Microbial Natural Products with Anti-Hepatitis Virus

Subjects: Infectious Diseases

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The hepatitis virus is one of the major burdens on the global health system. There are numerous types of hepatitis virus, with both known and unknown etiologies. Hepatitis C virus (HCV) and hepatitis B virus (HBV) are the most prevalent infectious agents linked to chronic liver disease, including hepatocellular carcinoma and cirrhosis. In healthcare facilities, the use of contaminated blood poses a risk; the infection can be transmitted through unsafe injection practices, the injection of drugs, the transfusion of unscreened blood, and sexual practices involving blood inflammation.

Keywords: Anti-Hepatitis Virus ; Microbial Natural Products ; HBV ; HCV

1. Anti-Hepatitis C Virus

Chronic Hepatitis C virus (HCV) infection affects approximately 71 million people, and approximately 400,000 people have died due to the infection, with 3–4 million new infections occurring each year [1]. Antiviral medications have been shown to cure approximately 95% of people infected with hepatitis C. The mechanism of action varies, but it involves the inhibition of viral-derived proteins, such as non-structural protein (NS)5A [2], NS5B [3], and NS3/4A [4]. Several direct acting antiviral drugs are currently available to combat HCV, including NS3/4A inhibitors (paritaprevir, asunaprevir, simeprevir, telaprevir, grazoprevir, and boceprevir), NS5A inhibitors (ledipasvir, ombitasvir, elbasvir, daclatasvir, and velpatasvir), and NS5B inhibitors (dasabuvir and sofosbuvir) [5]. However, these therapeutic drugs have some side effects and are quite expensive.

As shown in **Table 1**, a number of natural products produced by microorganisms have the potential to be developed into anti-hepatitis B virus (HBV) medications. It is widely believed that fungi represent one of the most promising sources of bioactive compounds from which anti-HBV drugs could be developed. In 1977, Marchelli and her colleagues purified for the first time a didehydropeptide, which was given the name NeoB. It is an abbreviation for neoechinulin B, which was isolated from the fungus *Aspergillus amstelodami* [6]. Nakajima and his colleagues later demonstrated that NeoB inhibited the development of infectious HCV in Huh-7 cells [7]. By inhibiting the liver X receptors (LXRs), its molecule improved the efficacy of all known anti-HCV drugs and demonstrated a significant synergistic effect when combined with either an HCV NS5A inhibitor or interferon [7]. To achieve high yields, Nishiuchi and his colleagues also developed the synthetic antiviral agent NeoB and other derivatives [8].

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 [9]	alkaloid	*Podospora vesticola* XJ03-56-1	glacier	HIV-1	EC_{50} = 8.01 μM	ND
pestalofone A [10]	terpenoid	*Pestalotiopsis fici* W106-1	plant endophyte	HIV-1	EC_{50} = 90.4 μM	ND
pestalofone B [10]	terpenoid	*P. fici* W106-1	plant endophyte	HIV-1	EC_{50} = 64.0 μM	ND
pestalofone E [10]	terpenoid	*P. fici* W106-2	plant endophyte	HIV-1	EC_{50} = 93.7 μM	ND
pestaloficiol G [10]	terpenoid	*P. fici* W106-3	plant endophyte	HIV-1	EC_{50} = 89.2 μM	ND
pestaloficiol H [10]	terpenoid	*P. fici* W106-4	plant endophyte	HIV-1	EC_{50} = 89.2 μM	ND
pestaloficiol J [10]	terpenoid	*P. fici* W106-5	plant endophyte	HIV-1	EC_{50} = 8 μM	ND
pestaloficiol K [10]	terpenoid	*P. fici* W106-6	plant endophyte	HIV-1	EC_{50} = 78.2 μM	ND

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
epicoccin G [11]	alkaloid	*Epicoccum nigrum* XZC04-CS-302	*Cordyceps sinensis* fungus	HIV-1	EC_{50} = 13.5 μM	ND
epicoccin H [11]	alkaloid	*E. nigrum* XZC04-CS-302	*C. sinensis*	HIV-1	EC_{50} = 42.2 μM	ND
diphenylalazine A [11]	peptide	*E. nigrum* XZC04-CS-302	*C. sinensis*	HIV-1	EC_{50} = 27.9 μM	ND
bacillamide B [12]	peptide	*Tricladium sp.* No. 2520	soil in which *C. sinensis* grow	HIV-1	EC_{50} = 24.8 μM	ND
armochaetoglobin K [13]	alkaloid	*Chaetomium globosum* TW 1-1	*Armadillidium vulgare* insect	HIV-1	EC_{50} = 1.23 μM	ND
armochaetoglobin L [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.48 μM	ND
armochaetoglobin M [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.55μM	ND
armochaetoglobin N [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.25 μM	ND
armochaetoglobin O [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.61 μM	ND
armochaetoglobin P [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.68 μM	ND
armochaetoglobin Q [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.31 μM	ND
armochaetoglobin R [13]	alkaloid	*C. globosum* TW 1-1	*A. vulgare* insect	HIV-1	EC_{50} = 0.34 μM	ND
stachybotrin D [14]	terpenoid	*Stachybotrys chartarum* MXH-X73	*Xestospongia testudinaris* sponge	HIV-1	EC_{50} = 8.4 μM	replication
stachybotrysam A [15]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 9.3 μM	ND
stachybotrysam B [15]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 1.0 μM	ND
stachybotrysam C [15]	alkaloid	*S. chartarum* CGMCC 3.5365.	ND	HIV-1	EC_{50} = 9.6 μM	ND
chartarutine B [16]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 4.90 μM	ND
chartarutine G [16]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 5.57 μM	ND
chartarutine H [16]	alkaloid	*S. chartarum* WGC-25C-6	*Niphates* sp. sponge	HIV-1	IC_{50} = 5.58 μM	ND
malformin C [17]	peptide	*Aspergillus niger* SCSIO Jcsw6F30	marine	HIV-1	IC_{50} = 1.4 μM	entry
aspernigrin C [18]	alkaloid	*A. niger* SCSIO Jcsw6F30	marine	HIV-1	IC_{50} = 4.7 μM	entry
eutypellazine E [19]	alkaloid	*Eutypella* sp. MCCC 3A00281	deep sea sediment	HIV-1	IC_{50} = 3.2 μM	ND
truncateol O [20]	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 [20]	terpenoid	*T. angustata* XSB-01-43	*Amphimedon* sp. sponge	HIV-1	IC_{50} = 16.1 μM	ND
penicillixanthone A [21]	polyketide	*Aspergillus fumigatus*	jellyfish	HIV-1	IC_{50} = 0.26 μM	entry

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DTM [22]	polyketide	*C. globosum*	deep sea sediment	HIV-1	75.1% at 20 μg/mL	ND
epicoccone B [22]	polyketide	*C. globosum*	deep sea sediment	HIV-1	88.4% at 20 μg/mL	ND
xylariol [22]	polyketide	*C. globosum*	deep sea sediment	HIV-1	70.2% at 20 μg/mL	ND
phomonaphthalenone A [23]	polyketide	*Phomopsis sp.* HCCB04730	*Stephania japonica*-plant endophyte	HIV-1	IC_{50}: 11.6 μg/mL	ND
bostrycoidin [23]	polyketide	*Phomopsis sp.* HCCB04730	*S. japonica* plant endophyte	HIV-1	IC_{50}: 9.4 μg/mL	ND
altertoxin I [24]	phenalene	*Alternaria tenuissima* QUE1Se	*Quercus emoryi* plant endophyte	HIV-1	IC_{50}: 1.42 μM	ND
altertoxin II [24]	phenalene	*A. tenuissima* QUE1Se	*Q. emoryi* plant endophyte	HIV-1	IC_{50}: 0.21 μM	ND
altertoxin III [24]	phenalene	*A. tenuissima* QUE1Se	*Q. emoryi* plant endophyte	HIV-1	IC_{50}: 0.29 μM	ND
alternariol 5-O-methyl ether [25]	phenolic	*Colletotrichum* sp	plant endophyte	HIV-1	EC_{50}: 30.9 μM	replication
ergokonin A [26]	terpenoid	*Trichoderma* sp. Xy24	*Xylocarpus granatum* plant endophyte	HIV-1	IC_{50}: 22.3 μM	ND
ergokonin B [26]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 1.9 μM	ND
sorrentanone [26]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 4.7 μM	ND
cerevisterol [26]	terpenoid	*Trichoderma* sp. Xy24	*X. granatum* plant endophyte	HIV-1	IC_{50}: 9.3 μM	ND
phomopsone B [27]	alkaloid	*Phomopsis* sp. CGMCC 5416	*Achyranthes bidentata* plant endophyte	HIV-1	IC_{50}: 7.6 μmol/L	ND
phomopsone C [27]	alkaloid	*Phomopsis* sp. CGMCC 5416	*A. bidentata* plant endophyte	HIV-1	IC_{50}: 0.5 μmol/L	ND
pericochlorosin B [28]	polyketide	*Periconia* sp. F-31	plant endophyte	HIV-1	IC_{50}: 2.2 μM	ND
asperphenalenone A [29]	alkaloid	*Aspergillus* sp.	*Kadsura longipedunculata* plant endophyte	HIV-1	IC_{50}: 4.5 μM	ND
asperphenalenone D [29]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 2.4 μM	ND
cytochalasin Z_8 [29]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 9.2 μM	ND
epicocconigrone A [29]	alkaloid	*Aspergillus* sp.	*K. longipedunculata* plant endophyte	HIV-1	IC_{50}: 6.6 μM	ND
neoechinulin B/NeoB [6][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

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
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 [26]	terpenoid	*Trichoderma harzianum* LZDX-32-08	*Xestospongia testudinaria* sponge	HCV	IC_{50}: 5.5 μM	entry
harzianoic acid B [26]	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 [11]	alkaloid	*Epicoccum nigrum* HDN17-88	*Amphilophus* sp. fish gill	HSV-2	IC_{50}: 70 μM	ND
amphiepicoccin C [11]	alkaloid	*E. nigrum* HDN17-88	*Amphilophus* sp. fish gill	HSV-2	IC_{50}: 64 μM	ND
amphiepicoccin F [11]	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
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

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
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
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

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
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
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

Compound Name [Ref.]	Compound Type	Microbial Strain	Strain Origin/Host	Viral Target	$IC_{50}/EC_{50}/ED_{50}$	Target Inhibition
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.

Natural products made by fungi that thrive in unique marine environments have also been particularly useful in drug discovery. Marine fungi have been the source of the discovery of many novel bioactive natural compounds with anticancer, antifungal, cytotoxic, and antibacterial properties for the past decade [62][63][64]. *Penicillium raistrickii* IMB17-034, a marine-derived fungus, was cultured to isolate raistrickindole A and raistrickin. Both chemicals inhibited Huh7.5 human liver cells infected with HCV, with EC_{50} values of 5.7 and 7.0 μM, respectively [32]. Harzianoic acid A and B are sesquiterpene-based analogues discovered in the symbiotic relationship of the *Trichoderma harzianum* ascomycete fungus with sponges [65]. These purified compounds demonstrated high efficacy in lowering HCV RNA levels in Huh7.5 cells [65]. Furthermore, both compounds are proposed to block HCV entry into the host, with potential targets including the viral E1/E2 and host cell CD81 proteins [65]. In 2016, Nishikori and his colleagues discovered peniciherquamide C, produced by *Penicillium herquei* P14190 and isolated from seaweed collected in Toba, Mie, Japan, after being incubated at 37 °C for 1–2 weeks [33]. Its anti-HCV molecule has an IC_{50} of 5.1 μM [33]. Furthermore, the cyclo (L-Tyr-L-Pro) diketopiperazine isolated from the endophytic fungus *Aspergillus versicolor* isolated from the Red Sea black sponge *Spongia officinalis* significantly inhibited HCV replication by inhibiting the activity of the HCV NS3/4A protease with an IC_{50} value of 8.2 μg/mL [34]. Similarly, an ethyl acetate extract of the fungus *Penicillium chrysogenum* obtained from the red alga *Liagora viscida* also secretes antiviral metabolites that inhibit the HCV NS3/4A protease [66].

Endophytic fungi have also been identified as a significant source of secondary metabolites, due to their complex and dynamic interactions with host plants [67]. A growing body of evidence suggests that endophytic fungi metabolites play an essential role in plant immunity against herbivores and pathogen defense and establish symbiosis with the host plant [67][68][69][70]. These secondary metabolites are expected to be a novel source of natural antiviral compounds, due to their diverse biological activities and wide structural variety. The activities of 44 endophytic fungi isolated from the Red Sea sponge *Hyrtios erectus* were studied and screened [71]. HCV inhibition was observed in extracts of *Penicillium chrysogenum* MERVA42, *Diaporthe rudis* MERVA25, *Auxarthron alboluteum* MERVA32, *Fusarium oxysporum* MERVA39, *Trichoderma harzianum* MERVA44, *Aspergillus versicolor* MERVA29, *Lophiostoma* sp. MERVA36, and *Penicillium polonicum* MERVA43 [71]. In addition, the HCV protease inhibitory activity of fourty-eight endophytic fungal strains isolated and purified from ten Egyptian medicinal plants was investigated. *Alternaria alternata* PGL-3, *Cochlibolus lunatus* PML-17, *Nigrospora sphaerica* EPS-38, and *Emerecilla nidulans* RPL-21 extracts inhibited the most HCV NS3/4A protease [72].

2. Anti-Hepatitis B Virus

People who are infected with HBV, of which there are over 350 million worldwide, are responsible for up to 80% of cases of primary liver cancer [73]. This disease is the leading cause of death worldwide. HBV infection may be responsible for 3% of total mortality in countries where HBV carrier rates reach 10%, a higher level than the mortality rate associated with polio before the introduction of the polio vaccine [74]. The WHO recommends the use of oral treatments, including tenofovir or entecavir, as the most potent drugs to suppress HBV [75]. A number of natural products produced by microorganisms, as shown in **Table 1**, have the potential to be developed into anti-HBV medications.

As part of the effort to discover new bioactive metabolites with anti-HBV properties from microbes, Ai and colleagues isolated 7-dehydroxyl-zinniol from *Alternaria solani*, an endophytic fungal strain found in the roots of the perennial herb *Aconitum transsectum*, which was shown to have moderate antiviral efficacy against HBV in the HBV-transfected HepG2.2.15 cell line (IC_{50} value of 0.38 μM), as evidenced by a decrease in hepatitis B surface antigen (HBsAg) secretion [35]. Furthermore, Jin and his colleagues investigated the secondary metabolite of the acidophilic fungus *Penicillium* sp. (strain OUCMDZ-4736) isolated from the root sediment of the mangrove *Acanthus ilicifolius*, also known as the holy mangrove [36]. Three new anthraquinone derivatives were successfully isolated from the low-pH fermentation broth of the OUCMDZ-4736 strain [36]. However, only two of them demonstrated anti-HBV activity, including 1-hydroxyisorhodoptilometrin and methyl 6,8-dihydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylate, which significantly inhibited HepG2.2.15 human hepatoblastoma cells with IC_{50} of 4.63 and 11.35 μM, respectively [36]. Both could prevent HepG2.2.15 cells from secreting HBsAg and (hepatitis B early antigen) HBeAg [36]. Regarding anti-HBV activity, both outperformed the positive control, lamivudine (IC_{50}: 68.94 μM) [36]. Other derivatives produced by the OUCMDZ-4736 strain, on the other hand, did not show anti-HBV activity [36]. Another fungus, *Talaromyces* sp., produces secondary metabolites with anti-hepatitis properties, such as vanitaracin A. It is a tricyclic polyketide isolated from *Talaromyces* sp. broth. Vanitaracin A has potent anti-HBV activity in HBV-susceptible HepG2-hNTCP-C4 cells, with an IC_{50} value of 10.5 μM [37]. Furthermore, this molecule inhibits HBV viral entry signaling pathways in human hepatocytes. All HBV genotypes (A-D) were recognized by vanitaracin A, including a drug-resistant HBV isolate. According to these findings, vanitaracin A could be used in antiviral treatments to prevent HBV recurrence [76].

Even though pathogenic microbes, such as fungi, can cause severe diseases in hosts, many of them produce bioactive chemicals that could be used to develop new drugs [77][78][79]. Dong and colleagues investigated the anti-HBV properties of crude destruxins (a combination of cyclodepsipeptidic molecules, including destruxin A, B, and E, isolated from *Metarhizium anisopliae* var. *dcjhyium*, an entomopathogenic fungus that has a symbiotic relationship with the termite *Odontoternes formosanus* [38]. In HepG2.2.15 cells, these crude destruxins inhibited HBV-DNA replication, as well as HBsAg and HBeAg production [38]. An in vivo trial using ducks infected with duck HBV and treated for 15 days with crude destruxins revealed that the treated group had significantly lower levels of duck serum DHBV-DNA than the control group [38]. Furthermore, a pure form of destruxin B from the plant pathogenic fungus *Alternaria brassicae* suppresses HBsAg gene expression in human hepatoma Hep3B cells. Destruxin B had no negative effects on cell viability, implying that it could be developed in the future as a specialized anti-HBV medication [80].

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