Microbial Natural Products with Anti-Human Immunodeficiency Virus

Subjects: Infectious Diseases

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The resurgence and re-emergence of fatal viral infections pose a grave threat to public health. The emergence and spread of animal viruses are existential threats to humanity due to a number of intertwined and synergistic events, such as altered human behaviors, high-density rapid urbanization and demographic shift, modernization that encourages people with high mobility, large gatherings, global warming and destruction that altered the ecosystem, and an inadequate global public health system. Human immunodeficiency virus (HIV) is a type of retrovirus that infects humans.

Keywords: Microbial Natural Products ; HIV ; Human Immunodeficiency Virus

1. Brief Introduction to Anti-Human Immunodeficiency Virus

The primary transmission mode of HIV is genital-to-genital contact, blood, sperm, and blood transfusion. This virus attacks the body's immune system, leading to acquired immunodeficiency syndrome (AIDS), a condition in which the immune system gradually fails, allowing dangerous opportunistic infections and cancer to develop. HIV primarily infects cluster of differentiation 4^+ ($CD4^+$) T cells, dendritic cells, and macrophages [1].

Furthermore, the condition may reduce the number of $CD4^+$ T cells to a critical level, resulting in a loss of cell-mediated immunity and greater susceptibility to opportunistic infection, eventually leading to AIDS [2]. As of 2019, the World Health Organization (WHO) estimates that 38 billion people worldwide are infected with HIV [3]. However, approximately 1.7 million people were unaware they were HIV-positive [3]. Therefore, several antiretroviral drugs that may slow the progression of HIV in the body have been discovered and developed. Antiretroviral drugs were only recently available to 67% of the world's population. Lopinavir, darunavir, atazanavir, and saquinavir are protease inhibitors, while lamivudine, stavudine, emtricitabine, efavirenz, nevirapine, and rand aziridine are reverse transcription inhibitors [4]. However, no HIV drug on the market can cure HIV.

2. Microbial Natural Products with Anti-Human Immunodeficiency Virus

Natural products produced by microorganisms, as shown in **Table 1**, could be used to develop anti-HIV medications. Anti-HIV bioactive compounds from fungi are widely considered to be one of the most promising sources. Several compounds, including alachalasin A from *Podospora vesticola* fungus cultures, have been identified as effective HIV-1 replication suppressors in cellosaurus cells C8166 [5][6]. The half-maximal effective concentration, or EC_{50}, of alachalasin is 8.01 μM. Pestalofone A, as well as its derivatives, including pestalofone B and E, as well as pestaloficiol G, H, J, and K isolated from the *Pestalotiopsis fici* fungus, possess anti-HIV activity [7][8]. Furthermore, epicoccin G and H were isolated from ascomycete *Epicoccum nigrum* fermentation culture, in addition to its diphenylalazine A [9]. Another study discovered that bacillamide B, derived from the ascomycete *Tricladium* sp., exhibited anti-HIV activity [10]. Furthermore, cytochalasan alkaloids, such as armochaetoglobin K, L, M, N, O, P, Q, and R, purified from the arthropod-associated *Chaetomium globosum* fungus had significant anti-HIV activity (EC_{50} = 0.25–0.55 μM) [11].

Table 1. Natural product produce by microbes and its target.

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
alachalasin A [5]	alkaloid	*Podospora vesticola* XJ03-56-1	glacier	HIV-1	EC_{50} = 8.01 μM	ND

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
pestalofone A [8]	terpenoid	*Pestalotiopsis fici* W106-1	plant endophyte	HIV-1	EC_{50} = 90.4 μM	ND
pestalofone B [8]	terpenoid	*P. fici* W106-1	plant endophyte	HIV-1	EC_{50} = 64.0 μM	ND
pestalofone E [8]	terpenoid	*P. fici* W106-2	plant endophyte	HIV-1	EC_{50} = 93.7 μM	ND
pestaloficiol G [8]	terpenoid	*P. fici* W106-3	plant endophyte	HIV-1	EC_{50} = 89.2 μM	ND
pestaloficiol H [8]	terpenoid	*P. fici* W106-4	plant endophyte	HIV-1	EC_{50} = 89.2 μM	ND
pestaloficiol J [8]	terpenoid	*P. fici* W106-5	plant endophyte	HIV-1	EC_{50} = 8 μM	ND
pestaloficiol K [8]	terpenoid	*P. fici* W106-6	plant endophyte	HIV-1	EC_{50} = 78.2 μM	ND
epicoccin G [12]	alkaloid	*Epicoccum nigrum* XZC04-CS-302	*Cordyceps sinensis* fungus	HIV-1	EC_{50} = 13.5 μM	ND
epicoccin H [12]	alkaloid	*E. nigrum* XZC04-CS-302	*C. sinensis*	HIV-1	EC_{50} = 42.2 μM	ND
diphenylalazine A [12]	peptide	*E. nigrum* XZC04-CS-302	*C. sinensis*	HIV-1	EC_{50} = 27.9 μM	ND
bacillamide B [10]	peptide	*Tricladium sp.* No. 2520	soil in which *C. sinensis* grow	HIV-1	EC_{50} = 24.8 μM	ND
armochaetoglobin K [11]	alkaloid	*Chaetomium globosum* TW 1-1	*Armadillidium vulgare* insect	HIV-1	EC_{50} = 1.23 μM	ND
armochaetoglobin L [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.48 μM	ND
armochaetoglobin M [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.55μM	ND
armochaetoglobin N [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.25 μM	ND
armochaetoglobin O [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.61 μM	ND
armochaetoglobin P [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.68 μM	ND
armochaetoglobin Q [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.31 μM	ND
armochaetoglobin R [11]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.34 μM	ND
stachybotrin D [13]	terpenoid	*Stachybotrys chartarum* MXH-X73	*Xestospongia testudinaris* sponge	HIV-1	EC_{50} = 8.4 μM	replication
stachybotrysam A [14]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 9.3 μM	ND
stachybotrysam B [14]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 1.0 μM	ND
stachybotrysam C [14]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 9.6 μM	ND
chartarutine B [15]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 4.90 μM	ND
chartarutine G [15]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 5.57 μM	ND
chartarutine H [15]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 5.58 μM	ND
malformin C [16]	peptide	*Aspergillus niger* SCSIO Jcsw6F30	marine	HIV-1	IC_{50} = 1.4 μM	entry

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aspernigrin C [17]	alkaloid	*A. niger* SCSIO Jcsw6F30	marine	HIV-1	IC_{50} = 4.7 μM	entry
eutypellazine E [18]	alkaloid	*Eutypella* sp. MCCC 3A00281	deep sea sediment	HIV-1	IC_{50} = 3.2 μM	ND
truncateol O [19]	terpenoid	*Truncatella angustata* XSB-01-43	*Amphimedon* sp. sponge	HIV-1 and H1N1	IC_{50} = 39.0 μM (HIV) and 30.4 μM (H1N1)	ND
truncateol P [19]	terpenoid	*T. angustata* XSB-01-43	*Amphimedon* sp. sponge	HIV-1	IC_{50} = 16.1 μM	ND
penicillixanthone A [20]	polyketide	*Aspergillus fumigatus*	jellyfish	HIV-1	IC_{50} = 0.26 μM	entry
DTM [21]	polyketide	*C. globosum*	deep sea sediment	HIV-1	75.1% at 20 μg/mL	ND
epicoccone B [21]	polyketide	*C. globosum*	deep sea sediment	HIV-1	88.4% at 20 μg/mL	ND
xylariol [21]	polyketide	*C. globosum*	deep sea sediment	HIV-1	70.2% at 20 μg/mL	ND
phomonaphthalenone A [22]	polyketide	*Phomopsis sp.* HCCB04730	*Stephania japonica*-plant endophyte	HIV-1	IC_{50}: 11.6 μg/mL	ND
bostrycoidin [22]	polyketide	*Phomopsis sp.* HCCB04730	*S. japonica* plant endophyte	HIV-1	IC_{50}: 9.4 μg/mL	ND
altertoxin I [23]	phenalene	*Alternaria tenuissima* QUE1Se	*Quercus emoryi* plant endophyte	HIV-1	IC_{50}: 1.42 μM	ND
altertoxin II [23]	phenalene	*A. tenuissima* QUE1Se	*Q. emoryi* plant endophyte	HIV-1	IC_{50}: 0.21 μM	ND
altertoxin III [23]	phenalene	*A. tenuissima* QUE1Se	*Q. emoryi* plant endophyte	HIV-1	IC_{50}: 0.29 μM	ND
alternariol 5-O-methyl ether [24]	phenolic	*Colletotrichum* sp	plant endophyte	HIV-1	EC_{50}: 30.9 μM	replication
ergokonin A [25]	terpenoid	*Trichoderma* sp. Xy24	*Xylocarpus granatum* plant endophyte	HIV-1	IC_{50}: 22.3 μM	ND
ergokonin B [25]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 1.9 μM	ND
sorrentanone [25]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 4.7 μM	ND
cerevisterol [25]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 9.3 μM	ND
phomopsone B [26]	alkaloid	*Phomopsis* sp. CGMCC 5416	*Achyranthes bidentata* plant endophyte	HIV-1	IC_{50}: 7.6 μmol/L	ND
phomopsone C [26]	alkaloid	*Phomopsis* sp. CGMCC 5416	*A. bidentata* plant endophyte	HIV-1	IC_{50}: 0.5 μmol/L	ND
pericochlorosin B [27]	polyketide	*Periconia* sp. F-31	plant endophyte	HIV-1	IC_{50}: 2.2 μM	ND
asperphenalenone A [28]	alkaloid	*Aspergillus* sp.	*Kadsura longipedunculata* plant endophyte	HIV-1	IC_{50}: 4.5 μM	ND
asperphenalenone D [28]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 2.4 μM	ND

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cytochalasin Z_8 [28]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 9.2 μM	ND
epicocconigrone A [28]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 6.6 μM	ND
neoechinulin B/NeoB [29][30][31]	alkaloid	*Aspergillus amstelodami*	ND	HCV and SARS-CoV-2	IC_{50}: 5.5 μM (HCV) and 32.9 μM (SARS-CoV-2)	replication
		Eurotium rubrum F33	marine sediment	H1N1	IC50; 7 μM	entry
raistrickindole A [32]	alkaloid	*Penicillium raistrickii* IMB17-034	mangrove sediment	HCV	EC_{50}: 5.7 μM	ND
raistrickin [32]	alkaloid	*P. raistrickii* IMB17-035	mangrove sediment	HCV	EC_{50}: 7.0 μM	ND
sclerotigenin [32]	alkaloid	*P. raistrickii* IMB17-036	mangrove sediment	HCV	EC_{50}: 5.8 μM	ND
harzianoic acid A [25]	terpenoid	*Trichoderma harzianum* LZDX-32-08	*Xestospongia testudinaria* sponge	HCV	IC_{50}: 5.5 μM	entry
harzianoic acid B [25]	terpenoid	*T. harzianum* LZDX-32-08	*X. testudinaria* sponge	HCV	IC_{50}: 42.9 μM	entry
peniciherquamide C [33]	peptide	*Penicillium herquei* P14190	seaweed	HCV	IC_{50}: 5.1 μM	ND
cyclo (L-Tyr-L-Pro) [34]	peptide	*Aspergillus versicolor*	*Spongia officinalis* sponge	HCV	IC_{50}: 8.2 μg/mL	replication
7-dehydroxyl-zinniol [35]	alkaloid	*Alternia solani*	*Aconitum transsectum* plant endophyte	HBV	IC_{50}: 0.38 mM	ND
THA [36]	polyketide	*Penicillium* sp. OUCMDZ-4736	mangrove sediment	HBV	IC_{50}: 4.63 μM	ND
MDMX [36]	polyketide	*Penicillium* sp. OUCMDZ-4736	*mangrove* sediment	HBV	IC_{50}: 11.35 μM	ND
vanitaracin A [37]	polyketide	*Talaromyces* sp.	sand	HBV	IC_{50}: 10.58 μM	entry
destruxin A [38]	peptide	*Metarhizium anisopliae* var. *dcjhyium*	*Odontoternes formosanus* termite	HBV	IC_{50}: 1.2 μg/mL (mix A+B+E)	ND
destruxin B [38]	peptide	*M. anisopliae* var. *dcjhyium;*	*O. formosanus* termite	HBV	IC_{50}: 1.2 μg/mL (mix A+B+E)	ND
destruxin E [38]	peptide	*M. anisopliae* var. *dcjhyium*	*O. formosanus* termite	HBV	IC_{50}: 1.2 μg/mL (mix A+B+E)	ND
amphiepicoccin A [12]	alkaloid	*Epicoccum nigrum* HDN17-88	*Amphilophus* sp. fish gill	HSV-2	IC_{50}: 70 μM	ND
amphiepicoccin C [12]	alkaloid	*E. nigrum* HDN17-88	*Amphilophus* sp. fish gill	HSV-2	IC_{50}: 64 μM	ND
amphiepicoccin F [12]	alkaloid	*E. nigrum* HDN17-88	*Amphilophus* sp. fish gill	HSV-2	IC_{50}: 29 μM	ND
aspergillipeptide D [39]	peptide	*Aspergillus* sp. SCSIO 41501	gorgonian coral	HSV-1	IC_{50}: 7.93 μM	entry
aspergilol H [40]	polyketide	*Aspergillus versicolor* SCSIO 41501	deep sea sediment	HSV-1	EC_{50} = 4.68 μM	ND

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
aspergilol I [40]	polyketide	*A. versicolor* SCSIO 41503	deep sea sediment	HSV-1	IC_{50} = 6.25 μM	ND
coccoquinone A [40]	polyketide	*A. versicolor* SCSIO 41504	deep sea sediment	HSV-1	IC_{50} = 3.12 μM	ND
trichobotrysin A [41]	alkaloid	*Trichobotrys effuse* DFFSCS021	deep sea sediment	HSV-1	IC_{50} = 3.08 μM	ND
trichobotrysin B [41]	alkaloid	*Trichobotrys effuse* DFFSCS021	deep sea sediment	HSV-1	IC_{50} = 9.37 μM	ND
trichobotrysin D [41]	alkaloid	*Trichobotrys effuse* DFFSCS021	deep sea sediment	HSV-1	IC_{50} = 3.12 μM	ND
11a-dehydroxyisoterreulactone A [42]	terpenoid	*Aspergillus terreus* SCSGAF0162	gorgonian corals *Echinogorgia aurantiaca*	HSV-1	IC_{50} = 16.4 μg/mL	ND
arisugacin A [42]	terpenoid	*Aspergillus terreus* SCSGAF0162	gorgonian corals *E. aurantiaca*	HSV-1	IC_{50} = 6.34 μg/mL	ND
isobutyrolactone II [42]	terpenoid	*Aspergillus terreus* SCSGAF0162	gorgonian corals *E. aurantiaca*	HSV-1	IC_{50} = 21.8 μg/mL	ND
aspernolide A [42]	terpenoid	*Aspergillus terreus* SCSGAF0162	gorgonian corals *E. aurantiaca*	HSV-1	IC_{50} = 28.9 μg/mL	ND
halovir A [43]	peptide	*Scytalidium* sp.	NI	HSV-1 and HSV-2	ED_{50} = 1.1 μM (HSV-1) and 0.28 (HSV-2)	ND
halovir B [43]	peptide	*Scytalidium* sp.	NI	HSV-1	ED_{50} = 3.5 μM	ND
halovir C [43]	peptide	*Scytalidium* sp.	NI	HSV-1	ED_{50} = 2.2 μM	ND
halovir D [43]	peptide	*Scytalidium* sp.	NI	HSV-1	ED_{50} = 2.0 μM	ND
halovir E [43]	peptide	*Scytalidium* sp.	NI	HSV-1	ED_{50} = 3.1 μM	ND
balticolid [44]	polyketide	Ascomycetous fungus	driftwood	HSV-1	IC_{50} = 0.45 μM	ND
alternariol [45]	phenolic	*Pleospora tarda*	*Ephedra aphylla* endphyte	HSV-1	IC_{50} = 13.5 μM	ND
alternariol-(9)-methyl ether [45]	phenolic	*Pleospora tarda*	*E. aphylla* endophyte	HSV-1	IC_{50} = 21.3 μM	ND
oblongolide Z [46]	polyketide	*Phomopsis* sp. BCC 9789	*Musa acuminata* endophyte	HSV-1	IC_{50}: 14 μM	ND
DHI [47]	phenolic	*Torrubiella tenuis* BCC 12732	Homoptera scale insect	HSV-1	IC_{50}: 50 μg/mL	ND
cordyol C [48]	polyketide	*Cordyceps* sp. BCC 1861	Homoptera-cicada nymph	HSV-1	IC_{50}: 1.3 μg/mL	ND
DTD [49]	polyketide	*Streptomyces hygroscopicus* 17997	GdmP mutant	HSV-1	IC_{50}: 0.252 μgmol/L	ND
labyrinthopeptin A1/LabyA1 [50]	peptide	*Actinomadura namibiensis* DSM 6313	desert soil	HSV-1 and HSV-2	EC_{50} = 0.56 μM (HSV-1) and 0.32 μM (HSV-2)	entry
				HIV-1 and HIV-2	EC_{50} = 2.0 μM (HIV-1) and 1.9 μM (HIV-2)	entry

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
monogalactopyranose [51]	polyphenol	*Acremonium* sp. BCC 14080	palm leaf	HSV	IC_{50}: 7.2 μM	ND
mellisol [52]	polyketide	*Xylaria mellisii* BCC 1005	NI	HSV	IC_{50}: 10.5 μg/mL	ND
DOG [52]	polyketide	*Xylaria mellisii* BCC 1005	NI	HSV	IC_{50}: 8.4 μg/mL	ND
spirostaphylotrichin X [53]	polyketide	*Cochliobolus lunatus* SCSIO41401	marine algae	H1N1 and H3N2	IC_{50}: 1.6 μM (H1N1) and 4.1 μM (H3N2)	replication
cladosin C [54]	polyketide	*Cladosporium sphaerospermum* 2005-01-E3	deep sea sludge	H1N1	IC_{50}: 276 μM	ND
abyssomicin Y [50]	polyketide	*Verrucosispora* sp. MS100137	deep sea sediment	H1N1	inhibition rate: 97.9%	ND
purpurquinone B [55]	polyketide	*Penicillium purpurogenum* JS03-21	acidic red soil	H1N1	IC_{50}: 61.3 μM	ND
purpurquinone C [55]	polyketide	*Penicillium purpurogenum* JS03-22	acidic red soil	H1N1	IC_{50}: 64 μM	ND
purpurester A [55]	polyketide	*Penicillium purpurogenum* JS03-23	acidic red soil	H1N1	IC_{50}: 85.3 μM	ND
TAN-931 [55]	polyketide	*Penicillium purpurogenum* JS03-24	acidic red soil	H1N1	IC_{50}: 58.6 μM	ND
pestalotiopsone B [56]	polyketide	*Diaporthe* sp. SCSIO 41011	*Rhizophora stylosa* mangrove endophte	H1N1 and H3N2	IC_{50}: 2.56 μM (H1N1) and 6.76 μM (H3N2)	ND
pestalotiopsone F [56]	polyketide	*Diaporthe* sp. SCSIO 41012	*R. stylosa* mangrove endophte	H1N1 and H3N2	IC_{50}: 21.8 μM (H1N1) and 6.17 μM (H3N2)	ND
DMXC [56]	polyketide	*Diaporthe* sp. SCSIO 41013	*R. stylosa* mangrove endophte	H1N1 and H3N2	IC_{50}: 9.4 μM (H1N1) and 5.12 μM (H3N2)	ND
5-chloroisorotiorin [56]	polyketide	*Diaporthe* sp. SCSIO 41014	*R. stylosa* mangrove endophte	H1N1 and H3N2	IC_{50}: 2.53 μM (H1N1) and 10.1 μM (H3N2)	ND
3-deoxo-4b-deoxypaxilline [57]	alkaloid	*Penicillium camemberti*	mangrove sediment	H1N1	IC_{50}: 28.3 μM	ND
DCA [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 38.9 μM	ND
DPT [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 32.2 μM	ND
9,10-diisopentenylpaxilline	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 73.3 μM	ND
TTD [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 34.1 μM	ND
emindole SB [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 26.2 μM	ND
21-isopentenylpaxilline [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 6.6 μM	ND
paspaline [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 77.9 μM	ND

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
paxilline [57]	alkaloid	*P. camemberti* OUCMDZ-1492	mangrove sediment	H1N1	IC_{50}: 17.7 μM	ND
(14S)-oxoglyantrypine [58]	alkaloid	*Cladosporium* sp. PJX-41	mangrove sediment	H1N1	IC_{50}: 85 μM	ND
norquinadoline A [58]	alkaloid	*Cladosporium* sp. PJX-42	mangrove sediment	H1N1	IC_{50}: 82 μM	ND
deoxynortryptoquivaline [58]	alkaloid	*Cladosporium* sp. PJX-43	mangrove sediment	H1N1	IC_{50}: 85 μM	ND
deoxytryptoquivaline [58]	alkaloid	*Cladosporium* sp. PJX-44	mangrove sediment	H1N1	IC_{50}: 85 μM	ND
tryptoquivaline [58]	alkaloid	*Cladosporium* sp. PJX-45	mangrove sediment	H1N1	IC_{50}: 89 μM	ND
quinadoline B [58]	alkaloid	*Cladosporium* sp. PJX-46	mangrove sediment	H1N1	IC_{50}: 82 μM	ND
22-O-(N-Me-l-valyl)-21-epi-aflaquinolone B [59]	alkaloid	*Aspergillus* sp strain XS-2009	*Muricella abnormaliz* gorgonian	RSV	IC_{50}: 0.042 μM	ND
aflaquinolone D [59]	alkaloid	*Aspergillus* sp strain XS-2009	*M. abnormaliz* gorgonian	RSV	IC_{50}: 6.6 μM	ND
aurasperone A [60]	polyphenol	*Aspergillus niger* No.LC582533	*Phallusia nigra* tunicate	SARS-CoV-2	IC_{50}: 12.25 μM	replication
neoechinulin A [30]	alkaloid	*Aspergillus fumigatus* MR2012	marine sediment	SARS-CoV-2	IC_{50}: 0.47 μM	replication
aspulvinone D [61]	polyphenol	*Cladosporium* sp. 7951	*Paris polyphylla* endophyte	SARS-CoV-2	IC_{50}: 10.3 μM	replication
aspulvinone M [61]	polyphenol	*Cladosporium* sp. 7951	*P. polyphylla* endophyte	SARS-CoV-2	IC_{50}: 9.4 μM	replication
aspulvinone R [61]	polyphenol	*Cladosporium* sp. 7952	*P. polyphylla* endophyte	SARS-CoV-2	IC_{50}: 7.7 μM	replication

Abbreviations: * ND: not yet described, * NI; no information, * DTM: 1,3-dihydro-4,5,6-trihydroxy-7-methylisobenzofuran, * THA: 1,2,4,5-tetrahydroxy-7-((2R)-2-hydroxypropyl) anthracene-9,10-dione, * MDMX: methyl 6,8-dihydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylate, * DHI: 6,8-dihydroxy-3-hydroxymethyl isocoumarin, * DOG: 1,8-dihydroxynaphthol 1-O-glucopyranoside, * DMXC: 3,8-dihydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate, * TTD: (6S,7R,10E,14E)-16-(1H-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol, * DTD: 4,5-dihydro-thiazinogeldanamycin, * DCA: 4a-demethylpaspaline-4a-carboxylic acid, * DPT: 4a-demethylpaspaline-3,4,4a-triol.

An ocean-dwelling fungus is one of the most potent sources of HIV-combating compounds. Meroterpenoids with a phenylspirodrimane skeleton, such as stachybotrin D, derived from the sponge-derived fungus *Stachybotrys chartarum* MXH-X73, were able to inhibit HIV-1 replication by targeting the reverse transcriptase enzyme [13]. This fungus was discovered on the island of Xisha in China, where it was isolated from the marine sponge *Xestospongia testudinaris* [13]. Furthermore, stachybotrysams A, B, and C, extracted from a different strain of *Stachybotrys chartarum*, also showed strong HIV-inhibitory activity [14]. Another report showed that chartarutine B, G, and H, which are all derived from the sponge-associated *Stachybotrys chartarum*, have shown significant antiviral activity against the HIV-1 virus [15]. In addition, malformin C, derived from the marine fungus *Aspergillus niger* SCSIO Jcsw6F30, demonstrated significant anti-HIV-1 activity with an IC_{50}, a half-maximal inhibitory concentration, of 1.4 μM when tested on HIV-infected TZM-bl cells (also called JC.53bl-13) [16]. In addition, aspernigrin C from the same fungus also demonstrated similar action with an IC_{50} of 4.7 μM [16].

An anti-HIV bioassay conducted in 293T cells, also refered as a highly transfectable derivative of human embryonic kidney 293 cells, revealed that eutypellazine E, extracted from a fungus found in the depths of the ocean named *Eutypella* sp., significantly inhibited HIV-1 proliferation [18]. Furthermore, unlike truncateol P, truncateol O, which is derived from the ascomycete *Truncatella angustata*, was found to inhibit the replication of both the H1N1 and HIV-1 viruses [19]. In addition,

penicillixanthone A which is derived from the fungus *Aspergillus fumigatus* that is native to jellyfish, has been shown to possess significant anti-HIV-1 activity by inhibiting the infection of CXCR4-tropic HIV-1 NL4-3 and CCR5-tropic HIV-1 SF162 [20]. Additionally, the fungus *Chaetomium globosum* found in the depths of the ocean was able to produce 1,3-dihydro-4,5,6-trihydroxy-7-methylisobenzofuran, epicoccone B, and xylariol [21]. They showed highly effective anti-HIV activity in vitro at the concentration of 20 µg/mL, with 75.10, 88.4, and 70.20% suppression rates, respectively [21].

Endophytic fungus metabolites have been demonstrated to possess a vast array of bioactivities, including anti-HIV properties. Phomonaphthalenone A and bostrycoidin, both of which were derived from the endophytic fungus *Phomopsis* sp., showed moderate anti-HIV activity and low cytotoxicity, with IC_{50} values of 11.6 and 9.4 µg/mL, respectively [22]. In addition, altertoxin I, II and III derived from the endophytic fungus *Alternaria tenuissima* QUE1Se inhibited HIV-1 virus replication completely [23]. The epoxyperylene structure of these molecules is a promising scaffold for the development of potent and non-toxic anti-HIV therapies [23]. Alternariol 5-O-methyl ether, on the other hand, was identified as a molecule that inhibits HIV-1 pre-integration processes after screening a library of bioactive compounds from the endophytic fungus *Colletotrichum* sp. [24]. Ergokonin A and B isolated from the endophytic fungus *Trichoderma* sp. Xy24 had IC_{50} values of 1.9 µM, which indicated that it significantly suppressed the HIV-1 virus [25]. Recently, it was discovered that the endophytic fungus *Phomopsis* sp. CGMCC No. 5416 produces phomopsone B and C, and these two phomopsones have significant antiviral activity, with IC_{50} values of 7.6 and 0.5 µmol/L, respectively [26]. Furthermore, the phenol pericochlorosin B, isolated from the endophytic fungus *Periconia* sp. F-31, showed significant anti-HIV activity in 293T cells, with an IC_{50} value of 2.2 µM [27]. In 2017, Pang et al. discovered four compounds produced by the plant endophytic fungus *Aspergillus* sp. That belong to phenalenone derivatives [28]. These compounds include asperphenalenone A and D, cytochalasin Z_8, and epicocconigrone A, which have anti-HIV activities in vitro with IC_{50} values of 4.5, 2.4, 9.2, and 6.6 µM, respectively [28]. The endophytic fungus was isolated from the *Kadsura longipedunculata* plant, also known as the Chinese Kadsura Vine, and used in traditional Chinese medicine [28]. Lamivudine and efavirenz, two control positives, demonstrated a greater activity level, with IC_{50} values of 0.1 and 0.0004 µM, respectively [28].

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