Natural Compounds against RNA Viruses

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Natural products from plants or other organisms are a rich source of structurally novel chemical compounds including antivirals. Indeed, in traditional medicine, many pathological conditions have been treated using plant-derived medicines. Thus, the identification of novel alternative antiviral agents is of critical importance.

viral infections | natural bioactive compounds | novel antiviral drugs

1. Human Immunodeficiency Virus (HIV)

Human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2) infection leads to immunological failure and Acquired Immunodeficiency Syndrome (AIDS). HIV is a member of the lentivirus genus, which includes retroviruses that possess complex genomes. All lentiviruses are enveloped by a lipid bilayer that is derived from the membrane of the host cell. HIV-1 particles bind specifically to cells bearing the CD4 receptor, lymphocytes, and cause their destruction with a half-life of fewer than two days [1]. This leads to the fusion of HIV-1 to the host cell, thereby leading to the release of viral RNA into the cell. The reverse transcriptase enzyme presents in the virus (HIV-1) converts single-stranded viral RNA to double-stranded viral DNA. The formed viral DNA enters the host cell nucleus and incorporates the viral DNA within the host cell's DNA by the viral enzyme integrase. This integrated viral DNA as provirus could reproduce few or no copies or remain inactive for many years. Since the introduction of highly active antiretroviral therapy (HAART), as well as the impact of preventive measures, the prevalence and incidence of HIV, have declined globally over the last decade except for parts of Eastern Europe and Central Asia [2]. However, the present therapy finds its limitations in the emergence of multidrug resistance as well as HIV persistence within latent cellular reservoirs. Compounds derived from plant, marine, and other natural products have been found to combat HIV infection and/or target HIV reservoirs, and these discoveries have substantially guided current HIV therapy-based studies. Accordingly, finding new drugs and novel targets is needed to treat infected people and to eliminate HIV reservoirs in order to ultimately block HIV infection. Recently, several anti-HIV compounds obtained from natural products have been extensively reported [3]. However, a limited number of those are in the advanced development stage associated with well-known mechanisms of action [4] (Table 1).

Table 1. Natural compounds and their antiviral targets against Immunodeficiency virus.

Natural Source	Compound	Immunodeficiency Virus	Target	CC_{50}	EC_{50}-IC_{50}	SI	Reference
Griffithsia sp.	Griffithsin	HIV	Entry inhibitors		0.043–0.63 nM		[5]

Natural Source	Compound	Immunodeficiency Virus	Target	CC_{50}	EC_{50}-IC_{50}	SI	Reference
Nostoc ellipsosporum	Ascyanovirin-N	HIV					[6]
Siliquariaspongia mirabilis Stelletta clavosa	Mirabamide-A	HIV			40–140 nM		[7]
Syzygium claviflorum	Betulinic acid Dihydro betulinic	HIV	Maturation inhibitors		1.4 µM 0.9 µM	9.3 14	[8]
Synthetic derivative of betulinic acid	Bevirimat	HIV		25 µM	7.8 nM	>2500	[9]
Rheum palmatum	Sennoside A	HIV	Reverse transcriptase and Integrase inhibitors				[10]
Morus nigra	Kuwanon-L						[11]
Justica gendarussa	Patentiflorin A	HIV			24−37 nM		[12]
Calophyllum lanigerum	Calanolides	HIV			0.1–0.4 µM		[13]
Euphorbia kansui	Ingenol Bryostatin Prostratin	HIV	Latency-reversing agents (LRAs)				[14]
Theobroma cacao	Procyanidin C1-flavonoids	HIV					[15]

CC_{50}: Half maximal cytotoxic concentration; EC_{50}-IC_{50}: Half maximal inhibitory concentration; SI: Selectivity index = CC_{50}/IC_{50}.

2. Influenza Viruses

Influenza viruses are negative-stranded, segmented RNA viruses, and are members of the *Orthomyxoviridae* family. Influenza viruses comprise three types (A, B, and C), while type A is divided into different subtypes which are distinguishable by antigenicity of their surface glycoproteins, haemagglutinin (HA), and neuraminidase (NA) [16]. Influenza viruses, based on their genetic mutations can be categorized into two different entities: seasonal or pandemic representing a major public health problem, with high rates of morbidity and mortality [17]. Airway epithelial cells lining the respiratory mucosa are the primary target of influenza infection. The recognition of

influenza virus antigens through antigen-presenting cells and pattern recognition receptors (PRRs) can consequently upregulate several correspondent downstream molecules including interleukin-6 (IL-6), IL-1β, and tumour necrosis factor α (TNF-α) which causes influenza mediated signs and symptoms [18]. To date, anti-influenza drugs include M2 ion channel inhibitors and neuraminidase inhibitors [19]. M2 ion channel inhibitors, such as amantadine and rimantadine, act as inhibitors of the uncoating process, which is essential for the release of the virus into the cytoplasm. Neuraminidase inhibitors, including oseltamivir and zanamivir, are directed against the enzymatic activity of neuraminidase, which assures the release of progeny viruses from infected cells. It has been suggested that herbal medicines might be beneficial in the prevention or management of seasonal or pandemic influenza (Table 2). An in vitro study showed that oligonol extracted from lychee fruit (*Litchi chinensis*) inhibits proliferation of influenza virus H3N2 by blocking reactive oxygen species (ROS)-dependent ERK (extracellular-signal-regulated kinases) phosphorylation [20]. Another in vitro investigation showed that green tea catechins possess higher inhibitory effects on the endonuclease activity of influenza A virus RNA polymerase [21]. Slaine and collaborators showed that the macrolide pateamine A (from *Mycale hentscheli*) and the rocagalte silvestrol (from *Aglaia*), two inhibitors of the eukaryotic initiation factor-4A (eIF4A), caused the block of influenza A viral protein synthesis as well as the failure of the viral genome replication [22]. The inhibitory effect of silvestrol was fully reversible while the pateamine A irreversibly binds to eIF4A and caused the inhibition of genetically divergent influenza A strains replication [22].

Table 2. Natural products against Influenza viruses.

Natural Source	Compound	Influenza Viruses	Target	CC_{50}	EC_{50}-IC_{50}	SI	Reference
Litchi chinensis	Oligonol	H3N2	Blocking (ROS)-dependent ERK phosphorylation				[20]
Green tea	Catechins	H1N1	Inhibiting RNA polymerase				[21]
Aglaia	Silvestrol	H1N1	Inhibitors of the cellular factor eIF4A				[22]
Mycale hentscheli	Pateamine A	H1N1 H3N2					
Curcuma longa L.	Curcumin	H1N1 H6N1	Haemagglutinin inhibitors	43 µM	0.47 µM	92.5	[23]
Cistus incanus	Polyphenol rich extract	A549			50 µg/mL		[24]
Punica granatum	Punicalagin	H3N2					[25]
Green tea	Epigallocatechin gallate	H1N1					[26]

CC_{50}: Half maximal cytotoxic concentration; EC_{50}-IC_{50}: Half maximal inhibitory concentration; SI: Selectivity index = CC_{50}/IC_{50}.

Natural Products as Hemagglutinin Inhibitors

Given the rapid emergence of drug-resistant influenza virus strains, hemagglutinin (HA) is a promising target for developing anti-influenza drugs. HA is an envelope protein that plays a critical role in viral binding, fusion and entry processes. Curcumin showed anti-influenza activity against influenza viruses PR8, H1N1, and H6N1. The results showed more than a 90% reduction in virus yield in cell culture using 30 μM of curcumin. The plaque reduction test elicited the approximate EC50 of 0.47 μM for curcumin against influenza viruses [23]. In H1N1 and also H6N1 subtypes, the inhibition of HA interaction reflected the direct effect of curcumin on infectivity of viral particles and this has proved by the time of the drug addiction experiment [23]. An in vitro investigation indicated that *Cistus incanus*, a member of *the Cistaceae* family, has anti-influenza virus activity in A549 (human lung epithelial cell) or MadinDarby canine kidney (MDCK) cell cultures infected with prototype avian and human influenza strains of different subtypes by the reduction of progeny virus titers of up to two logs without any toxicity [24]. Furthermore, the binding of the polyphenol components of the extract to the virus surface showed protective effects through inhibition of HA binding to cellular receptors [24]. In another study, *Cistus incanus* exhibited antiviral activity against a highly pathogenic avian influenza A virus (H7N7) in both cell cultures and a mouse infection model [27]. Haidari and colleagues indicated that punicalagin from *Punica granatum* polyphenol-rich extract had anti-influenza properties in MDCK and chicken red blood cells (cRBC) infected by human influenza A (H3N2) through inhibiting the virus replication as well as inhibiting virus-induced agglutination of cRBCs [25]. Furthermore, an investigation showed that epigallocatechin gallate (EGCG) and theaflavin digallate (TF3) from green tea and black tea respectively, inhibit the infectivity of both influenza A and B viruses in MDCK cells through binding to virus HA and prevention of virus adsorption to MDCK cells [26].

3. Hepatitis C Virus

Hepatitis C virus (HCV) is an enveloped, positive-sense single-stranded RNA virus belonging to the *Flaviviridae* family. The HCV genomic RNA encodes a polyprotein that is then cleaved by both the host and virus proteases into mature proteins. The nonstructural proteins; NS2, NS3, NS4A, NS4B, NS5A, and NS5B, core proteins, glycoproteins E1, and E2; the ion channel p7 (Banerjee et al. 2010). The (NS5B), an RNA-dependent RNA polymerase (RdRp) is responsible for replicating the viral RNA genome [28]. Infected individuals have treated with standard treatment, consisting of PEGylated (PEG)-interferon (IFN)-α in combination with ribavirin (RBV) for over a decade. Recently, several protease inhibitors such as boceprevir and telaprevir have been approved as treatments for hepatitis C. However, these new inhibitors are associated with drug toxicity and the development of resistant mutants [29]. Based on this, many phytochemical constituents have been identified that display considerable inhibition of the HCV life cycle at different steps (Table 3).

Table 3. Natural products against the Hepatitis C virus.

Natural Source	Compound	HCV	Target	CC_{50} (μg/mL)	EC_{50}-IC_{50} (μg/mL)	SI or TI	Reference
Trichilia dregeana	Root extract	HCV	Inhibition of viral entry		16.6	37	[30]
Detarium microcarpum	Stem bark extract				1.42	211	
Phragmanthera capitata	Leave extract				13.17		
Bupleurum kaoi	Saikosaponin B2			740.4 ± 28.35 μM	16.13 ± 2.41 μM	45.9	[31]
Bupleurum kaoi	Methanolic extract			16.82 ± 1.89	215.4 ± 10.7	12.8	
Anthocyanidin	Delphinidin				3.7 ± 0.8 μM		[32]
Alloeocomatella polycladia	Ethyl acetate-soluble fraction		Suppression of the helicase activity of HCV NS3		11.7 ± 0.7		[33]
Fusarium equiseti	Crude extracts		Inhibition of HCV NS3/4A protease		19–77 μM		[34]
Eclipta alba	Aqueous extract		Inhibition of HCV NS5B replicase activity		11		[35]
Taraxacum officinale	Flavonoids						[36]
Swietenia macrophylla	3-hydroxy caruilignan C		Reduction of HCV protein and HCV-RNA levels		10.5 ± 1.2μM		[37]
Entada africana	Methylene chloride-methanol (MCM) stem bark crude extract		Broad antiviral activity		453 ± 0.00117		[38]
Grapeseed	Phenolic compounds		Suppression of HCV-induced Cox-2		7.5 ± 0.3		[39]
Flavanone	Naringenin		Release/Assembly		109 μM		[40]

CC_{50}: Half maximal cytotoxic concentration; EC_{50}-IC_{50}: Half maximal inhibitory concentration; SI: Selectivity index = CC_{50}/IC_{50}.

4. Picornaviruses

The family *Picornaviridae* currently contains 147 species grouped into 63 genera. Viruses in the family *Picornaviridae* have non-enveloped particles with a single-stranded RNA (ssRNA) genome and include numerous human pathogens such as poliovirus, enterovirus 71, foot and mouth disease virus (FMDV), hepatitis A virus and rhinovirus. The broadly studied and most well-characterized group is represented by an enterovirus, including enterovirus A71 (EV71), coxsackievirus, poliovirus, and rhinovirus. The viral infection initiates by attaching to a receptor on the host cell plasma membrane and viruses belonging to different genera use different receptors to bind to and infect cells, thus exhibiting a different tissue tropism [41]. The antiviral drugs used in the picornaviruses treatment target virus entry (pleconaril, WIN54954 and CAR-Fc), the viral translation and/or transcription (antisense oligodeoxynucleotide and short interfering RNA) or intracellular signalling pathway (immune response activators) but do not completely eradicate the infection. To date, the antiviral activity of several natural products and herbal medicines have been tested against various *picornavirus* (Table 4).

Table 4. Natural compounds and their antiviral targets against Picornaviruses.

Natural Source	Compound	Picornaviruses	Target	CC_{50} (μg/mL)	EC_{50}-IC_{50} (μg/mL)	SI	Reference
Lagerstroemia speciosa L.	Orobol 7-O-d-glucoside (O7G)	Human rhinovirus A Human rhinovirus B	Broad spectrum antiviral activity	100	0.58-8.80	12	[42]
Ocimum basilicum	Crude aqueous extracts	Coxsackievirus B1 Enterovirus 71		1469.3	105.7 ± 2.6 200.2 ± 3.2	13.9 7.3	[43]
Ocimum basilicum	Ethanolic extracts	Coxsackievirus B1 Enterovirus 71		684.8	146.3 ± 2.9 198.9 ± 1.8	4.7 3.4	
Woodfordia fruticosa	Gallic acid	Enterovirus 71		100	0.76	132	[44]
Raoulia australis	Raoulic acid	Human rhinovirus 2 Human rhinovirus 3 Coxsackievirus B3		201.78 65.86	0.1 0.19 0.33 0.40 0.1		[45][46]

Natural Source	Compound	Picornaviruses	Target	CC_{50} (μg/mL)	EC_{50}-IC_{50} (μg/mL)	SI	Reference
		Coxsackievirus B4 Enterovirus 71					
Ocimum basilicum	Ursolic acid	Coxsackievirus B1 Enterovirus 71	Targets viral structures and inhibits viral infection and replication process	100.5	0.4 ± 0.1 0.5 ± 0.2	251 201	[43]
Silybum marianum	Silymarin	Enterovirus 71		160.20 ± 1.56	7.99 ± 3.0	20.05	[47]
Macaranga barteri	DCM fraction	Echoviruses E7 Echoviruses E19		0.18	7.54×10^{-6} 1.75×10^{-6}	19.9 8581.24	[48]
Syzygium brazzavillense	Aqueous extract	Coxsackievirus B4		2800	0.8		[49]
Rheum palmatum	Ethanol extract	Coxsackievirus B3			4	10	[50]
Lagerstroemia speciosa L.	Quercetin-7-glucoside (Q7G)	Human rhinovirus 2		>100	4.85–0.59	>20.62	[51]
Salvia miltiorrhiza	Rosmarinic acid	Enterovirus A71		327.68 ± 14.43	31.57–114	2.87–10.36	[52]
Green tea	Epigallocatechin-3-gallate (EGCG)	Hepatitis virus A					[53]
Vitis vinifera	Grapeseed extract (GSE)	Hepatitis virus A					[54][55]
Lagerstroemia speciosa L.	Tannin ellagic acid	Human rhinovirus 2 Human rhinovirus 3 Human rhinovirus 4	Targets host cellular factors	>100	38 ± 3.2 31 ± 5.2 29 ± 2.5	>2.6 >3.2 >3.4	[56]
Bupleurum kaoi	Roots extract	Coxsackievirus B1		883.56	50.93		[57]
Mix of seven medicinal	Xiao chai hu tang	Coxsackievirus B1		945.75	50.93	18.92	[58]

Natural Source	Compound	Picornaviruses	Target	CC_{50} (μg/mL)	EC_{50}-IC_{50} (μg/mL)	SI	Reference
herbs							
Ornithogalum saundersiae	Orsaponin (OSW-1)	Enterovirus 71, Coxsackievirus A21 Human rhinovirus 2		>100 nM	2.4–9.4 nM		[59][60]
Panax ginseng	Ginsenosides	Hepatitis virus A					[61]

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[62]

RNA genome. Norovirus utilizes cell surface molecules as mediators for binding and cellular entry. Murine norovirus (MNV-1) and feline calicivirus (FCV) were successfully grown and served as a surrogate model system for HuNoV [63]. Several medicinal plants and herb extracts were screened for antiviral activity against MVN-1 and FCV as a surrogate of norovirus (Table 5). The work of Lee and colleagues showed that the components of *Morus alba* L. possess antiviral effects against foodborne enteric virus surrogates. It was found that *Morus alba* juice and its fractions inhibit the internalization and replication of MNV-1 as well as the internalization of FCV-F9 virions [64]. Black raspberry juice (*Rubus coreanus*) was found to decrease MNV-1 plaque formation by blocking viral entry into the cell and inhibiting its internalization or through direct effects on viral particles or host cell receptors [65]. Green tea polyphenolic chatechins from *Camellia sinensis* exhibited anti-FCV-F9 antiviral activity with epigallocatechin gallate showing the best combination of antiviral activity and low cytotoxicity [66]. The essential oil from oregano (*Origanum vulgare*) decreased FCV-F9 and MNV-1 replication in a dose-dependent manner. Besides, it has been shown that oregano essential oil and its primary component carvacrol caused the loss of viral capsid integrity of MNV-1 virions as determined by transmission electron microscopy experiments [67]. Persimmon (*Diospyros kaki*) extracts containing persimmon tannin was found to reduce noroviral genome replication with no cytotoxicity effect [68].

Table 5. Natural products against Noroviruses.

Natural Source	Compound	Noroviruses	Target	CC_{50}	EC_{50}-IC_{50}	SI	Reference
Morus alba L	Juice	MNV-1 FCV-F9	Inhibiting internalization and replication	>0.1% >2.5%	0.005% 0.25%	20 10	[64]
Camellia sinensis	Epigallocatechin gallate	FCV-F9			12 mg/mL		[66]
Rubus coreanus	Juice	MNV-1					[65]
Origanum vulgare	Carvacrol	MNV-1					[67]
Diospyros kaki	Persimmon tannin	HuNoV	Reduce genome replication				[68]

CC_{50}: Half maximal cytotoxic concentration; EC_{50}-IC_{50}: Half maximal inhibitory concentration; SI: Selectivity index = CC_{50}/IC_{50}.

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