



## Antiviral Natural Products and Herbal Medicines

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### ABSTRACT

Viral infections play an important role in human diseases, and recent outbreaks in the advent of globalization and ease of travel have underscored their prevention as a critical issue in safeguarding public health. Despite the progress made in immunization and drug development, many viruses lack preventive vaccines and efficient antiviral therapies, which are often beset by the generation of viral escape mutants. Thus, identifying novel antiviral drugs is of critical importance and natural products are an excellent source for such discoveries. In this mini-review, we summarize the antiviral effects reported for several natural products and herbal medicines.

**Key words:** Antiviral, Drug development, Herbal medicines, Natural products

### INTRODUCTION

Viruses are responsible for a number of human pathogenesises including cancer. Several hard-to-cure diseases and complex syndromes including Alzheimer's disease, type 1 diabetes, and hepatocellular carcinoma have been associated with viral infections.<sup>[1-3]</sup> Moreover, due to increased global travel and rapid urbanization, epidemic outbreaks caused by emerging and re-emerging viruses represent a critical threat to public health, particularly when preventive vaccines and antiviral therapies are unavailable. Examples include the recent emergence of dengue virus, influenza virus, measles virus, severe acute respiratory syndrome (SARS) virus, and West Nile virus outbreaks.<sup>[4-6]</sup> To date, however, many viruses remain without effective immunization and only few antiviral drugs are licensed for clinical practice. The situation is further exacerbated by the potential development of drug-resistant mutants, especially when using

viral enzyme-specific inhibitors, which significantly hampers drug efficacy.<sup>[7-10]</sup> Hence, there is an urgent need to discover novel antivirals that are highly efficacious and cost-effective for the management and control of viral infections when vaccines and standard therapies are lacking.

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions. In this brief report, we summarize the antiviral activities from several natural products and herbal medicines against some notable viral pathogens including coronavirus (CoV), coxsackievirus (CV), dengue virus (DENV), enterovirus 71 (EV71), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), influenza virus, measles virus (MV), and respiratory syncytial virus (RSV) [Table 1].

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**Table 1.** Antiviral effects from several natural products and herbal medicines against specific viruses.

Virus	Natural product(s) evaluated	Proposed mechanism(s)	References
Coronavirus	Saikosaponins (A, B <sub>2</sub> , C, D) against HCoV-229E9	Saikosaponin B <sub>2</sub> inhibits viral attachment and penetration stages	[14]
	<i>Lycoris radiata</i> and its active component lycorine, <i>Artemisia annua</i> , <i>Pyrrhosia lingua</i> , and <i>Lindera aggregata</i> against SARS-CoV	Unclear	[15]
	Phenolic compounds of <i>Isatis indigotica</i> against SARS-CoV	SARS-CoV 3CL protease inhibitor	[16]
	Amentoflavone isolated from <i>Torreya nucifera</i> against SARS-CoV	SARS-CoV 3CL protease inhibitor	[17]
	Myricetin and scutellarein against SARS-CoV	SARS-CoV helicase inhibitor	[18]
	<i>Houttuynia cordata</i> water extract against SARS-CoV	SARS-CoV 3CL protease inhibitor; viral polymerase inhibitor	[19]
Coxsackievirus	Aqueous and ethanolic extracts of <i>Ocimum basilicum</i> as well as its component compounds linalool, apigenin, and ursolic acid against CVB	Ursolic acid interferes with viral infection and replication	[21]
	Raoulic acid from <i>Raoulia australis</i> against CVB	Unclear	[22]
	Herbal prescription Xiao-Chai-Hu-Tang against CVB	Induction of type I interferon response	[23]
Dengue virus	<i>Bupleurum kaoi</i> against CVB	Induction of type I interferon response	[24]
	Baicalein against DENV-2	Virucidal activity against extracellular virus; impedes viral adsorption onto the host cell; inhibits viral replication post entry	[28]
	Quercetin against DENV-2	Inhibits viral replication but not the viral attachment and entry processes	[29]
	Narasin against DENV-2	Disrupts viral protein synthesis without affecting viral RNA replication	[30]
	Marine seaweed extracts against DENV serotypes 1–4; <i>Canistrocarpus cervicornis</i> , <i>Padina gymnospora</i> , <i>Palisada perforate</i> , and <i>Caulerpa racemosa</i> are most effective	Act at the early stage of viral infection	[31]
	Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> Retz. against DENV-2	Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission	[32]
Enterovirus 71	Aqueous and ethanolic extracts of <i>Ocimum basilicum</i> as well as its component compounds linalool, apigenin, and ursolic acid	Ursolic acid inhibits viral infection and replication	[21]
	Raoulic acid from <i>Raoulia australis</i>	Unclear	[22]
	Gallic acid from <i>Woodfordia fruticosa</i> flowers	Unclear	[36]
	Epigallocatechin gallate from green tea	Interferes with viral replication via modulation of the cellular redox environment	[37]
Hepatitis B virus	Isochlorogenic acid A from <i>Laggera alata</i>	Unclear	[46]
	Amide alkaloid from <i>Piper longum</i>	Unclear	[47]
	Dehydrocheilanthifoline isolated from <i>Corydalis saxicola</i>	Unclear	[48]
	Herbal prescription Xiao-Chai-Hu-Tang	Inhibits the production of HBV and the expression of HBeAg	[49]
	Saikosaponins (C, D) from <i>Bupleurum</i> species	Saikosaponin C inhibits HBeAg expression and HBV DNA replication	[50]
	Ethanol extract from <i>Polygonum cuspidatum</i> Sieb. et Zucc. Curcumin	Unclear Viral transcription suppressor via down-regulation of the coactivator PGC-1 $\alpha$	[51] [52]
Hepatitis C virus	Standardized extracts of <i>Silybum marianum</i>	Antiviral effect partly due to enhancement of the IFN-associated JAK-STAT pathway	[55]
	Flavonolignans from <i>Silybum marianum</i> /silymarin	Antiviral effect probably related to antioxidant functions of the flavonolignans	[56]
	Curcumin	HCV replication inhibitor via suppressing Akt-SREBP-1 pathway	[60]

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Virus	Natural product(s) evaluated	Proposed mechanism(s)	References
Herpes simplex virus		Inhibits viral entry by affecting the fluidity of the HCV envelope	[61]
	Epigallocatechin-3-gallate	Inhibits viral entry	[62,63]
	Griffithsin	Prevents infection and inhibits viral cell-to-cell transmission	[64,65]
	Ladanein	Inhibits viral entry	[66]
	Tellimagrandin I from <i>Rosae Rugosae Flos</i> .	HCV invasion inhibitor	[67]
	Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> Retz.	Inactivate free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread	[32]
	ent-Epiatzelechin-(4 $\alpha$ →8)-epiatzelechin isolated from <i>Cassia javanica</i> against HSV-2	Inhibits viral replication	[72]
	Herbal prescription Long-Dan-Xie-Gan-Tan against HSV-1 and HSV-2	Inactivation of virus particles	[73]
	Herbal prescription Yin-Chen-Hao-Tang against HSV-1 and HSV-2	Inactivation of virus particles	[74]
	Hippomanin A isolated from <i>Phyllanthus urinaria</i> against HSV-2	Unclear	[75]
	Geraniin and 1,3,4,6-tetra- <i>O</i> -galloyl- $\beta$ -D-glucose isolated from <i>Phyllanthus urinaria</i> against HSV-1 and HSV-2	Unclear	[76]
	Excoecarianin isolated from <i>Phyllanthus urinaria</i> against HSV-2	Inactivation of virus particles	[77]
	Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> Retz. against HSV-1	Cell surface GAG-competitors; inhibit viral entry (binding and fusion) and post-infection cell-to-cell spread	[78]
	Meliacine derived from <i>Melia azedarach</i> against HSV-2 infection in a mouse model	Induces TNF- $\alpha$ and IFN- $\gamma$ production	[81]
	Houttuynoids A-E from <i>Houttuynia cordata</i> against HSV-1	Unclear	[82]
Aqueous extract from <i>Rhododendron ferrugineum</i> L. against HSV-1	Inhibits viral adsorption and penetration	[83]	
Blackberry extract against HSV-1	Inhibits viral replication and exhibits virucidal activity	[84]	
Proanthocyanidin-enriched extract from <i>Myrothamnus flabellifolia</i> Welw. against HSV-1	Inhibits viral adsorption and penetration steps	[85]	
Glucoevatromonoside from <i>Digitalis lanata</i> against HSV-1	Inhibits viral protein synthesis	[86]	
Human immunodeficiency virus	<i>Artemisia annua</i> and <i>Artemisia afra</i> against HIV-1	Unclear	[102]
	Tricyclic coumarin from stem bark of <i>Calophyllum brasiliense</i> against HIV-1	Inhibits viral replication in both acute and chronic infections by suppressing NF- $\kappa$ B activation	[105]
	Melittin against HIV-1	Inactivates virus through disruption of the viral lipid envelope	[106]
Influenza virus	Elderberry liquid extract from <i>Sambucus nigra</i> against IFA and IFB	Unclear	[115]
	Extract from <i>Pelargonium sidoides</i> roots against IFA	Inhibits viral entry and release; inhibits viral hemagglutination and NA activity	[116]
	Aqueous extract from dandelion ( <i>Taraxacum officinale</i> ) against IFA	Inhibits viral NP RNA levels and polymerase activity	[117]
	Spirooliganone B from the roots of <i>Illicium oligandrum</i> against IFA	Unclear	[118]
	Chalcones from <i>Glycyrrhiza inflata</i> against IFA	IFA NA inhibitors	[120]
	Xanthenes from <i>Polygala karensium</i> against IFA	IFA NA inhibitors	[121]
	Homoisoflavonoids from <i>Caesalpinia sappan</i> against IFA	IFA NA inhibitors	[122]

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Virus	Natural product(s) evaluated	Proposed mechanism(s)	References
Measles virus	Herbal prescription Sheng-Ma-Ge-Gen-Tang	Antiviral effect may be modulated by TNF- $\alpha$ stimulation	[129]
	Cherokee remedy spicebush	Unclear	[130]
	Biflavonoids from <i>Rhus succedanea</i> and <i>Garcinia multiflora</i> , as well as their methyl ethers and acetates	Unclear	[131]
	Calcium spirulan from the blue-green alga <i>Spirulina platensis</i>	Unclear	[132]
	<i>Crotolus durissus terrificus</i> snake venom	Probably virucidal or targets viral entry	[133]
	Extracts of <i>Zanthoxylum chalybeum</i> and <i>Warburgia ugandensis</i>	Unclear	[135]
	<i>Olinia rochetiana</i> (Olkirenyi) and <i>Warburgia ugandensis</i> (Osokonoi)	Neutralize virus particles	[137]
	Stem and root extract of <i>Cajanus cajan</i>	Unclear	[138]
	Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> Retz.	Inactivate free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread	[32]
	Respiratory syncytial virus	Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> Retz.	Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission
Uncinoside A and B from <i>Selaginella uncinata</i>		Unclear	[148]
Genkwanol B, genkwanol C, and stelleranol extracted from <i>Radix Wikstroemiae</i>		Unclear	[149]
Flavones from the leaves of <i>Lophatherum gracile</i>		Unclear	[150]
Herbal prescription Sheng-Ma-Ge-Gen-Tang		Inhibits viral attachment and internalization steps; stimulates IFN- $\beta$ secretion	[151]
<i>Cimicifuga foetida</i> L.		Inhibits viral attachment and internalization steps; stimulates IFN- $\beta$ secretion	[152]
Cimicifugin from <i>Cimicifuga foetida</i> L.		Inhibits viral attachment and internalization steps; stimulates IFN- $\beta$ secretion	[153]
Resveratrol against RSV-induced inflammation		Reduces virus-induced airway inflammation via down-regulation of IFN- $\gamma$ levels during RSV infection	[154]

## CORONAVIRUS

CoV is an enveloped, positive-sense single-stranded RNA (ss-RNA) virus belonging to the *Coronaviridae* family. The CoV family consists of several species and causes upper respiratory tract and gastrointestinal infections in mammals and birds. In humans, it mainly causes common cold, but complications including pneumonia and SARS can occur.<sup>[11]</sup> The known human CoV (HCoV) includes HCoV-229E, -OC43, -NL63, -HKU1, and the more widely known severe acute respiratory syndrome coronavirus (SARS-CoV) which caused a global threat with high mortality in 2003.<sup>[12]</sup> In 2012, the World Health Organization (WHO) designated a sixth type of HCoV infection identified as the Middle East respiratory syndrome coronavirus (MERS-CoV) which is associated with high fatality.<sup>[13]</sup>

There are no specific treatments for CoV infection and preventive vaccines are still being explored. Thus, the situation reflects the need to develop effective antivirals for prophylaxis and treatment of CoV infection. We have previously reported that saikosaponins (A, B<sub>2</sub>, C, and D), which are naturally occur-

ring triterpene glycosides isolated from medicinal plants such as *Bupleurum* spp. (柴胡 Chái Hú), *Heteromorpha* spp., and *Scrophularia scorodonia* (玄參 Xuán Shēn), exert antiviral activity against HCoV-229E.<sup>[14]</sup> Upon co-challenge with the virus, these natural compounds effectively prevent the early stage of HCoV-229E infection, including viral attachment and penetration. Extracts from *Lycoris radiata* (石蒜 Shí Suàn), *Artemisia annua* (黃花蒿 Huáng Huā Hāo), *Pyrrhosia lingua* (石葦 Shí Wěi), and *Lindera aggregata* (烏藥 Wū Yào) have also been documented to display anti-SARS-CoV effect from a screening analysis using hundreds of Chinese medicinal herbs.<sup>[15]</sup> Natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, have been identified as well and include myricetin, scutellarein, and phenolic compounds from *Isatis indigotica* (板藍根 Bǎn Lán Gēn) and *Torreya nucifera* (榿 Fěi).<sup>[16-18]</sup> Other anti-CoV natural medicines include the water extract from *Houttuynia cordata* (魚腥草 Yú Xīng Cǎo), which has been observed to exhibit several antiviral mechanisms against SARS-CoV, such as inhibiting the viral 3CL protease and blocking the viral RNA-dependent RNA polymerase activity.<sup>[19]</sup>

## COXSACKIEVIRUS

CV, including subgroups A (CVA) and B (CVB), is a member of the *Picornaviridae* family, and the non-enveloped positive-sense ssRNA virus is typically transmitted by fecal–oral route and contact with respiratory secretions. While the symptoms of infection can include mild illnesses such as fever, malaise, rashes, and common cold-like presentation, more severe cases may result in diseases of the central nervous system, including aseptic meningitis, encephalitis, and paralysis.<sup>[20]</sup> CVA is best known as one of the causative agents of hand, foot, and mouth disease (HFMD) in young children.

Unfortunately, there is no vaccine or specific antiviral therapy available to prevent CV infection or the diseases it causes. Nevertheless, drugs discovered from natural products, herbs, and traditional decoctions have shown some promise for the development of therapeutics against CV infection. The aqueous extract, ethanolic extract, and bioactive compounds including linalool, apigenin, and ursolic acid from the popular culinary/medicinal herb *Ocimum basilicum* (sweet basil) (羅勒 Luó Lè) have been observed to possess antiviral activity against CVB1.<sup>[21]</sup> In particular, ursolic acid interferes with CVB1 replication post-infection.<sup>[21]</sup> Raoulic acid from *Raoulia australis* has also been reported as a potential antiviral agent against several CVB subtypes, but the mechanism of its effect is unclear.<sup>[22]</sup> In addition, we have previously reported that both the medicinal prescription Xiao-Chai-Hu-Tang (小柴胡湯 Xiǎo Chái Hú Tang) and its major component herb *Bupleurum kaoi* (柴胡 Chái Hú) inhibit CVB1 infection via the induction of type I interferon response.<sup>[23,24]</sup> This finding suggests that type I interferon inducers may be helpful in controlling CVB infection and could be further explored as a treatment strategy.

## DENGUE VIRUS

DENV is an enveloped positive-sense ssRNA virus of the *Flaviviridae* family. As a prominent arbovirus in Southeast Asia, DENV is transmitted by mosquito bites, typically by *Aedes aegypti*.<sup>[25]</sup> Four serotypes of the virus exist (DENV1–4) and all can cause dengue fever.<sup>[26]</sup> Clinical manifestations of DENV infection can include inapparent/mild febrile presentation, classical dengue fever (fever, headache, myalgias, joint pains, nausea, vomiting, and skin rash), and life-threatening hemorrhagic diseases, specifically dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) in severe cases.<sup>[27]</sup>

Despite being an old disease, current immunization and therapeutic options available for prevention and control of DENV infection are severely limited. Management of dengue-associated diseases consists of preventing the viral infection by mosquito control and relieving symptoms in the infected individuals. Development of prophylactic/therapeutic treatment against DENV infection using natural products may help address some of these current limitations. The flavone baicalein, for example, exerts potent activity against DENV adsorption to the host and post-entry viral replication.<sup>[28]</sup> In addition, several natural products such as quercetin and narasin, as well as marine seaweed extracts have been observed to possess significant anti-DENV properties.<sup>[29–31]</sup> Recently, we

have reported chebulagic acid and punicalagin, two hydrolysable tannins isolated from *Terminalia chebula* (訶子 Hē Zi), as broad-spectrum antiviral agents against several viruses including DENV.<sup>[32]</sup> Specifically, chebulagic acid and punicalagin can directly inactivate free DENV particles and interfere with the attachment and fusion events during early viral entry. Identification of these natural viral inhibitors could help the development of therapeutics against DENV infection and reduce the risks of DHF/DSS.

## ENTEROVIRUS 71

EV71 is a member of the *Picornaviridae* family, possessing a positive-sense ssRNA genome and is non-enveloped. EV71 is ordinarily transmitted by fecal–oral route, but transmission by respiratory droplet is also possible. It is one of the major causes of HFMD in children, is sometimes associated with severe neurological diseases, and can be fatal.<sup>[20]</sup> The transmission rate in children under 5 years of age is typically high in endemic areas and several outbreaks have occurred over the past few decades.<sup>[33–35]</sup>

Medication and preventive vaccines against EV71 are presently in development and palliative care is used to ameliorate the symptoms. Nevertheless, several natural products and herbal medicines have been shown to possess inhibitory activity against EV71 infection. Extracts and pure constituents of *O. basilicum* effectively block EV71 infection and replication.<sup>[21]</sup> In addition, raoulic acid, which has previously been mentioned as an inhibitor to CVB, also suppresses EV71.<sup>[22]</sup> Gallic acid from *Woodfordia fruticosa* flowers (蝦子花 Xiǎ Zi Huā) has also been observed to exert anti-EV71 activity.<sup>[36]</sup> Finally, epigallocatechin gallate from green tea has been identified to interfere with EV71 replication via modulation of the cellular redox environment.<sup>[37]</sup> Without efficient medical treatment for the prevention and control of infection by EV71, further studies in identifying novel antivirals against the enterovirus are encouraged.

## HEPATITIS B VIRUS

HBV is the prototype virus of the *Hepadnaviridae* family. It is an enveloped virus possessing a relaxed circular, partially double-stranded DNA (dsDNA) genome.<sup>[38]</sup> HBV causes hepatitis B and the infection is transmitted by exposure to blood or body fluids containing the virus. Although spontaneous recovery is common following acute hepatitis B, medication is recommended for chronic infection because of the risk of developing cirrhosis and hepatocellular carcinoma (HCC). The development of HBV vaccine and nationwide hepatitis B vaccination program in endemic countries such as Taiwan have helped control HBV infection as well as reduce the incidence of childhood HCC.<sup>[39]</sup>

Despite the existence of preventive vaccines, the present HBV-infected population, including those in areas where vaccination program is unavailable, remains at risk for end-stage liver diseases. Therapeutic treatment against HBV includes nucleotide/nucleoside analogs such as lamivudine, adefovir, tenofovir, telbivudine, and entecavir, as well as the immune modulator pegylated interferon- $\alpha$  (Peg-IFN- $\alpha$ ).<sup>[40]</sup> However, eradication of HBV from

the host proves difficult once persistent infection is established, and the situation is further aggravated by risks of selecting drug-resistant viral mutants, treatment failure in non-responders, and potential future viral reactivation. Therefore, anti-HBV drug discovery is still a matter of importance for supporting current therapy and hepatitis B management program to treat some current 300-400 million carriers globally.<sup>[41]</sup>

Extensive studies have been conducted over the past few decades to identify anti-HBV agents from natural products and herbal medicines, and some have been thoroughly covered elsewhere.<sup>[42-45]</sup> As examples, isochlorogenic acid A from *Lagdera alata*, amide alkaloid from *Piper longum* (假蒟 Jiǎ Jù), and dehydrocheilanthifoline from *Corydalis saxicola* have been reported for their anti-HBV activities.<sup>[46-48]</sup> We have also previously demonstrated the antiviral effects of the herbal prescription Xiao-Chai-Hu-Tang (小柴胡湯 Xiǎo Chái Hú Tang), the saikosaponins from *Bupleurum* species (柴胡 Chái Hú), and the ethanol extract from *Polygonum cuspidatum* sieb. et zucc (虎杖 Hǔ Zhàng) against HBV *in vitro*.<sup>[49-51]</sup> Another example is curcumin, which has been shown to inhibit HBV gene replication and expression by down-regulating the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), the coactivator of HBV transcription.<sup>[52]</sup> As novel anti-HBV inhibitory agents are being discovered, future studies should also evaluate potential combination treatments with standard nucleotide/nucleoside analogs or IFN- $\alpha$ -based therapies for the management of hepatitis B.

## HEPATITIS C VIRUS

HCV is an enveloped flavivirus possessing a positive-sense ssRNA. Transmission of HCV mainly occurs by blood-to-blood contact, such as through intravenous injections, blood transfusion, and various exposures to blood contaminants (tattooing, piercing, razor and toothbrush sharing, etc.). Due to the highly mutable nature of HCV, a preventive vaccine is not yet available. About 70% of infections become persistent, resulting in an estimated 300 million carriers worldwide of which 1-3% may progress to end-stage liver diseases including cirrhosis and HCC.<sup>[53]</sup> The present standard of care consists of parenteral Peg-IFN- $\alpha$  plus oral ribavirin, and will soon incorporate the new protease inhibitors boceprevir and telaprevir for combination therapy. However, several obstacles remain in the current method of therapeutic treatment against HCV, including limited efficacy for certain viral genotypes, inevitable selection of drug-resistant mutants, serious side-effects, high cost of medication, patient adherence issues, and challenges in the difficult-to-treat populations such as non-responders and liver transplant patients.<sup>[54]</sup> Thus, continuous development of anti-HCV agents is necessary to meet these shortcomings.

Various natural products have been explored for their antiviral effects against HCV infection. *Silybum marianum* (also known as "Milk Thistle" or "silymarin") and its flavonolignans have been demonstrated to exert anti-HCV activity *in vitro*,<sup>[55,56]</sup> and several clinical evaluations have shown promising effects in reducing the viral load.<sup>[57-59]</sup> Curcumin has been identified as a potential inhibitor of HCV replication, potentially by suppressing sterol regulatory element binding protein-1 (SREBP-1)-Akt pathway,<sup>[60]</sup> and more

recently its negative effect on HCV entry has been demonstrated.<sup>[61]</sup> Other natural compounds have been observed to prevent HCV entry as well, and these include epigallocatechin-3-gallate, griffithsin, ladanein, and tellimagrandin I.<sup>[62-67]</sup> Similarly, we have recently identified the hydrolyzable tannins chebulagic acid and punicalagin as potent inhibitors of HCV entry.<sup>[32]</sup> The two tannins inactivate free virus particles, prevent viral attachment and penetration into the host cell, and disrupt post-infection cell-to-cell transmission of HCV. Since immunization against HCV is at present unavailable, the discovery of novel anti-HCV entry inhibitors could help develop preventive therapies/measures against hepatitis C.

## HERPES SIMPLEX VIRUS

Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) are enveloped dsDNA viruses belonging to the *Herpesviridae* family. HSV infection usually causes mucocutaneous lesions that occur in oral/perioral (typically by HSV-1) and genital (commonly by HSV-2) areas, as well as on other body sites. HSV causes lifelong infection by establishing itself in sensory neurons and can be reactivated by various stimuli including sunlight, fever, immunosuppression, menstruation, or stress.<sup>[68]</sup> Transmission of HSV results from contact with infected lesions and can occur via vertical transmission from infected mother to newborn. Although the disease is usually self-limited and can be treated with antivirals, severe complications can occur, particularly in neonates and immunosuppressed individuals, leading to risk of blindness with keratoconjunctivitis, and the potentially fatal meningitis and encephalitis.<sup>[69,70]</sup>

No vaccine is available against HSV and there are currently no drugs that can eradicate latent HSV infection. Although primary and recurrent infections can be controlled by nucleoside analogs such as acyclovir, penciclovir, and their prodrugs, the development of drug-resistant virus is becoming a serious problem, especially in immunocompromised patients.<sup>[71]</sup> Thus, identifying novel anti-HSV agents that act with different mechanisms is crucial for clinical management of HSV. We have previously reported several natural products and herbal medicines that inhibit HSV infection and replication. For instance, ent-epiafzelechin-(4 $\alpha$ →8)-epiafzelechin, extracted from *Cassia javanica*, inhibits HSV-2 replication; the herbal prescriptions Long-Dan-Xie-Gan-Tan (龍膽瀉肝湯 Lóng Dǎn Xiè Gān Tāng) and Yin-Chen-Hao-Tang (茵陳蒿湯 Yīn Chén Hāo Tāng) both possess broad efficiency in diminishing HSV-1 and HSV-2 infectivity; hippomanin A, geraniin, 1,3,4,6-tetra-O-galloyl-beta-d-glucose, and excoecarianin isolated from *Phyllanthus urinaria* (葉下珠 Yè Xià Zhū) can potentially impede HSV infection.<sup>[72-77]</sup> In addition, we have also identified the hydrolyzable tannins chebulagic acid and punicalagin as cell surface glycosaminoglycan (GAG) competitors that can inhibit HSV-1 entry and cell-to-cell spread.<sup>[78]</sup> HSV-1 and also a multitude of viruses employ GAGs as initial attachment receptors during infection of their host cell. Both chebulagic acid and punicalagin are observed to target HSV-1 glycoproteins that interact with GAGs and, in turn, prevent their association with cell surface GAGs as well as subsequent binding receptors.<sup>[78]</sup> This inhibitory effect is shown (1) against cell-free virus, (2) during the viral attachment and fusion stages, and (3) in

the intercellular junction spread of HSV-1, which is mediated by its glycoproteins. Thus, both tannins are demonstrated to be efficient entry inhibitors to HSV-1 and similar effects have been observed on another herpesvirus, the human cytomegalovirus, as well as on several other viruses known to engage GAGs for entry.<sup>[32]</sup>

Besides the natural products and traditional decoctions mentioned above, a plethora of other natural anti-HSV agents have also been identified.<sup>[79,80]</sup> Meliacine derived from *Melia azedarach* is observed to stimulate tumor necrosis factor-alpha (TNF- $\alpha$ ) and IFN- $\gamma$  production, and reduce HSV-2 shedding with improvement of virus-induced pathogenesis in a mouse vaginal model of herpetic infection.<sup>[81]</sup> Houttuynoids A-E are flavonoids isolated from *Houttuynia cordata* (蕺菜 Jí Cài), which have been found to exhibit potent anti-HSV-1 activity.<sup>[82]</sup> Similarly, the aqueous extract from *Rhododendron ferrugineum* L., blackberry extract, and proanthocyanidin-enriched extract from *Myrothamnus flabellifolia* Welw. have been reported to inhibit HSV-1 infection.<sup>[83-85]</sup> Another example is glucoevatromonoside, a cardenolide from *Digitalis lanata*, which has been suggested to alter cellular electrochemical gradient and block HSV-1 and HSV-2 propagation in cells.<sup>[86]</sup> In addition, natural products from the marine environment represent a whole biodiversity in which many algae and sponges have been observed to contain active metabolites with anti-HSV activity.<sup>[87,88]</sup> The abundance of natural anti-HSV agents discovered should provide novel pharmacological activities against the virus, which could be further explored for potential application in the management of HSV infections.

## HUMAN IMMUNODEFICIENCY VIRUS

HIV is a lentivirus of the *Retroviridae* family. The enveloped virus is characterized by targeting of the immune cells for infection, reverse transcription of its ssRNA genome, and integration into the host chromosomal DNA.<sup>[89]</sup> Transmission of HIV occurs via exchange of virus-containing blood and body fluids, such as through sexual contact, sharing of contaminated needles/sharp instruments, childbirth, as well as breastfeeding.<sup>[90]</sup> HIV is the causative agent of acquired immunodeficiency syndrome (AIDS), which is a progressive failure of the immune system due to CD4<sup>+</sup> T-lymphocyte depletion that leads to manifestation of life-threatening opportunistic infections and malignancies.<sup>[91]</sup> To date, AIDS has resulted in more than 25 million deaths and there are currently about 34 million HIV-infected individuals with an estimated 2-3 million newly diagnosed cases annually.<sup>[13]</sup>

Despite nearly 30 years of research since its discovery, at present there is no effective preventive vaccine or cure for HIV infection. The high antigenic diversity and multiple mechanisms that the virus employs to subvert recognition by the human immune system have made prophylactic/therapeutic management of HIV infection difficult.<sup>[92]</sup> Nevertheless, the development of the highly active antiretroviral therapy (HAART), which consists of a cocktail of nucleoside analog/non-nucleoside reverse-transcriptase inhibitors, has dramatically decreased the morbidity and mortality associated with HIV/AIDS.<sup>[93]</sup> However, there is still a pressing need for alternative treatment strategies against HIV infection due to drug resistance problems, treatment-associated toxicity, patient

adherence, and restricted accessibility in resource-poor areas.<sup>[94-96]</sup>

An exhaustive list of natural products has been evaluated for anti-retroviral/anti-HIV activity and recently reviewed.<sup>[97,98]</sup> Moreover, many marine natural products with anti-HIV activities have also been identified in search of novel therapeutics against the AIDS virus.<sup>[99-101]</sup> To briefly mention some examples, the crude extracts of *Artemisia annua* (黄花蒿 Huáng Huā Hāo) and *Artemisia afra* have recently been reported as potential anti-HIV medicines.<sup>[102]</sup> The *Calophyllum* species is known to contain several coumarins that are observed to exert inhibitory effect against HIV.<sup>[103,104]</sup> More recently, a tricyclic coumarin derived from the stem bark of *Calophyllum brasiliense* has been shown to inhibit HIV replication in *in vitro* models by suppressing nuclear factor-kappa B (NF- $\kappa$ B) activation.<sup>[105]</sup> Another novel anti-HIV agent is the small peptide melittin, which is the active component of bee venom. The nanoformulated melittin is demonstrated to possess robust efficiency in capturing and inactivating HIV particles by disrupting the viral lipid envelope.<sup>[106]</sup> Based on the discoveries made so far, the recent progress in identifying natural antivirals against HIV should yield potential novel therapeutics that could play an important role in overcoming the current urgency in anti-HIV/AIDS therapies.

## INFLUENZA VIRUS

The influenza A, B, and C viruses (IFA, IFB, and IFC) are enveloped, negative-sense ssRNA viruses classified in the *Orthomyxoviridae* family. These viruses cause respiratory infection yielding symptoms that include fever, headache, sore throat, sneezing, and muscle and joint pains, and can develop into more severe and potentially fatal conditions such as pneumonia.<sup>[107,108]</sup> IFA (most epidemic) has a wide host range including birds and humans as well as other mammals, whereas IFB seems to naturally infect humans and IFC (less frequently encountered) can be isolated from humans and swine.<sup>[109]</sup> Influenza virus infection has produced considerable morbidity in humans. An estimated 250,000-500,000 deaths occur annually due to seasonal epidemics, and in major pandemics, this number has been observed to rise to some 20-40 million deaths, as in the case of the 1918 H1N1 Spanish Flu.<sup>[13]</sup>

Despite the availability of vaccines based on predicted circulating strains, influenza viruses are known to continuously evolve their hemagglutinin (HA) and neuraminidase (NA) envelope proteins.<sup>[110,111]</sup> This variation renders any preexisting circulating antibody from earlier exposure or immunization ineffective at neutralizing the virus, hence making the host vulnerable to infection. Furthermore, potential risks of cross-species transmission and host adaptation of influenza viruses between animals and humans resulting in highly pathogenic strains have also raised concerns.<sup>[112]</sup> Another issue is the widespread development of drug resistance, which has been observed with the first generation of anti-influenza medications, specifically the M2 ion channel blockers amantadine and rimantadine.<sup>[113]</sup> Resistant strains against the currently approved neuraminidase inhibitors (which prevent the release of mature influenza viruses) including oseltamivir and zanamivir have also already appeared.<sup>[114]</sup> Due to the drug resistance prob-

lems, the rapid evolution of influenza viruses, and the occurrence of several recent outbreaks (e.g., H5N1, H1N1, H7N9),<sup>[13]</sup> more sophisticated antiviral strategies are urgently needed to prevent and control potential pandemics with emerging influenza strains.

Several natural products have been examined for their effects against influenza. Standardized elderberry (接骨木 Jiē Gǔ Mù; *Sambucus nigra*) liquid extract exerts *in vitro* antiviral effects against IFA, IFB, as well as respiratory bacterial pathogens.<sup>[115]</sup> A licensed commercial extract from *Pelargonium sidoides* roots inhibits the entry of IFA, impairs viral hemagglutination as well as neuraminidase activity, and improves the symptoms of influenza-infected mice.<sup>[116]</sup> The aqueous extract from dandelion (蒲公英 Pú Gōng Yīng; *Taraxacum officinale*) impedes IFA infection and decreases its polymerase activity as well as the nucleoprotein (NP) RNA level.<sup>[117]</sup> Spirooliganone B from the roots of *Illicium oligantrum* exhibits potent anti-IFA activities.<sup>[118]</sup> A multitude of secondary plant metabolites have also been identified as potential influenza NA inhibitors,<sup>[119]</sup> and more recent ones include chalcones from *Glycyrrhiza inflata*,<sup>[120]</sup> xanthenes from *Polygala karensium*,<sup>[121]</sup> and homoisoflavonoids from *Caesalpinia sappan* (蘇木 Sū Mù).<sup>[122]</sup> Further exploration of these natural anti-influenza agents for clinical application will help broaden the drug portfolio for prophylactic/therapeutic treatment of potential flu epidemics or pandemics.

## MEASLES VIRUS

MV is an enveloped, negative-sense ssRNA virus of the *Morbivirus* genus in the *Paramyxoviridae* family. MV causes measles, an acute infection of the respiratory system characterized by fever, conjunctivitis, coughing, runny nose, nausea, and a generalized macular red rash over the body. Complications can occur leading to pneumonia and encephalitis, which can be potentially fatal.<sup>[123]</sup> Although highly contagious through contact of respiratory droplets or airborne aerosols, immunization against measles given as a three-part MMR vaccine (measles, mumps, and rubella) has made MV infection relatively uncommon in developed countries. As recovery usually follows uncomplicated MV infection, there are currently no specific antiviral treatments for measles. Despite the existence of a successful vaccine against MV, the virus remains a major killer of children in developing countries.<sup>[124,125]</sup> Another serious problem is the re-emergence of measles in vaccinated populations and in non-immunized adults, as highlighted by outbreaks in recent years.<sup>[6,126,127]</sup> These issues emphasize MV's medical importance and the need to develop suitable drug therapies.

Efforts have been made at identifying natural products that inhibit MV and include a number of East and South-east Asian traditional medicines,<sup>[128]</sup> the herbal decoction Sheng-Ma-Ge-Gen-Tang (升麻葛根湯 Shēng Má Gé Gēn Tang),<sup>[129]</sup> the Cherokee remedy spicebush,<sup>[130]</sup> plant biflavonoids isolated from *Rhus succedanea* (野漆 Yě Qī) and *Garcinia multiflora*,<sup>[131]</sup> calcium spirulan from the blue-green alga *Spirulina platensis*,<sup>[132]</sup> *Crotalus durissus terrificus* snake venom,<sup>[133]</sup> and several Rwandan and Ugandan medicinal plant extracts,<sup>[134,135]</sup> among others previously reviewed.<sup>[136]</sup> In addition, several traditional dietary herb additives of the Maasai, including *Olinia*

*rochetiana* (Olkirenyi) and *Warburgia ugandensis* (Osokonoi), have been reported to inhibit MV infection *in vitro*.<sup>[137]</sup> Another example is the plant extracts of *Cajanus cajan* which have been recently suggested to possess anti-MV activity, although the bioactive constituents remain elusive.<sup>[138]</sup> The two tannins chebulagic acid and punicalagin also show robust effects against MV infection, particularly by inactivating the virus particles, interrupting the binding and fusion phases during viral entry, and preventing post-infection virus spread.<sup>[32]</sup> Chebulagic acid and punicalagin could, therefore, serve as potential entry inhibitors to MV.

## RESPIRATORY SYNCYTIAL VIRUS

RSV is an enveloped negative-strand ssRNA virus of the *Paramyxoviridae* family. It is a ubiquitous pathogen and the leading cause of viral lower respiratory tract infection in infants and children.<sup>[139]</sup> Virtually all children become infected with RSV before the age of 2 years.<sup>[140]</sup> RSV infection typically results in mild symptoms in healthy adults, but can lead to bronchiolitis or pneumonia in infants and immunocompromised individuals. Moreover, infant RSV infection poses a potential risk for childhood asthma.<sup>[141,142]</sup> Although RSV causes the most severe disease in young infants, it continues to plague humans throughout the course of a lifetime. Immunity to RSV is generally not sufficient to provide protection and, consequently, humans are prone to repeated reinfections<sup>[143-145]</sup> which can be life-threatening in the elderly or immunocompromised.<sup>[146,147]</sup>

Currently, immunization against RSV is unavailable, and the few therapies that exist for the treatment of RSV infections such as palivizumab (monoclonal antibody against RSV fusion protein) and ribavirin (nucleoside analogue) are only moderately effective or limited in efficacy. Thus, there is a need to develop novel antivirals for the management of RSV infections. Several plant-derived natural products have been demonstrated to exhibit anti-RSV activity. Uncinoside A and B, the two chromone glycosides isolated from *Selaginella uncinata*, potently inhibit RSV infection.<sup>[148]</sup> Three biflavonoids, namely genkwanol B, genkwanol C, and stelleranol, extracted from *Radix Wikstroemiae*, have been observed to display antiviral activity against RSV.<sup>[149]</sup> Several flavone 6-C-monoglycosides from the leaves of *Lophatherum gracile* (淡竹葉 Dàn Zhú Yè) have been shown to reduce RSV infection in cytopathic effect-reduction assay.<sup>[150]</sup> We have previously also identified several anti-RSV natural medicines, including the herbal prescription Sheng-Ma-Ge-Gen-Tang (升麻葛根湯 Shēng Má Gé Gēn Tang) which is used for treating respiratory diseases, its major component herb *Cimicifuga foetida* L. (升麻 Shēng Má), as well as the plant-associated bioactive compound cimicifugin.<sup>[151-153]</sup> In addition, the broad-spectrum antiviral activity that we have demonstrated for the hydrolyzable tannins chebulagic acid and punicalagin also includes antiviral effects against RSV infection.<sup>[32]</sup> Specifically, the two tannins can inactivate RSV particles and also block viral entry-related events, including binding and fusion. Interestingly, both chebulagic acid and punicalagin are, however, ineffective against RSV post-infection spread, but could abrogate the same event in MV, which is another paramyxovirus.<sup>[32]</sup>



Besides targeting the viral infection, some natural products may help improve RSV-induced respiratory tract symptoms, including airway inflammation. Resveratrol is one such example, which has been observed to down-regulate IFN- $\gamma$  levels and prevent airway inflammation/hyperresponsiveness during RSV infection in mice, suggesting its applicability in reducing RSV-induced airway symptoms.<sup>[154]</sup>

## PROSPECTS AND CONCLUSION

As many viruses remain without preventive vaccines and effective antiviral treatments, eradicating these viral diseases appears difficult. Nonetheless, natural products serve as an excellent source of biodiversity for discovering novel antivirals, revealing new structure–activity relationships, and developing effective protective/therapeutic strategies against viral infections. Many natural products and herbal ingredients are observed to possess robust antiviral activity and their discoveries can further help develop derivatives and therapeutic leads (e.g., glycyrrhetic acid derivatives as novel anti-HBV agents, acetoxime derivative from the Mediterranean mollusk *Hexaplex trunculus* as inhibitor against HSV-1, and caffeic acid derivatives as a new type of influenza NA antagonist).<sup>[155-157]</sup> Our discovery of chebulagic acid and punicalagin being capable of inhibiting entry of several viruses due to their GAG-competing properties could help develop broad-spectrum antivirals for prevention and control of these viral pathogens. As many studies in this domain are only preliminary, further exploration in characterizing the bioactive ingredients, defining the underlying mechanisms, as well as assessing the efficacy and potential application *in vivo* is encouraged in order to help develop effective antiviral treatments. Furthermore, additional studies should also examine the possibility of combination therapies with other natural agents or with standard therapeutics, as a multi-target therapy may help reduce the risk of generating drug-resistant viruses. We believe that natural products will continue to play an important role and contribute to antiviral drug development.

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