, 56.9, and 29.1 μg/mL, respectively (ribavirin as a positive control, IC_{50} = 24.6 μg/mL; Zanamivir as a positive control, IC_{50} = 28.4 μg/mL) [38]. In addition, only compound **13** showed effective inhibition against H_1N_1 viral neuraminidase (NA), and docking of two

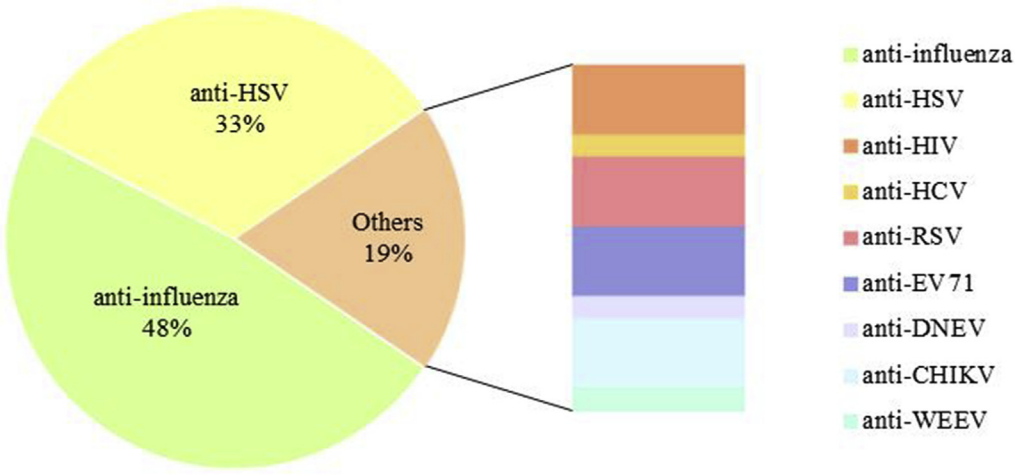

Fig. 1. The percentage of antiviral compounds isolated from marine microbes according to anti-virus types.

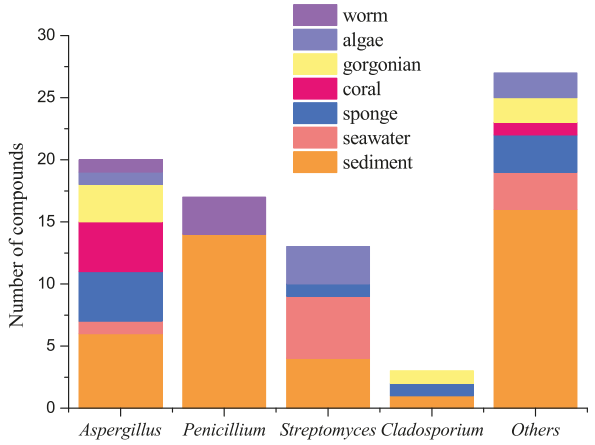

Fig. 2. The number of antiviral compounds isolated from marine microbes according to genera and sampling sources.

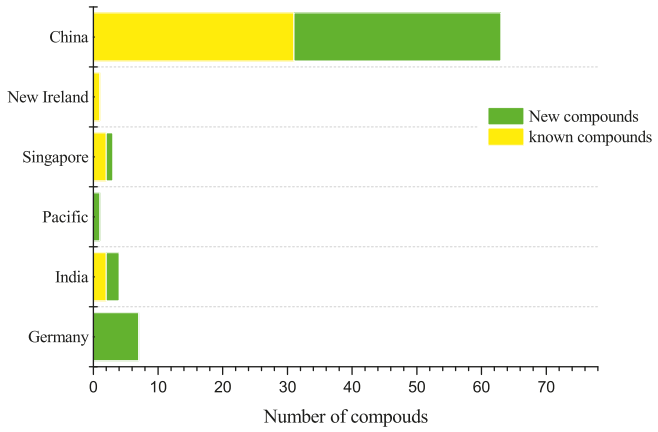

Fig. 3. Marine microbial sampling sites for new and known antiviral compounds reported from 2009 to 2019.

isomers (**13** and **14**) into the active sites of NA showed that the *E* double bond was essential to achieve activity [38]. Anthranoside C (**15**, Fig. 5) was purified from the marine sponge-derived *Streptomyces* sp. CMN-62 collected from Naozhou Island of the Guangdong Province, China [39]. This compound exhibited inhibitory activity against H_1N_1 with IC_{50} value of 171 μM (ribavirin as positive control, IC_{50} = 133 μM) [39].

Chemical investigation of the extract of sponge-associated fungus *Truncatella angustata* XSB-01-43 isolated from a finger sponge *Amphimedon* sp. collected from the reef at a depth of 10 m in Yongxing Island, Hainan Province of China, in June 2012, resulted in the isolation of truncateol O (**16**, Fig. 6) [27]. Compound **16** showed anti-H_1N_1 activity with IC_{50} value of 30.4 μM, which was stronger than that of oseltamivir (OSV), a positive control with IC_{50} value of 46.7 μM [27]. The marine sponge-derived *Streptomyces* sp. CMN-62 was associated with the marine green algae *E. prolifera*, and produced three new phenolic polyketides, wailupemycin J (**17**, Fig. 6), *R*-wailupemycin K (**18**, Fig. 6), deoxyenterocin (**19**, Fig. 6) [28]. It was first reported that compounds **17**, **18** and **19** displayed comparable anti-H_1N_1 activity with 47.8%, 42.5% and 60.6% inhibitions, respectively at 50 μg/mL, while the positive control, ribavirin, with the inhibition rates of 45.3% at the same concentration [28]. Two new meroterpenoids, chrodrimanins K (**20**, Fig. 6) and N (**21**, Fig. 6), as well as the known 3-hydroxypentacecilide A (**22**, Fig. 6) were separated from the fermentation broth of *Penicillium* sp. SCS-KFD09, which was gathered from a marine worm, *Sipunculus nudus*, from Haikou Bay, China [40]. Compounds **20**, **21**, and **22** exhibited inhibitory activity against H_1N_1 virus with IC_{50} values of 74, 58, and 34 μM, respectively (ribavirin as positive control, IC_{50} = 103 μM) [40]. The *Aspergillus* sp. SCSIO XWS02F40 derived from a marine sponge resulted in the discovery of two new asteltoxins named asteltoxins E (**23**, Fig. 6) and F (**24**, Fig. 6) [41]. These compounds were shown to have significant anti-H_3N_2 activities with IC_{50} values of 6.2 ± 0.08 and 8.9 ± 0.3 μM, respectively. Additionally, compound **23** also showed inhibitory activity against H_1N_1 with IC_{50} value of 3.5 ± 1.3 μM [41]. Oseltamivir was used as the positive control with IC_{50} values of 18.5 and 16.9 nM, respectively [41]. A new compound named 6-*O*-demethylmonocerin (**25**, Fig. 6) and a known analogue, (+)-monocerin (**26**, Fig. 6), were obtained from marine *Aspergillus* sp. OUCMDZ-1583, and collected from the Xisha Islands of China [42]. Compounds **25** and **26** showed anti-H_1N_1 activity with IC_{50} values of 172.4 and 175.5 μM, respectively (ribavirin as positive control, IC_{50} = 137.3 μM) [42].

Five new indole-diterpenoids (**27**–**31**, Fig. 7), were collected from the fermentation broth of *Penicillium camemberti* OUCMDZ-1492 that was isolated from an acidic marine niche, mangrove soil and mud, around the roots of *Rhizophora apiculata* at pH 5.0, together with emindole SB (**32**, Fig. 7), 21-isopentenylpaxilline (**33**,

Table 1
Secondary metabolites with anti-H_1N_1 and anti-H_3N_2 activities from marine microbes.

Metabolites	Species	Activities	Ref
Rubrolide S (**1**)	*A. terreus* OUCMDZ-1925.	IC_{50} = 87.1 μM (H_1N_1 virus).	[33]
VLPs Q–T (**2**–**5**)	*S. youssoufiensis* OUC6819	IC_{50} = 30.6–68.4 μM, resp. (H_1N_1 virus) IC_{50} = 45.3–95.0 μM, resp. (H_3N_2 virus)	[34]
Cladosin C (**6**)	*C. sphaerospermum* 2005-01-E3	IC_{50} = 276 μM (H_1N_1 virus)	[35]
Sorbicatechol A (**7**), B (**8**)	*P. chrysogenum* PJX-17	IC_{50} = 85 and 113 μM, resp. (H_1N_1 virus)	[36]
(3*Z*,6*Z*)-3-(4-hydroxybenzylidene)-6-isobutylidenepiperazine-2,5-dione (**9**) (3*Z*,6*S*)-3-benzylidene-6-isobutylpiperazine-2,5-dione (**10**) Albonoursin (**11**)	*Streptomyces* sp. FXJ7.328	IC_{50} = 41.5 ± 4.5, 28.9 ± 2.2 and 6.8 ± 1.5 μM, resp. (H_1N_1 virus)	[37]
Isoaspulvinone E (**12**) Aspulvinone E (**13**) Pulvic acid (**14**)	*A. terreus* Gwq-48	IC_{50} = 32.3, 56.9, and 29.1 μg/mL, resp. (H_1N_1 virus)	[38]
Anthranoside C (**15**)	*Streptomyces* sp. CMN-62	IC_{50} = 171 μM (H_1N_1 virus)	[39]
Truncateol O (**16**)	*T. angustata* XSB-01-43	IC_{50} = 30.4 μM (H_1N_1 virus)	[27]
Wailupemycin J (**17**) *R*-wailupemycin K (**18**) Deoxyenterocin (**19**)	*Streptomyces* sp. OUCMDZ-3434	47.8%, 42.5% and 60.6% inhibitions at 50 μg/mL, resp. (H_1N_1 virus)	[28]
Chrodrimanin K (**20**), N (**21**) 3-Hydroxypentacecilide A (**22**)	*Penicillium* sp. SCS-KFD09	IC_{50} = 74, 58, and 34 μM, resp. (H_1N_1 virus)	[40]
Asteltoxins E (**23**), F (**24**)	*Aspergillus* sp. SCSIO XWS02F40	IC_{50} = 3.5 ± 1.3 μM (H_1N_1 virus) IC_{50} = 6.2 ± 0.08 and 8.9 ± 0.3 μM, resp. (H_3N_2 virus)	[41]
6-*O*-demethylmonocerin (**25**) (+)-Monocerin (**26**)	*Aspergillus* sp. OUCMDZ-1583	IC_{50} = 172.4 and 175.5 μM, resp. (H_1N_1 virus)	[42]
Indole diterpenoids (**27**–**31**) Emindole SB (**32**) 21-Isopentenylpaxilline (**33**) Paspaline (**34**) Paxilline (**35**)	*P. camemberti* OUCMDZ-1492	IC_{50} = 28.3, 38.9, 32.2, 73.3, 34.1, 26.2, 6.6, 77.9, and 17.7 μM, resp. (H_1N_1 virus)	[43]
Asperterrestide A (**36**)	*A. terreus* SCSGAF0162	IC_{50} = 20.2 and 0.41 μM, resp. (H_1N_1 and H_3N_2 virus)	[44]
Cladosporisteroid B (**37**)	*Cladosporium* sp. SCSIO41007	IC_{50} = 16.2 μM (H_3N_2 virus)	[45]
6*β*,9*α*-dihydroxy-14-*p*-nitrobenzoylcinnamolide (**38**)	*A. ochraceus* Jcma1F17	IC_{50} = 17.0 μM (H_3N_2 virus)	[46]

Table 2
Secondary metabolites with anti-HSV activities from marine microbes.

Metabolites	Species	Activities	Ref.
(4*S*)-10-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide (**39**)	*S. koyangensis*	EC_{50} = 25.4 μM (HSV-1 virus)	[53]
Simplicilliumtide J (**40**) Verlamelin A (**41**), B (**42**)	*S. obclavatum*	IC_{50} = 14.0, 16.7, and 15.6 μM, resp. (HSV-1 virus)	[54]
Aspergilols H (**43**), I (**44**) Coccoquinone A (**45**)	*A. versicolor* SCSIO 41502	EC_{50} = 4.68, 6.25, and 3.12 μM, resp. (HSV-1 virus)	[55]
Trichobotrysins A (**46**), B (**47**), D (**48**)	*T. effusa* DFFSCS021	IC_{50} = 3.08, 9.37, and 3.12 μM, resp. (HSV-1 virus)	[56]
Acremonpeptides A (**49**), B (**50**) Al(III)-acremonpeptide D (**51**)	*A. persicinum* SCSIO 115	EC_{50} = 16, 8.7, and 14 μM, resp. (HSV-1 virus)	[57]
Aspergillipeptides D (**52**), E (**53**)	*Aspergillus* sp. SCSIO 41501	IC_{50} = 9.5 and 19.8 μM, resp. (HSV-1 virus)	[58]
12*α*-Dehydroxyisoterreulactone A (**54**) Arisugacin A (**55**) Isobutyrolactone II (**56**) Aspernolide A (**57**)	*A. terreus* SCSGAF0162	IC_{50} = 16.4 ± 0.6, 6.34 ± 0.4, 21.8 ± 0.8 and 28.9 ± 0.8 μg/mL, resp. (HSV-1 virus)	[59]
Balticolid (**58**)	Marine ascomycetous strain 222	IC_{50} = 0.45 μM (HSV-1 virus)	[60]
Balticols A–F (**59**–**64**)	Marine ascomycetous strain 222	IC_{50} = 1, 1, 1, 0.1, 0.01, 0.1 μg/mL, resp. (HSV-1 virus)	[61]

Fig. 7), and paspaline (**34**, Fig. 7), paxilline (**35**, Fig. 7) [43]. When compared with ribavirin (IC_{50} = 113.1 μM), compounds **27**–**35** displayed significant activities against influenza virus A (H_1N_1) virus with IC_{50} values of 28.3, 38.9, 32.2, 73.3, 34.1, 26.2, 6.6, 77.9, and 17.7 μM, respectively [43]. Moreover, the results showed that 3-oxo,4*β*-hydroxy, and 9-isopentenyl substitutions tended to increase the anti-H_1N_1 activity of hexacyclic indole-diterpenoids [43]. A marine-derived fungal strain, *Aspergillus terreus* SCSGAF0162, was isolated from the tissue of the gorgonian *Echinogorgia aurantiaca* collected from Sanya, Hainan Province, China [44]. Asperterrestide A (**36**, Fig. 7), a new alkaloid purified from the fermentation broth of the *A. terreus* SCSGAF0162, had a rare 3-OH-*N*-CH_3-Phe residue and exhibited inhibitory activity against H_1N_1 and H_3N_2 virus with IC_{50} values of 15 and 8.1 μM, respectively (ribavirin as positive control, IC_{50} = 20.2 and 0.41 μM, respectively) [44].

Table 3
Secondary metabolites with other antivirus activities from marine microbes.

Metabolites	Species	Activities	Ref
Truncateols O (**2**), P (**65**)	*T. angustata*	IC_{50} = 39.0 and 16.1 μM, resp. (HIV virus)	[27]
Trypilepyrazinol (**66**)	*Penicillium* sp. IMB17-046	IC_{50} = 4.6 and 3.5 μM, resp. (HIV-1 virus)	[66]
3β-hydroxyergosta-8,14,24 (28)-trien-7-one (**67**)		IC_{50} = 7.7 μM (HCV virus)	
Aspernigrin C (**68**)	*A. niger* SCSIO Jcsw6F30	IC_{50} = 4.7 ± 0.4 and 1.4 ± 0.06 μM, resp. (HIV-1 virus)	[67]
Malformin C (**69**)			
3α-hydroxy-7-ene-6,20-dione (**70**)	*Cladosporium* sp. WZ-2008-0042	IC_{50} = 0.12 mM (RSV virus)	[70]
Cytosporin L (**71**)	*Eutypella* sp.	IC_{50} = 72.01 and 30.25 μM, resp. (RSV virus)	[71]
Cytosporin D (**72**)			
Penicitrinone F (**73**)	*P. chrysogenum* SCSIO 41001	IC_{50} = 14.5 μM (EV71 virus)	[74]
6β,9α-dihydroxy-14-*p*-nitrobenzoylcinnamolide (**38**)	*A. ochraceus* Jcma1F17	IC_{50} = 9.4 μM (EV71 virus)	[46]
ZSU-H85 A (**74**)	*Trichoderma* sp. SCSIO41004	IC_{50} = 25.7 μM (EV71 virus)	[75]
Scequinadoline A (**75**)	*D. cejpii* F31-1	50% inhibition, at 50 μM (DENV virus)	[77]
Debromoaplysiatoxin (**76**) Anhydrodebromoaplysiatoxin (**77**)	*T. erythraeum*	EC_{50} = 1.3, 22.3 and 2.7 μM, resp. (CHIKV virus)	[79]
3-Methoxydebromoaplysiatoxin (**78**)			
Antimycin A10a (**79**)	*S. kaviengensis*	IC_{50} = 3 nM (WEEV virus)	[81]

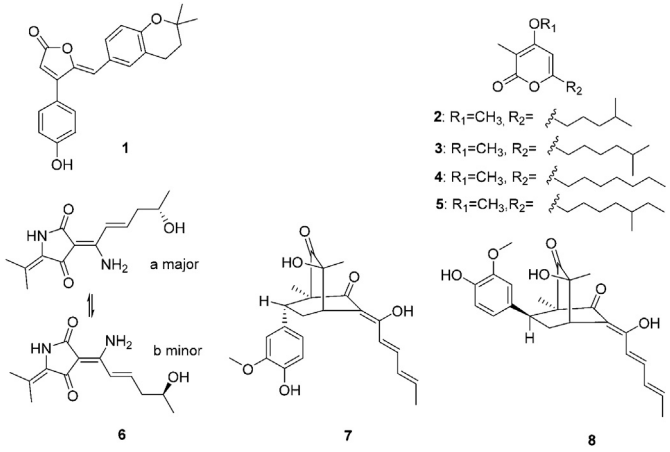

Fig. 4. Chemical structures of compounds **1**–**8** with anti-H_1N_1 activities.

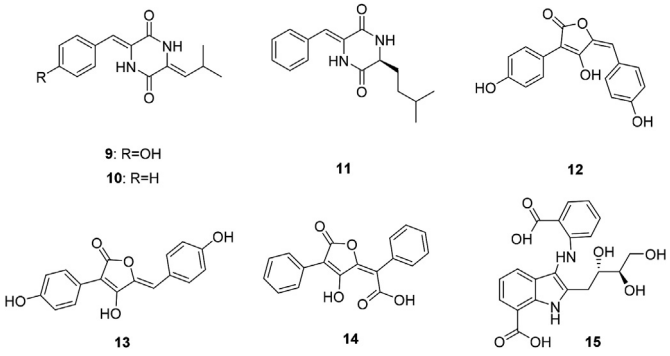

Fig. 5. Chemical structures of compounds **9**–**15** with anti-H_1N_1 activities.

Cladosporisteroid B (**37**, Fig. 8) was a new highly oxygenated sterol that was obtained from the extracts of the culture of a sponge-derived fungus *Cladosporium* sp. SCSIO41007 collected from the sea area near Xuwen County, Guangdong Province, China [45]. Compound **37** showed weak anti-H_3N_2 activity with IC_{50} value of 16.2 μM (IC_{50} = 34.0 nM for the positive control oseltamivir) [45]. The fungal strain *Aspergillus ochraceus* Jcma1F17 was isolated from a marine algae *Coelarthrum* sp. collected in Paracel Islands, South China Sea, which produced a new nitrobenzoyl sesquiterpenoid, 6β,9α-dihydroxy-14-*p*-nitrobenzoylcinnamolide (**38**, Fig. 8) [46]. Nitrobenzoyl sesquiterpenoids are rare in natural sources, and

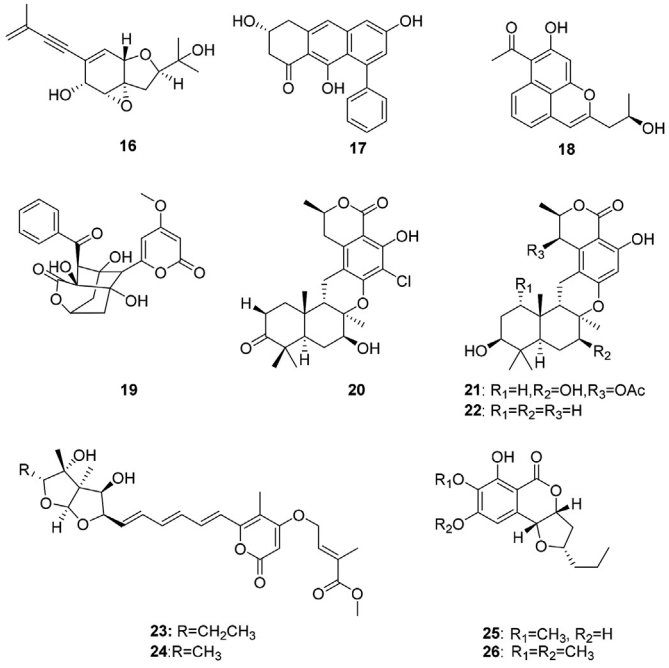

Fig. 6. Chemical structures of compounds **16**–**26** with anti-H_1N_1 activities.

Aspergillus species are the only sources of them. Compound **38** showed inhibitory activity against H_3N_2 with IC_{50} value of 17.0 μM (oseltamivir as positive control, IC_{50} = 0.008 μM) [46].

2.2. Anti-HSV virus compounds

HSV-1 is regularly correlative to oral-facial infections and encephalitis, whereas HSV-2 frequently causes genital ulcers worldwide [47,48]. Herpes virus has a unique incubation period and physiological reactivation characteristics [49]. The chronic incubation period makes the host susceptible to repeated attacks by virus activation and increases the possibility of virus transmission [50]. At present, clinically effective anti-herpes virus drugs such as acyclovir, valacyclovir and other nucleoside analogues are mainly used as nucleoside inhibitors of DNA polymerase [51]. However, due to antiherpetic drugs resistance and lack of validated vaccines for effective prevention, it is urgent to develop novel medicines against HSV virus [52]. A strain of marine-derived *Streptomyces koyangensis* SCSIO 5802, which was isolated from the South China

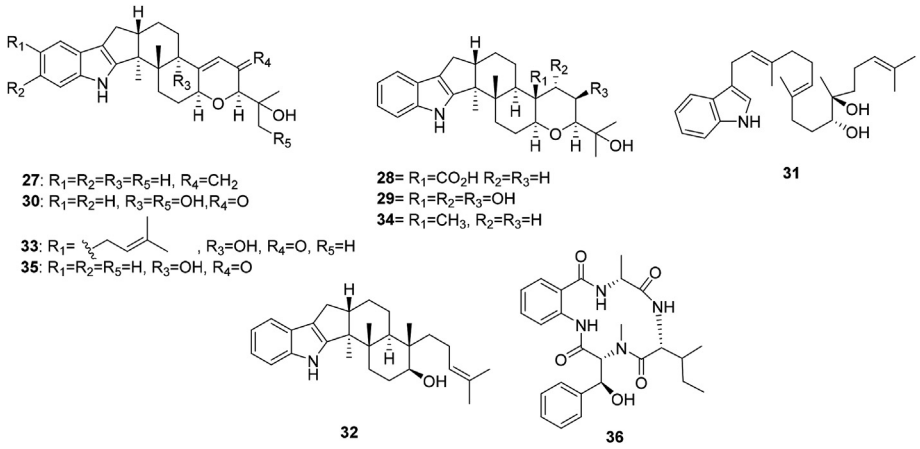

Fig. 7. Chemical structures of compounds **27**–**36** with anti-H_1N_1 activities.

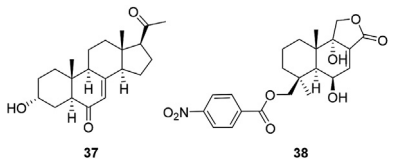

Fig. 8. Chemical structures of compounds **37**–**38** with anti-H_3N_2 activities.

Sea at a depth of 3536 m, resulted in the discovery of a novel butenolide derivative, (4*S*)-10-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide (**39**, Fig. 9) featuring octyl substitution at γ-position [53]. The new compound **39**, displayed anti-HSV-1 activity with EC_{50} value of 25.4 μM (Ganciclovir as positive control, EC_{50} = 0.025 μM) [53]. Xiao Liang et al. separated simplicilliumtide J (**40**, Fig. 9), and verlamelins A and B (**41**, **42**, Fig. 9) from the deep-sea-derived fungal strain *Simplicillium obclavatum* EIODSF 020 [54]. These compounds displayed significant anti-HSV-1 activity with

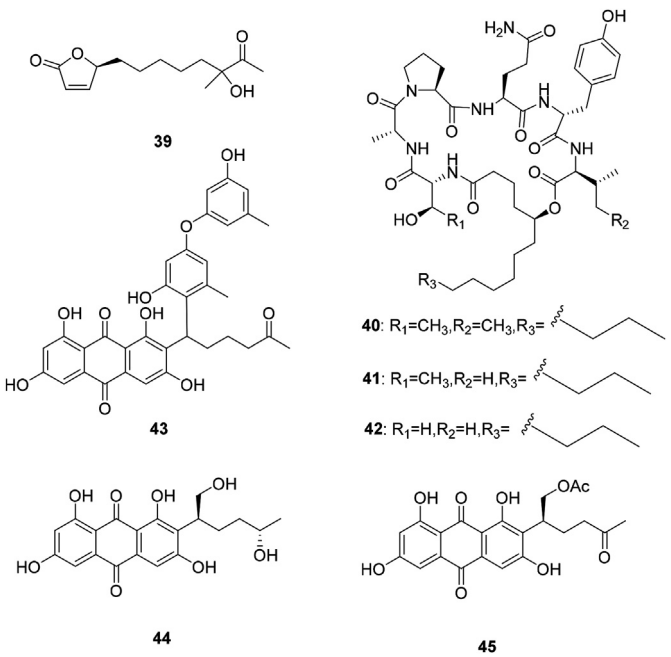

Fig. 9. Chemical structures of compounds **39**–**45** with anti-HSV activities.

IC_{50} values of 14.0, 16.7, and 15.6 μM, respectively (acyclovir as positive control, EC_{50} = 3.0 μM). This is the first time to report the antiviral activity of these cyclic peptides [54]. Two new anthraquinones, aspergilols H, I (**43**, **44**, Fig. 9) and coccoquinone A (**45**, Fig. 9) were purified from the deep-sea-associated fungus *Aspergillus versicolor* SCSIO 41502, collected from marine sediment sample at a depth of 2326 m from the South China Sea [55]. These compounds displayed significant antiviral activity towards HSV-1 with EC_{50} values of 4.68, 6.25, and 3.12 μM, respectively (acyclovir as positive control, EC_{50} = 3.0 μM) [55].

Chemical investigation of the culture of *Trichobotrys effuse* DFFSCS021 that was isolated from the deep sea sediment collected from the South China Sea, resulted in the isolation of three new tetramic acid derivatives with a decalin ring, trichobotrysins A, B and D (**46**–**48**, Fig. 10) [56]. Compounds **46**–**48** possessed evidently anti-HSV-1 activity with IC_{50} values of 3.08, 9.37, and 3.12 μM (acyclovir as positive control, IC_{50} = 3.5 μM). This is the first time to report the anti-HSV-1 activity of this type of compounds [56]. Minghe Luo et al. separated two novel hydroxamate-containing natural product cyclopeptides designated acremonpeptides A (**49**, Fig. 10) and B (**50**, Fig. 10), along with Al(III)−acremonpeptide D (**51**, Fig. 10) from the extract of the fungal strain *Acremonium persicinum* SCSIO 115, which was isolated from a marine sediment sample collected in the South China Sea [57]. These compounds *in vitro* exhibited moderate antiviral activities for HSV-1 with EC_{50} values of 16, 8.7, and 14 μM, respectively [57]. A gorgonian sample collected from the South China Sea, Sanya, Hainan Province, resulted in the isolation of *Aspergillus* sp. SCSIO 41501, which further led to the isolation of two new linear peptides, namely, aspergillipeptides D and E (**52**, **53**, Fig. 10) [58]. Compounds **52** and **53** exhibited evidently inhibition against herpes simplex virus type 1 (HSV-1) with IC_{50} values of 9.5 and 19.8 μM under their non-cytotoxic concentrations against a Vero cell line, respectively [58]. Additionally, compound **53** also had antiviral activity against acyclovir-resistant clinical isolates of HSV-1 [58].

Xu-Hua Nong et al. separated eight territrem derivatives along with nine butyrolactone derivatives from a marine-derived fungus *Aspergillus terreus* SCSGAF0162 under rice solid-state fermentation, which was gathered from South China Sea gorgonian coral *Echinogorgia aurantiaca* [59]. All the isolated metabolites were evaluated for anti-HSV-1 activities, only 12α-dehydroxyisoterreulactone A (**54**, Fig. 11), arisugacin A (**55**, Fig. 11), isobutyrolactone II (**56**, Fig. 11), and aspernolide A (**57**, Fig. 11) were shown to have obviously inhibitory effects with IC_{50} values of 16.4 ± 0.6, 6.34 ± 0.4, 21.8 ± 0.8 and 28.9 ± 0.8 μg/mL, respectively [59]. Balticolid (**58**,

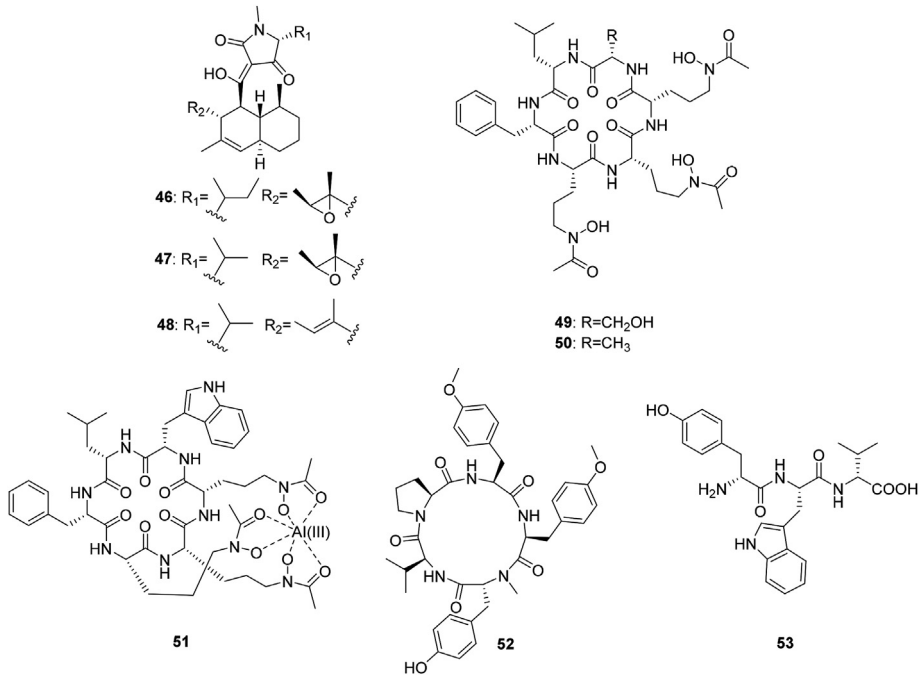

Fig. 10. Chemical structures of compounds **46**–**53** with anti-HSV activities.

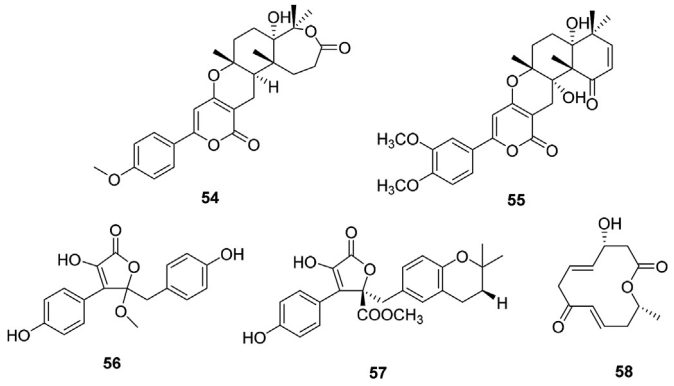

Fig. 11. Chemical structures of compounds **54**–**58** with anti-HSV activities.

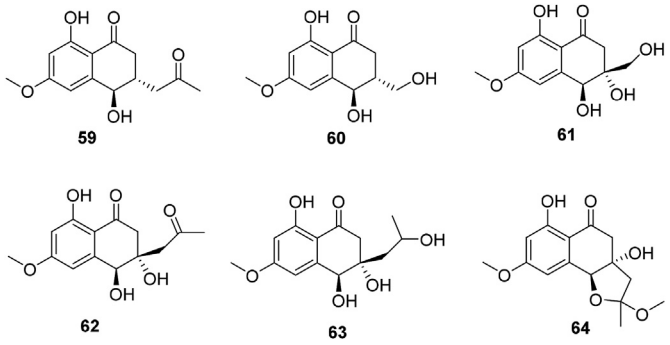

Fig. 12. Chemical structures of compounds **59**–**64** with anti-HSV virus activities.

Fig. 11), a novel 12-membered macrolide, was separated from the extraction of the culture broth of the fungal strain 222 belonging to the Ascomycota, which was found in driftwood collected from the coast of the Greifswalder Bodden, Baltic Sea, Germany [60]. This compound exhibited antiviral activity against HSV-1 with IC_{50} value of 0.45 μM [60].

Another study on the same fungal strain 222 resulted in the discovery of six novel naphthalenone derivatives, balticols A–F (**59**–**64**, Fig. 12) [61]. The balticols were tested at non-cytotoxic concentrations for their antiviral activity against Herpes simplex virus (HSV) type I. These compounds were found to showed inhibitory effect with IC_{50} values of 1, 1, 1, 0.1, 0.01, 0.1 μg/mL, respectively [61]. Balticol E had the most remarkable result with IC_{50} value of 0.01 μg/mL against HSV-1 [61].

2.3. Others including HIV, HCV, RSV, EV71, DENV, CHIKV, and WEEV antivirals

HIV-1 and HIV-2 can infect human beings and cause severe immunosuppression through decline of $CD4^+$ cells [62,63]. So far, over 30 antiretroviral drugs were on the market for the treatment of HIV infection and divided into six main groups: integrase inhibitors, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors, and entry inhibitors [64]. However, in the United States, the annual cost of the drugs per individual can be as high as $24,000 relying on the types of anti-HIV medicines [65]. Two undescribed isoprenylated, truncateols O (**2**, Fig. 6) and P (**65**, Fig. 13) were collected from the sponge-derived fungus *Truncatella angustata* [27]. Compounds **2** and **65** showed anti-HIV effects by blocking HIV replication in one-cycle infection assay with IC_{50} values of 39.0 and 16.1 μM, respectively [27]. Moreover, though efavirenz (positive control) displaying stronger activity than the data raising from the isolated compounds, the lower cytotoxicity of the collected compounds (IC_{50} > 100 μM) in comparison with efavirenz (IC_{50} = 40.6 μM) suggested that these compounds were worthy for further observation as anti-HIV leads [27]. Chemical investigation of the extract of marine-derived fungus *Penicillium* sp. IMB17-046 isolated from marine sediments collected from a mangrove swamp in Sanya, Hainan province, China, resulted in the isolation of trypilepyrazinol (**66**, Fig. 13) and 3β-hydroxyergosta-8,14,24 (28)-

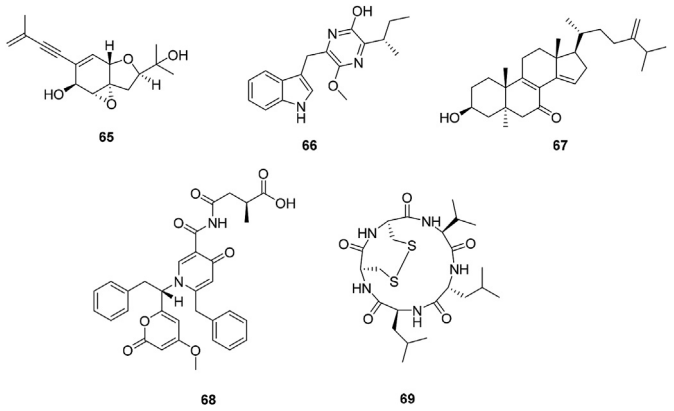

Fig. 13. Chemical structures of compounds **65**–**69** with anti-HIV or anti-HCV activities.

trien-7-one (**67**, Fig. 13) [66]. These compounds exhibited broad-spectrum inhibitory activities against different types of viruses, including human immunodeficiency virus (HIV), and hepatitis C virus (HCV) [66]. Compound **66** showed inhibitory activities against HIV-1 and HCV with IC_{50} values of 4.6 and 7.7 μM, respectively. Compound **67** displayed anti-HIV-1 activity with IC_{50} value of 3.5 μM [66]. The marine derived *Aspergillus niger* SCSIO Jcsw6F30 was associated with a marine algae *Sargassum* sp. collected in Yongxing Island, South China Sea, in July 2012, and produced a novel 2-benzylpyridin-4-one containing metabolite, aspernigrin C (**68**, Fig. 13) and malformin C (**69**, Fig. 13) [67]. These compounds exhibited obvious anti-HIV-1 activities with IC_{50} values of 4.7 ± 0.4, 1.4 ± 0.06 μM, respectively (abacavir as a positive control, IC_{50} = 0.8 ± 0.1 μM)[67].

RSV is considered to be the major pediatric respiratory pathogen, triggered by G protein combining host cell receptors [68]. Only limited therapeutic compounds for RSV have been reported, such as paclizumab and ribavirin, accounting for the urgency to develop novel anti-RSV drugs [68,69]. Meilin Yu et al. separated a new pregnane, 3α-hydroxy-7-ene-6,20-dione (**70**, Fig. 14) from the extract of the fungal strain *Cladosporium* sp. WZ-2008-0042, which was isolated from the gorgonian *Dichotella gemmacea* collected at the Weizhou Island coral reef, in the South China Sea, in September 2008 [70]. Compound **70** was tested for its inhibitory activity towards respiratory syncytial virus (RSV), displaying potential anti-RSV activity with IC_{50} value of 0.12 mM (ribavirin as a positive control, IC_{50} = 0.08 mM) [70]. A novel hexahydrobenzopyran derivative, named as cytosporin L (**71**, Fig. 14) and a known cytosporin D (**72**, Fig. 14) were obtained from the fungal strain *Eutypella* sp. isolated from the gorgonian *Dichotella gemmacea*, collected from the Weizhou coral reef in the South China Sea, Guangxi Province, China in 2008 [71]. The isolated secondary metabolites were evaluated for their anti-virus activities [71]. The antiviral activity against respiratory syncytial virus (RSV) induced cytopathogenicity in human laryngeal carcinoma (Hep-2) cell was determined by the cythopathic effect (CPE) inhibition assay, showing compounds **71** and **72** had significantly anti-RSV activities with IC_{50} values of 72.01 and 30.25 μM, respectively [71].

EV71 viruses can cause acute neurological disease in children, leading to heart and lung failure [72]. Despite broad research with extensive target-based chemical design, developing drugs has failed to meet pharmacological expectations [73]. Another study focused on a deep-sea-derived fungus *Penicillium chrysogenum* SCSIO 41001, which produced a citrinin dimer named penicitrinone F (**73**, Fig. 15) [74]. Using the CPE inhibition assay in accordance with protocols, this compound was evaluated for anti-EV71 activity, which exhibited moderate antivirus activity against EV71 with IC_{50} value of 14.5 μM (ribavirin as positive control, IC_{50} = 13.3 μM) [74]. Wei Fang et al. isolated a novel nitrobenzoyl sesquiterpenoid 6β,9α-dihydroxy-14-*p*-nitrobenzoylcinnamolide (**38**, Fig. 8) collected from the extracts of the culture of marine-derived fungus *Aspergillus ochraceus* Jcma1F17 [46]. This compound displayed anti-EV71 activity with IC_{50} value of 9.4 μM [46]. Ribavirin was used as the positive control against EV71 virus with IC_{50} value of 0.6 μM [46]. Chemical study of the extract of sponge-derived fungus *Trichoderma* sp. SCSIO41004 isolated from a *Callyspongia* sp. sponge collected from the sea area near Xuwen County, Guangdong Province, China, resulted in the isolation of ZSU-H85 A (**74**, Fig. 15) [75]. Compound **74** was tested for antivirus activity against EV71 on Vero cells, showing anti-EV71 effect with IC_{50} value of 25.7 μM (IC_{50} = 13.3 μM for the positive control ribavirin) [75].

DENV is considered as an urban disease, completing its cycle in humans by the biting of mosquito [76]. Currently, it is vital to develop new antivirus drugs due to the absence of proper treatment or vaccination for DENF [76]. A known fumiquinozaline, scequinadoline A (**75**, Fig. 16), was obtained from the marine-derived fungus *Dichotomomyces cejpii* F31-1 isolated from the inner tissue of the soft coral *Lobophytum crassum* which was acquired from Hainan Sanya National Coral Reef Reserve, China [77]. Compound **75** exerted obvious antivirus activity with 50% inhibition at 50 μM against dengue virus serotype 2 productions by standard plaque assay, equivalent to the positive control andrographlide at the same concentration, showing the potential for further development as a dengue virus inhibitor [77].

Chikungunya Virus (CHIKV) is a mosquito-tansmitted Alphavirus that has been spreading rapidly, causing more than one million people infected. Although over-the-counter anti-inflammatory drugs can alleviate the symptoms, currently, there is no therapy to cure this disease [78]. Debromoaplysiatoxin (**76,** Fig. 17) and anhydrodebromoaplysiatoxin (**77,** Fig. 17), and a new analogue, 3-methoxydebromoaplysiatoxin (**78,** Fig. 17) were purified from the bioactive organic extracts of *Trichodesmium erythraeum* (TLT/PSK/001), collected from Pulau Seringat Kias, Singapore [79]. Compounds **76**, **77** and 7**8** exhibited significant dose-dependent inhibition of CHIKV in post-treatment, with EC_{50} values of 1.3, 22.3 and 2.7 μM, respectively [79]. The antiviral mechanisms of these compounds probably targeted a step in the CHIKV replication cycle which occurred after viral entry. Compounds **76** and **78** may represent a new class of antiviral drugs, and further studies of essential pharmacophores probably produce modified leads with improved pharmacological properties [79].

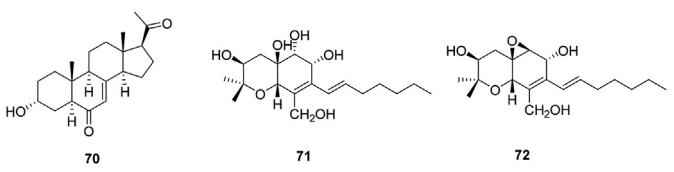

Fig. 14. Chemical structures of compounds **70**–**72** with anti-RSV activities.

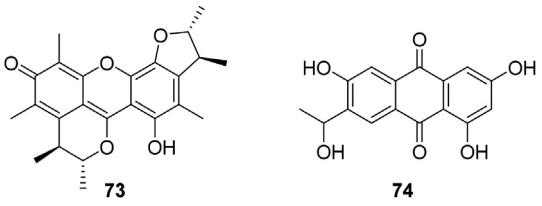

Fig. 15. Chemical structures of compounds **73**–**74** with anti-EV71 activities.

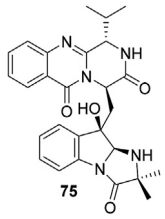

Fig. 16. Chemical structure of compound **75** with anti-DENV activity.

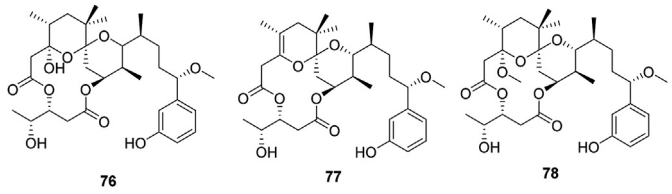

Fig. 17. Chemical structures of compounds **76**–**78** with anti-CHIKV activities.

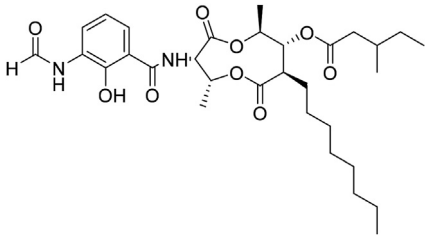

Fig. 18. Chemical structure of compound **79** with anti-WEEV activity.

The Western Equine Encephalitis Virus (WEEV) belongs to the encephalitic alpha viruses, which can directly infect neurons leading to CNS inflammation and neuronal destruction. It can cause severe diseases in human with high fatality of 70%. Unfortunately, there are currently no licensed vaccines or antivirus drugs for alpha virus infections [80]. Chemical investment of the extract of marine-derived *Streptomyces kaviengensis* (F7E2f) collected from the coast of New Ireland, Papua New Guinea, resulted in the isolation of antimycin A10a (**79**, Fig. 18) [81]. This compound exhibited potent activity against WEEV in cultured cells with IC_{50} value of approximately 3 nM [81]. The mechanism of action was that antimycin A1a can mediate in part by disruption of mitochondrial electron transport and pyrimidine biosynthesis [81].

3. Conclusions

Many epidemics broke out over the centuries, which have killed millions of people. Nevertheless, few treatments are available for deadly virus infectious diseases till now. Additionally, a great large of antiviral drugs have been described with viral resistance, which remains an unsolved challenge for antivirus therapy [63]. With increasing numbers of discovering novel types of viruses and drug resistant strains, it is urgent to develop new antiviral lead agents continuously. During the last decade, 79 marine microbes-derived natural products with 9 types of antivirus activities (anti-influenza, anti-HSV, anti-HIV, anti-HCV, anti-RSV, anti-EV71, anti-DNEV, anti-CHIKV, and anti-WEEV) were reported (Fig. 1), of which 40 compounds exhibited marked antiviral activities. Intriguingly, 18 compounds, rubrolide S (**1**), VLPs Q–T (**2**–**5**), (3Z,6S)-3-benzylidene-6-isobutylpiperazine-2,5-dione (**10**), albonoursin (**11**), truncateol O (**16**), *R*-wailupemycin K (**18**), chrodrimanins K and N (**20**–**21**), 3-hydroxypentacecilide A (**22**), asteltoxins E and F (**23**–**24**), asperterrestide A (**36**), trichobotrysins A (**46**) and D (**48**), and balticol E (**63**) displayed antivirus activities even stronger than the corresponding positive drugs. However, even if many *in vitro* studies showed promising results on these compounds, a limited account of *in vivo* studies has been performed to date. Statistically, these marine microbial compounds with antiviral activities were collected from different marine sources, including sediments, seawaters, algae, sponges, corals, worms as well as gorgonians (Fig. 2). It is notable that over half of these compounds were isolated from marine sediments (50.6%). Marine *Aspergillus* (24.1%), *Penicillium* (21.5%) and *Streptomyces* (16.5%) were recognized as the dominant genera to produce these antiviral natural products (Fig. 2). Collectively, reasonable pharmacological screening of these compounds will offer promising leads for the development of antiviral medicines or antiviral adjuvants. However, so far only Ara-A derived from marine with anti-HSV activity has entered the market and few marine-derived compounds have reached the clinical trials. In the context of the global spread of COVID-19, it is necessary to continue research on novel antiviral natural products in the ocean, especially marine microbes. The marine environment is recognized as a unique but currently under-exploited resource in regard to identifying new compounds as potential therapeutic drugs. These compounds derived from the ocean may possess antiviral activity with unique mechanisms of action. Using chemosynthesis and biosynthesis strategies, it is possible to bring these antiviral natural products into further clinical development. Additionally, a multidisciplinary method that comprised of genomics, metabolomics, microbiology, natural products chemistry, and pharmacology may enrich the pipeline of novel antiviral drugs development with potential lead compounds, which will conduce to a worldwide search for clinically antivirus molecules.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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