Introduction

Coronaviruses (CoVs) are enveloped viruses that cause multiple respiratory and intestinal infections in humans and animals. They are known to be zoonotic agents, indicating that they can cause disease in a wide range of hosts, including animals, birds, and bats. These viruses are characterized by a distinctive crown-like appearance of their envelope due to spike proteins from the membrane. These viruses were first described in the 1960s from patients with respiratory infections like the common cold. Since then, several human coronaviruses (HCoVs) have been identified including the HCoV-Hong Kong University 1 (HKU1), HCoV-NL63; severe acute respiratory syndrome (SARS)-CoV; and Middle East respiratory syndrome (MERS)-CoV. These viruses belong to the subfamilies Coronavirinae and Torovirinae of the family Coronaviridae in the order Nidovirales. Based on phylogeny, they are divided into four genera as α-CoV, β-CoV, γ-CoV and δ-CoV. The β-CoV genus is further subdivided into four lineages (A, B, C, and D) (Figure 1). Mammalian coronavirus include HCoV-229E and HCoV-NL63 which belong to the α-coronavirus class as well as HCoV-HKU1, SARS-CoV, MERS-CoV and HCoV-OC43 which are β-coronaviruses; while avian coronavirus is the γ-coronavirus and δ-coronavirus. The novel coronavirus, 2019-nCoV, that caused the current global COVID-19 pandemic was first identified in December 2019 in the Wuhan region (Hubei Province) of China. Since then, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses has formally designated the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).  

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**Review Article**

**ABSTRACT**

Infection by human Coronaviruses (CoVs) such as HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1 generally results in moderate to severe respiratory and intestinal infections in humans. The deadly human CoVs emerging in the last two decades however became the cause of great global concern. The severe acute respiratory syndrome (SARS) SARS-CoV, Middle East respiratory syndrome (MERS) (MERS-CoV) and the current SARS-CoV-2 that causes COVID-19 are related respiratory infections with high degree of mortality. With currently no available vaccine or approved therapy for COVID-19, the development of directly acting antiviral drugs becomes a sensible strategy. Viral infections, like many other disease conditions have been frequently managed using traditional medicine. COVID-19 and SARS-CoV-2 infections have also been treated with preparations from traditional Chinese medicine although their efficacy has not yet been well documented. Several antiviral agents have also been reported from natural sources and these could provide good opportunity for developing products and therapies that might be applicable in managing COVID-19. In this review, we discuss natural antiviral products that target the various infection stages of the different viruses including CoV, which may be useful for direct management of COVID-19 or provide insights for the development of effective therapies.

**Keywords:** Natural products, Antiviral, Corona viruses, Drug development, Phytochemicals.

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to antiviral drug discovery. In this review, we focus on various antiviral agents from nature, highlighting their possible use in drug development for the currently ongoing SARS-CoV-2 infection.

**Coronavirus genome and replication**

CoVs are single-stranded positive-sense RNA (+ssRNA) viruses having the largest genome size so far (~30 kb) with 5'-cap structure and 3'-poly-A tail. During CoVs infection cycle, the genomic RNA plays a critical role in the initial RNA synthesis and acts as a messenger RNA (mRNA). It is used as template for the translation of polyprotein 1a/1ab (pp1a/pp1ab) to replication-transcription complex (RTC) in a double-membrane vesicles (DMVs). The pp1a/pp1ab also encodes nonstructural proteins (nsps). The RTC then produces, in a manner of discontinuous transcription, a set of subgenomic RNAs (sgRNAs) that possess common 5'-leader and 3'-terminal sequences. This is followed by the termination of the transcription process and subsequent acquisition of a leader RNA, which takes place at the transcription regulatory sequences found in-between open reading frames (ORFs). There are at least six ORFs in a typical CoV. The ORF1a/b constitute about two-thirds of the entire genome length and encodes 16 nsps (nsp1-16) while the ORFs on the remaining one-third of the genome near the 3'-terminus encodes four structural proteins: spike protein (S), a type of glycoprotein I; membrane protein (M), that covers the membrane; envelope protein (E), a hydrophobic protein that covers the entire structure; and nucleocapsid (N) protein a basic RNA-binding protein. The polyproteins ORFs are processed by chymotrypsin-like protease (3CLpro) or main protease (Mpro) and papain-like protease into 16 nsps that are involved in genome transcription and replication.

Different CoVs can however encode additional special structural and accessory proteins apart from the four main structural proteins for instance, viruses in lineage A also encode a smaller protein called accessory proteins. Chemical compounds capable of interrupting any stage in the replication process would be a good candidate for therapeutic development.

**Mechanisms against human coronavirus viruses**

Mechanisms directed at combatting human coronavirus infections include elimination of the viruses directly using antiviral agents and modulating host’s immune system to be able to fight the viruses. Antiviral agents can be designed to target different stages of the virus replication process such as cell entry, viral transcription as well as translation and protein processing (Figure 2). The coronavirus S protein is used for binding to the cellular receptor through the receptor binding site (RBS) resulting in fusion with the cellular membrane. Following this binding, the virus can then enter their target cells either by fusion of viral membranes onto the cell surface or through endocytosis and subsequent acidification of the environment. This provides two distinct mechanisms of interrupting virus: inhibition of cell attachment/binding and inhibition of cell-virus fusion. Another therapeutic approach can involve inhibition and downregulation of the various viral receptors such as the ACE receptor. Though complex, CoVs replication process is also a therapeutic target. Possible therapies that can be developed include polymerase inhibitors, nucleoside analogues, helicase inhibitors and small interfering RNA and antisense phosphorodiamidate morpholino oligomers. Translation and protein processing such as by chymotrypsin-like proteinase and papain-like proteinase are also good anti-coronavirus targets.
Overview of the Current Pharmacotherapy of Covid 19
There is currently no consensus globally regarding effective therapies for managing SARS-CoV-2 infection. However, several therapies have been used in different parts of the world and many existing drugs are in clinical trial with a view of being repurposed. In the United States, remdesivir over no antiviral treatment and glucocorticoids rather than no glucocorticoids is suggested for use among hospitalized patients with severe COVID-19, while hydroxychloroquine/chloroquine plus azithromycin, lopinavir/ritonavir, tocilizumab, famotidine and COVID-19 convalescent plasma are to be used only in the context of a clinical trial.39 In India, hydroxychloroquine is recommended as prophylaxis for asymptomatic healthcare personnel handling COVID-19 cases, frontline workers, and asymptomatic contacts of the confirmed cases, while hydroxychloroquine-azithromycin combination is used for patients with serious sickness requiring ventilator.40 In other countries of the world, different therapy combinations have been employed as summarized by Chen et al., (2020)57 and guidelines for care by different relevant societies are available here https://www.uptodate.com/contents/society-guideline-links-coronavirus-disease-2019-covid-19-international-and-government-guidelines-for-general-care. There are also several review articles on the different therapeutic options.46,51

Antiviral drugs of natural origin and their mechanisms of action
Several drugs and bioactive compounds of natural origin have been previously reported active against many viruses. The application of some of these molecules, whose information are as summarized in Table 1, in drug development against coronavirus is hereby discussed.

1-Deoxynojirimycin
1-Deoxynojirimycin (1) is a piperidine alkaloid found in various plants such as Commelina communis, and in the Streptomyces and Bacillus bacteria.52,53 It has antihyperglycemic, anti-obesity, and antiviral activities.54 It has been reported to be effective against hepatitis,55 influenza56 and HIV.57 1-Deoxynojirimycin inhibits cellular α-glucosidase I-II activity. It also inhibited the envelope-mediated membrane fusion process at the CXCR4 binding step thus preventing the spread of human immunodeficiency virus in (HIV)-infected lymphocyte cultures.57 In fowl plague virus-infected chicken-embryo cells, N-methyl-1-deoxynojirimycin inhibited the trimming of the outermost glucose residue of the N-linked precursor-oligosaccharide Glc3Man9GlcNAc2, thus inhibiting oligosaccharide processing.58 The envelope-mediated membrane fusion inhibitory mechanism of this compound can be explored in designing possible therapy for coronavirus and/or SARS-CoV-2.

Aloe-emodin and Emodin
Emodin (3) is an anthraquinone obtained from the genus Rheum and Polygonum.59 It is known for its larvicidal60 and antitumor61 activities. It was investigated against SARS-CoV and reported to significantly inhibit the S protein and ACE2 interaction in a dose-dependent manner.59 Evaluation against herpes simplex virus (HSV) infections revealed that emodin inhibited the nuclear activity of HSV-1 UL12 as well as reduced plaque formation with an EC50 of 21.5 ± 4.4 mM.62 The effect of emodin on herpes virus was also confirmed by Xiong et al. (2011).59

The study by Li et al. (2014)64 on the effect and inhibitory mechanism of aloe-emodin (2) against influenza A virus revealed that aloe-emodin could reduce virus-induced cytopathic effect dose-dependently with an IC50 value less than 0.05 μg/mL. It also up-regulated galectin-3 and thioredoxin as well as down-regulated nucleoside diphosphate kinase A.64 It restored nonstructural protein 1 (NS1)-inhibited signal transducer and activator of transcription 1 (STAT1)-mediated antiviral responses in transfected cells, for instance, STAT1 phosphorylation of interferon (IFN) stimulation response element (ISRE)-driven promoter, RNA-dependent protein kinase (PKR) and 2′,5′-oligoadenylylate synthetase (2′,5′-OAS) expression.64 Aloe-emodin was identified as a potential interferon (IFN)-inducer when tested against Japanese encephalitis virus (JEV) and enterovirus 71 (EV71).65 It activated interferon-stimulated response element (ISRE) and gamma-activated sequence (GAS)-driven cis-reporting systems. It also up-regulated expression of IFN-stimulated genes such as dsRNA-activated protein kinase and 2′,5′-oligoadenylylate synthase as well as activated nitric oxide production.65 The several antiviral mechanisms of action of emodin (3) and aloe-emodin (2) against different viruses makes them a promising source of antiviral therapy. In particular,
emodin inhibited the S protein and ACE2 interaction of SARS-CoV while aloe-emodin restored NS1-inhibited signal transducer both of which can be adapted in developing suitable medication against coronavirus and/or SARS-CoV-2.

Amentoflavone
Amentoflavone (4) is a biflavones isolated from the ethanol extract of Torreya nucifera. It is reported to have many biological activities such as anti-inflammatory, anti-oxidative, and anti-diabetic activities. It has also been reported to be active against SARS-CoV by inhibiting SARS-CoV 3CLpro. Amentoflavone (4) also showed inhibitory activity against human immunodeficiency virus (HIV) and respiratory syncytial virus (RSV). Other antiviral activities reported for this compound are anti-dengue, anti-influenza and anti-herpes. Flavonoids in general are promising leads in drug development.

Apigenin
Apigenin (5) is a flavonoid found in many plants such as vegetables (onions; Allium cepa), fruits (oranges; Citrus aurantifolia), and herbs (basil; Ocimum basilicum). It is associated with many health-promoting effects and therapeutic functions. The antiviral effect of apigenin (5) has been reported against enterovirus-71 (EV71), hepatitis C virus (HCV), Foot-and-mouth disease virus (FMD), African swine fever virus (ASFV), and herpes virus HSV-2. It has also been implicated as constituent of herbal products used in the management of corona virus. In an in silico study, it was reported to have moderate binding energy on corona virus. Mechanisms of antiviral action of apigenin include reduction of the expression levels of mature MicroRNA122 (miR122) through inhibition of TAR RNA-binding protein (TRBP) phosphorylation, blocking EV71 RNA association with hnRNPA1 and A2 proteins, and inhibition of viral internal ribosome entry site driven translation. In silico binding energy study is a fair prediction of the possible use of a candidate molecule. Moreover, the ability of apigenin to inhibit viral translation is a promising mechanism for drug development against coronavirus and/or SARS-CoV-2.

Baicalin
Baicalin (6) a flavone glycoside, is the glucuronide of baicalein and is found in many plant species of the genus Scutellaria, such as S. baicalensis, S. lateriflora and S. galericulata. Baicalin is associated with several pharmacological activities including antioxidant, antifungal and antitumor effects. It is also found to be effective in treating cerebral ischemia. The antiviral activity against dengue virus (DENV), influenza virus, HIV-1, enterovirus 71 (EV71), chikungunya virus (CHIKV), and SARS-CoV-2 is well established. Liu et al., (2008) reported that the 4'-OH, 7-OH, C4 keto and C2-C3 double bond functionalities of flavonoids were essential for their anti-influenza effect. Testing of baicalin by viral neutralization assay against 10 strains of SARS-CoV in VERO-K4 cell line and against the prototype strains (39849) of SARS-CoV in Vero-E6 cell lines revealed that it was active. It was also active in the plaque reduction assay with an EC50 value of 11 μg/mL. This, combined with the numerous antiviral activities of baicalin (6), makes it a promising candidate for antiviral drug development. Moreover, baicalin capsules (250 mg per capsule) is an approved drug by the state food and drug administration of China as an adjuvant therapy for managing hepatitis.

Betulonic acid
Betulonic acid (7) is a triterpenoid found in several plants such as Betula pubescens. It has antitumor, antimalarial and anti-inflammatory activities. The antiviral efficacy against HIV-1, herpes simplex type I, influenza FPV/Rostock and ECHO 6 viruses, Herpes simplex virus (HSV-1) has been reported. Several derivatives of betulonic acid (7) are potent and highly selective inhibitors of HIV-1 whose mechanism of action include inhibition of HIV fusion and interference with a specific step in HIV-1 maturation. Synthetic derivatives containing nicotinyl-, methoxyxycinnamoyl-, alkylne and aminopropoxy-2-cyanoethyl-moieties of betulin have been produced through structure modifications at positions C-3, C-20 and C-28. Antiviral activity was reported for 3′f,28-di-O-nicotinoyl betulin against human papillomavirus type 11 while the 3′f,28-Dihydroxy-29-norul-20(30)-yne derivative was active against HCV replicon and the 28-O-Methoxyxycinnamoylbetulin derivative was active against influenza type A virus. The antiviral effect of betulinic acid against enveloped virus along with its possible structure modification associated with increased antiviral activity can be an added benefit in designing a drug against coronavirus and/or SARS-CoV-2.

Castanospermine
Castanospermine (8) is an indolizidine alkaloid obtained from the seeds of Castanopsis austral. It is known to inhibits β-glucosidase and β-glucotecrebrosidase. The antiviral effect of castanospermine has been documented against HIV, dengue virus, and influenza. It decreased viral replication by inhibiting syncytium formation induced by the envelope glycoprotein of the human immunodeficiency virus. This is achieved by inhibiting the processing of the envelope precursor protein gp160, with resultant decreased cell surface expression of the mature envelope glycoprotein gp20. Also, castanospermine caused defects in steps involved in membrane fusion after binding of CD4 antigen. Castanospermine inhibited dengue virus infection by preventing secretion and infectivity of viral particles. It also prevented mortality in a mouse model of dengue virus infection. Several synthetic derivatives with antiviral effect are available. This makes it easier to develop new therapies that can inhibit the processing of envelope precursor protein gp160 from this molecule, which may be useful in treating coronavirus and/or SARS-CoV-2 infection.

Chebulagic acid
Chebulagic acid is a tannin obtained from Terminalia species like T. chebula, T. citrina and T. catappa. It has been reported as an immunosuppressive, hepatoprotective and α-glucosidase inhibitor. The compound has satisfactory activity against several viruses, including herpes simplex virus, Human enterovirus 71, HIV-1, and Influenza A virus. Chebulagic acid inhibits Herpes simplex virus 1 (HSV-1) entry in A549 human lung cells by targeting and inactivating HSV-1 viral particles thus preventing binding, penetration, cell-to-cell spread and secondary infection. The inhibitory action targets at HSV-1 glycoproteins since it blocked polykaryocyte formation mediated by expression of recombinant viral glycoproteins involved in attachment and membrane fusion. Its broad spectrum of activity was demonstrated against human enterovirus (HCMV), hepatitis C virus (HCV), dengue virus (DENV), measles virus (MV), and respiratory syncytial virus (RSV), where it inhibited viral attachment, penetration, and spread supposedly through host cell Glycosaminoglycans cell entry mechanism. Chebulagic acid (EC50 = 1.41 ± 0.51 μg/mL) and Chebulic acid (EC50 = 0.06 ± 0.002 μg/mL) showed dose-dependent potent in vitro direct anti-viral activity against HSV-2 by preventing the attachment and penetration of the HSV-2 to Vero cells. Against influenza A virus, Chebulagic acid and Chebulic acid inhibited viral replication through inhibiting neuraminidase-mediated viral release. Basically, this compound’s broad anti-viral effect is due to its ability to block viral fusion and entry, two important targets in virus life cycle for drug development against coronavirus and/or SARS-CoV-2.

Cyanovirin-N
Cyanovirin-N (CV-N) is a protein produced by the cyanobacterium Nostoc ellipsosporum. It is an elongated, largely β-sheet protein that displays internal two-fold pseudosymmetry. Multiple antiviral activities have been observed with this compound. Cyanovirin-N inactivated different HIV-1 strains and other lentiviruses due to its irreversible binding to the viral envelope glycoprotein gp120. Tsai et al., 2006 reported that recombinant CV-N effectively blocks HIV-1Ba-L infection of human ectocervical explants thus making it a potential candidate for testing in humans as an anti-HIV topical microbicide. It has also been reported to targets N-linked high-mannose oligosaccharides found on the viral envelope of HIV-1, providing possible explanation for its broad antiviral activity. It binds to hepatitis C viral envelope glycoproteins and blocked the interaction...
between the envelope protein E2 and CD81.125 Against influenza virus, it showed considerable activity through binding with viral hemagglutinin.126 It also inhibits infectivity of Ebola virus by binding to the viral surface glycoprotein, GP1.2,127 This compound can be explored against coronavirus and/or SARS-CoV-2 due to its ability to bind viral envelope.

**Cyclosporine A**

Cyclosporine A is a cyclic peptide isolated from the fungus *Hypococadium inflatum gams.*128 It is known for its immunosuppressant,129 antimicrobial,130 anti-psoriatic131 activities. It was officially approved in 1997 by the US Food and Drug Administration for the treatment of plaque psoriasis.132 The antiviral activity of cyclosporine A has been reported against HIV.1 It has been shown to inhibit HIV-1 replication by binding with cyclophilin A and thus disrupting the ability of cyclophilin A to interact with HIV-1 Gag polyprotein.133 It also blocked HIV-1 infectivity by blocking HIV-1 capsid (CA) interaction with target cell cyclophilin A (CypA) as well as decreased gp120 and gp41 incorporation into HIV-1 virions thus impairing the fusion of these virions with susceptible target cells.134 Several reports are available on the effects of cyclosporine A on hepatitis C virus (HCV).135,136 It also inhibits the replication of Japanese Fulminant Hepatitis (JFH1) full-length genomes much more efficiently than subgenomic replicons by targeting cleavage at the nonstructural 2/nonstructural 3 (NS2/NS3) junction.137 It also inhibited hepatitis B replication by interacting with mitochondria, preventing the release of inter-mitochondria calcium, and blocking cytosolic calcium signaling.138 Against influenza viruses, it also inhibited the replication of influenza A virus through cyclophilin A (CypA)-dependent and -independent pathways.139 Furthermore, it inhibits the growth of human coronavirus HCoV-NL63 through cyclophilin A pathway.140 Other viruses against which cyclosporine has been found effective include *Herpes simplex,*141 *stomatitis,*142 *vaccinia,*143 *cytomegalovirus*144 and human papilloma virus.145 Its effectiveness in preventing viral fusion and replication, coupled with the fact that it has also been found effective against HIV, makes this molecule a valuable candidate for consideration in developing anti-coronavirus and/or SARS-CoV-2 drug.

**Droserone**

Droserone (9) is a naphthoquinone obtained from dicotyledonous plants.146 It is one of the pigments in *Drosera whittakeri*. The compound is antibacterial147 and weak antimarial148 properties. It has been reported to reduce measles virus entry considerably suggesting its interaction with viral particles to reduce infectivity.149 Some synthetic Bis-Naphthoquinones have also been reported effective against *Zika virus*150 and HSV-1,151 suggesting possible use of naphthoquinones as antiviral lead compounds. Optimizing synthetic derivatives of this compound as agents that can block viral entry is a possible consideration for anti-coronavirus and/or SARS-CoV-2 drug development.

**Escin**

Escin is a triterpene saponin mixture from the horse chestnut, *Aesculus hippocastanum.*152 The anti-edematous, anti-inflammatory and venotonic properties of β-escin have been linked to induction of cholesterol synthesis followed by decreased cytochrome oxidase activity leading to reduced responses to tumor necrosis factor alpha (TNFα) stimulation, including reduced migration, alleviated endothelial monolayer permeability, and inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal transduction leading to downregulation of TNF-α-induced effector proteins’ expression.153 It also has antitumor activity through intrinsic-mitochondrial apoptosis pathway by arresting G2/M and ROS generation.154 The antiviral activity of escin has been reported against porcine epidemic diarrhea virus (PEDV),155 HIV-1156 and SARS-CoV.157 Strong cytotoxicity of escins create a challenge for their drug development.158 However, SARS studies have shown that acylations at C-21 and C-22 with angelyol or tigloyl groups were important for their cytotoxic effects.159 Thus, escin derivatives with strong antiviral activities have been reported.160 Moreover, it is an approved, well tolerated anti-edematous, anti-inflammatory drug.153 Thus, adapting it as a drug template for repurposing against coronavirus and/or SARS-CoV-2 can be explored.

**Genistein**

Genistein (10) is an isoflavones originally from *Genista tinctoria* but also found to occur in soybeans, *Glycine max.*161 It has been implicated in the treatment of menopausal vasomotor symptoms,162 cancer,163 and memory loss164 among other uses. Antiviral studies indicated that it inhibits African swine fever virus replication by disrupting viral DNA synthesis.164 It also prevented plaque formation of Herpes B virus and reduced virus production.165 It was reported to show some efficacy against H1N1 influenza A virus.166 Against human immunodeficiency virus type 1 (HIV-1), it caused cell cycle arrest in G2.167 It was also reported effective against Lassa virus and Ebola virus infections.168 Other viruses against which it has been found effective include avian leucosis virus169 and Moloney murine leukemia virus (Mo-MLV).170 The broad spectrum of antiviral effect of this molecule makes it a good candidate for testing against coronavirus and/or SARS-CoV-2.

**Geraniin**

Geraniin is a dehydroechinulin isolated from *Geranium carolinianum*. Pharmacological activities associated with geraniin include antioxidant, liver protective, anticancer properties among others.171 Geraniin inhibits the replication of human immunodeficiency virus-1 (HIV-1) *in vitro* by inhibiting virus uptake and HIV-1 reverse transcriptase.172 It was also reported to suppress herpes simplex virus (HSV) with better activity on HSV-2 infection than HSV-1.173 It had antiviral activity against hepatitis B virus (HBV). It has been shown to inhibit hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBcAg) secretion by about 85.8% and 63.7%, respectively, at a concentration of 200 mg/mL.174 Geraniin also had inhibitory effect on human enterovirus 71 (EV71).175 The diverse effects against many viruses as well as different mechanisms of action makes it suitable for drug development against coronavirus and/or SARS-CoV-2.

**Glycyrrhizin**

Glycyrrhizin (11) is a triterpenoid saponin isolated from licorice (*Glycyrrhiza glabra, Glycyrrhiza inflata* and *G. uralensis,* root).176 It is reported to have several biological activities including antiviral activity against various enterovirus (VZV),177 human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 1 (HSV-1),178 Hepatitis virus (HCV)179 and coronavirus180,181 among others. Glycyrrhizin (11) is known to affect many cellular signaling pathways182,183 with one other possible mechanism of anti-coronavirus action being stimulation of inducible NO synthase (iNOS) expression and subsequent increase of the nitric oxide (NO) concentration.184 Nitric oxide (NO) plays diverse physiological functions in the body and there are evidences suggesting that NO and oxygen radicals are involved in the pathogenesis of various infectious diseases.185,186,187 NO biosynthesis through expression of inducible iNOS occurs in different microbial infections and iNOS produce large amount of NO over a long period. The production of NO leads to the generation of a highly reactive nitrogen oxide species, peroxynitrite, through radical coupling of superoxide and the generated peroxynitrite causes oxidative tissue injury through potent oxidation and nitration reactions of various biomolecules.188 NO is also known to modulate host's immune response189 thus acting as host response modulator rather than a simple antiviral agent.190 Glycyrrhizin is an already approved drug for clinical use as an intravenous medication and it is commercially available.191 Thus it can be easily adapted for use as possible anti-coronavirus and/or SARS-CoV-2 drug.

**Guggulsterone**

Guggulsterone (12) is a phytosteroid found in the resin of the guggul plant, *Commiphora mukul.*192 It has anti-inflammatory193 and anticancer194 activities. Guggulsterone (12) isolated from *Commiphora gileadensis* was reported to be responsible for the antiviral activity of the plant against herpes simplex virus type 2 (HSV-2), respiratory...
syncytial virus type B (RSV-B), coxsackie virus B type 3, and adenovirus type 5. High serum level of bile acids is known to be responsible for antiviral therapy failure in patients with hepatitis C (HCV) infection. Also, bile acids are important for the replication of the porcine enteric calicivirus. Free, and not conjugated bile acids up-regulated genotype 1 HCV RNA replication suggesting that this effect was mediated by a nuclear receptor. Guggulsterone inhibited basal level of HCV replication as well as blocked bile acids-induced up-regulation of genotype 1 HCV RNA replication through Farnesoid X receptor (FXR) silencing and FXR antagonism. Enveloped viruses such as influenza viruses, alphaviruses and coronaviruses, that uses host cells endocytic pathway, have fusion protein that is activated at low pH made possible in the presence of bile acids. Thus, guggulsterone might be a promising molecule in drug development for coronavirus and/or SARS-CoV-2 through the blockage of bile acid-induced viral replication.

Hirsutone

Hirsutone (13) is a diarylheptanoids obtained from the stem bark of Alnus japonica. It has been reported for its antitumor, anti-inflammatory and antiretroviral activity. Luteolin is also reported to be effective against SARS-CoV by inhibiting papain-like pro tease of SARS-CoV. Diarylheptanoids are a broad class of plant structurally divergent phenolics with diverse therapeutic applications. Park et al. correlated good antiviral activity with the α,β-unsaturated carbonyl group and catechol moiety while observing that monohydroxyl substitution and glycosidation led to reduced activity. Assessment against recombinant SARS-CoV 3CL protease also showed that Hirsutone had good selectivity towards the coronaviral proteases. Thus, Hirsutone can be a potential drug target for the treatment of SARS disease.

Juglalin

Juglalin (14) is a flavonol isolated from Juglans mandshurica and has also been identified in Polygonum aviculare. It has been reported to possess anti-influenza H1N1 and anticancer activities. The antiviral effect against some virus infections are also available in literature. It was evaluated for its ability to block the 3a channel of SARS coronavirus. Juglalin (14) was effective with an IC50 value of 2.3 μM for inhibition of the 3a-mediated current. In an in silico experiment against influenza virus, it was shown to have binding specificities to hemagglutinin (H7) and neuraminidase (N9). The effectiveness of this compound to block 3a channel of SARS coronavirus can be used in developing effective therapy against coronavirus and/or SARS-CoV-2 infection.

Labyrinthopeptin

Labyrinthopeptins are peptides produced by actinomycete Actinomadura namibiensis. Labyrinthopeptin A1 showed broad and high activity against HIV-1 (human immunodeficiency virus) activity. Labyrinthopeptin inhibited viral cell-cell transmission between persistently HIV-infected T cells and uninfected CD4+ T cells as well as the transmission of HIV captured by DC-SIGN+ cells to uninfected CD4+ T cells. Labyrinthopeptins A1 and A2, were found to inhibit the proliferation of many enveloped viruses including dengue virus, Zika virus, West Nile virus, hepatitis C virus, chikungunya virus, Kaposi’s sarcoma-associated herpes virus, cytomegalovirus (CMV), and human papillomavirus with mechanism of action showing that it induced virolytic effect through binding to the viral membrane lipid phosphatidyethanolamine (PE). Several derivatives are currently available for treating different viral infections, which makes it a promising compound for assessment against coronavirus and/or SARS-CoV-2 infection.

Lectins

The high glycosylation of the S protein makes it a good target for compounds like plant lectins, that can bind to sugar moieties thus forming a coat around the protein and blocking possible interaction with the receptor. Lectins are known inhibitors of glycosylated viruses like HIV-type 1, cytomegalovirus and human T-cell leukemia virus. Galanthus nivalis (Common Snowdrop), Narcissus tazetta, Hippeastrum hybrid (Amaryllis) and Allium porrum (leek) are sources of lectins that inhibited the replication of SARS-CoV, syncytial virus and feline coronavirus by blocking the S protein-receptor interaction. They can be explored in the ongoing search for good antiviral therapy for SARS-CoV-2.

Luteolin

Luteolin (15) is a flavone obtained from several plant species. It has been reported to show neuropharmacological, anticancer and anti-inflammatory activities, among others. The antiviral effect against HBV and Herpes virus HSV-2 has also been documented. In HepG2.2.15 cells, luteolin inhibited the expression of hepaticocyte nuclear factor 4α (HNF4α) in uninfected cells and primary lymphocytes with in a HBV replication mouse model, it decreased the levels of HBsAg, HBeAg, HBV DNA replication intermediates, and the HBsAg and HBeAg expression. In a time-of-addition assay, it was shown to interfere with viral replication at the early stage of infection as well as suppressed serum HBV-I complex expression. Against Japanese encephalitis virus (JEV), luteolin inhibited viral replication in A549 cells with IC50 was 2.5 μM and had effective anti-inflammatory activities. This compound has also been shown to be effective against SARS-CoV and H5N1 viruses with the inhibition by luteolin independent of viral entry. It also showed antiviral effect in a latent HIV-1 reactivation model and removed both clade-B- and C-Tat-driven LTR transactivation in reporter assays. Luteolin inhibited protein expression from Epstein-Barr virus (EBV) lytic genes in EBV-positive epithelial and B cell lines, reduced the numbers of EBV-reactivating cells detected by immunofluorescence analysis as well as regulated virus production. The study concluded that luteolin inhibited EBV reactivation by repressing the promoter activities of Zta (Zp) and Rta (Rp) genes. The diverse mechanisms of anti-viral action of luteolin, particularly inhibition of viral RNA replication and virion maturation makes it a promising candidate for drug development against coronavirus and/or SARS-CoV-2.

Mucroporin-M1

Mucroporin is a cationic host defense peptide isolated from the venom of Lychas mucronatus and mucroporin-M1 was designed by amino acid substitution based on its molecular template. Mucroporin-M1 has been evaluated for a variety of activities including antibacterial effect. This compound has also been shown to be effective against several viral infections. The antiviral activities of mucroporin-M1 against measles, SARS-CoV and influenza H1N1 viruses were reported with an EC50 of 7.15 μg/mL (3.52 μM) and a CC50 of 70.46 μg/mL (34.70 μM) against measles virus, an EC50 of 14.46 μg/mL (7.12 μM) against SARS-CoV and an EC50 of 2.10 μg/mL (1.03 μM) against H5N1 and the mechanism of action proposed to be inhibition of virus infectivity. Using both in vitro and in vivo studies, Zhao et al. established that mucroporin-M1 inhibited hepatitis B virus replication by activating the mitogen activated protein kinase (MAPK) pathway and down-regulating HNF4a. The therapeutic potentials of peptides have gained attention lately and investigation into their mechanisms of action with respect to establishing antiviral prospect is on the rise as a result of the global threat posed by viruses. Mucroporin M1 is proposed to directly interact with the virus envelope leading to decreased infectivity. Thus, rational modification of mucroporin would be a good approach to
developing antiviral agents with broad spectrum of activity against RNA viruses particularly SARS-CoVs.

**Mycocephalin acid**

Mycocephalin acid (16) which belongs to the class of organic compounds known as phthalides was first isolated from the fungus *Penicillium stoloniferum* and is an inhibitor of nucleic acid synthesis. It is known as an immunosuppressant and is an FDA approved immunosuppressive drug. It also has anti-fungal and antitumor effects. The antiviral effect against some unrelated viruses was reported by Plantatore (1969). Its inhibitory effect on Dengue virus was attributed to its ability to prevent the synthesis and accumulation of viral RNA. Smece et al. reported its effect against orthopoxviruses. It inhibited hepatitis E virus (HEV) replication through nucleoside deoxyribonucleoside, and it also inhibited HIV replication by depleting the substrate (guanosine nucleotides) for reverse transcriptase and depletions of the pool of activated CD4+ T lymphocytes. Hepatitis C virus (HCV) replication was shown to be inhibited by mycocephalin acid at 1.0–6.0 μg/mL to approximately 75% through a mechanism independent of guanosine depletion. Mycocephalin acid (16) significantly inhibited Japanese encephalitis virus both in vitro and in vivo, and Avian reoviruses (ARV).

**Niranthin**

Niranthin (17) is a lignan isolated from plants of the genus *Phyllanthus* like *P. niri* and *P. amarus*. It has been reported with anti-inflammatory activity. Initial screening revealed that it had anti-hepatitis activity. The anti-hepatitis B virus activity of niranthin (17) again evaluated both in vitro and in vivo showed that it significantly decreased the secretion of HBV surface antigen (HBsAg) and HBVe antigen (HBcAg) with IC50 values of 15.6 μM for HBsAg and IC50 values of 251 μM for HBcAg. It also reduced the serum duck hepatitis B virus (DHBV) DNA, HBsAg, HBcAg, ALT and AST in vivo228 suggesting that niranthin (17) acts as an anti-HBV agent through at least two mechanisms. It also inhibited HSV replication by the white spot syndrome virus showed it inactivated the virus.228 It thus is a potential inhibitor that can be evaluated against SARS-CoV antigen.

**Podophyllotoxin**

Podophyllotoxin (18) is an aryetyl tertiary lignan obtained from the roots of *Podophyllum peltatum* L. or *P. emodi*. It has several activities including insecticidal and anticaner activities. Antiviral evaluation on herpes simplex virus type 1 (HSV-CV-1) and vesicular stomatitis virus infecting fibroblasts of hamster kidney (VSVDHK) showed activity at concentration below 1 μM.229 Several analogues also showed against herpes simplex virus type II.231 Chen et al. also reported the anti-HIV effect of podophyllotoxin derivatives. Podophyllotoxin and its derivatives could be explored in the search for antiviral therapy in general and against coronavirus and/or SARS-CoV-2 in particular.

**Quercetin**

Quercetin (19) is a flavonoid found in many plant species. Numerous biological activities are reported for quercetin. This include neuronal protease,232 hypoglycemic,233 antioxidant,234 and antidiabetic activities.235 Different flavonoids including quercetin (19) were tested for their effect on infectivity and replication of herpes simplex virus type 1 (HSV-1), polio virus type 1, parainfluenza virus type 3 (PIF-3), and respiratory syncytial virus (RSV). Quercetin (19) caused a dose-dependent reduction in the infectivity and intracellular replication of each virus.236 It also, inhibited HIV-infection by preventing binding of gp120 to CD4.237 Again, the 4'-OH, 7-OH, C4 keto, and C2-C3 double bond group of flavonoids would come to play here and the broad spectrum of activity of quercetin (19) will be a major advantage in it prospect as a good antiviral drug template against coronavirus and/or SARS-CoV-2.

**Resverpine**

Resverpine (20) is an indole alkaloid obtained from the roots of *Rauwolfia serpentina* and *Rauwolfia vomitoria*. The compound has anti-arthritic,238 antibacterial,239 anti-parkinson,240 anticancer241 and anti-hypertensive242 activities, among others. It is an approved drug for the management of high blood pressure and has been reported active against SARS-CoVs.243 It inhibited viral replication with IC50 of 3.4 μM. Six other compounds related to resverpine were also shown to have activities toward SARS-CoV at ≤100 μM.244

**Yatein**

Yatein, (21) a lignan was isolated from *Chamaecyparis obtusa* and tested for its activity against h2-rna silencing virus type 1 (HSV-1). It significantly suppressed HSV-1 multiplication by suppressing the levels of glycoprotein B (gB) and gC mRNA expression, arresting the replication of HSV-1 DNA and decreasing ICP0 and ICP4 gene expression.247 Lignans are distributed widely in the plant kingdom and more than 200 classical lignans and 100 neolignans with vast structural diversity have been identified till date.248 Yatein is a dihydroxybutoxyflavone that inhibited SARS-CoV-1 expression by arresting HSV-1 DNA synthesis and structural protein expression in HeLa cells.248 This compound and it derivatives can be assessed for effectiveness against coronaviruses.

**Others**

Other natural products with reported antiviral activity include sorbinifolin (22) and pedatin (23), two flavonoids from *Pteroygen nitens* proven effective against Hepatitis C virus (HCV).249 Herbacetin (24), rhoifolin and pectolinarin blocked the enzymatic activity of SARS-CoV 3CLpro.250 Herbacetin, isobavachalcone (25), quercetin 3β-d-glucoside, and helichrysetin (26) blocked the enzymatic activity of MERS-CoV 3CLpro.251 Robustaflavone (27) inhibited influenza A and influenza B viruses with EC50 values of 2.0 μg/mL and 0.2 μg/mL, respectively.252 Ferraginol, dehydroabieta-7-one, sugiol, 8β-hydroxyabietic acid, sugiol 12-ene, 6,7-dehydroabietol, pinusolidic acid, c-adinol, hinokinin, and savinin purified from the ethyl acetate extracts of *Chamaecyparis obtusa*, 3β,12-diacetoxyabieta-6,8,11,13-tetraene, cedrane-3β,12-diol, and betulonic acid isolated from the ethyl acetate extracts of *Juniperus formosa* along with cryptopeonalo and 7β-hydroxydeoxycryptoponalo isolated from *Cryptomeria japonica* were evaluated for activity against SARS-CoV.253 All the compounds inhibited SARS-CoV at concentration between 3.3 and 10 μM.272 Gomisin M α is a lignand from *Schisandra rubriflora* that had potent anti-HIV activity with EC50 value of <0.65 μM.253 Rubrifloralignan A, from the fruits of *Schisandra rebriflora* is an anti-HIV-1 product with effect on early stage of HIV-1 replication.274 1α-hydroxybrussonal, a diterpeneoid from *Perovskia atriplicifolia* suppressed the replication of hepatitis B virus DNA with selectivity index of 1377.275 The anti-influenza virus activity of six stilbenoids from *Gnetum pendulum* showed that isorhapontigenin, gnetupedin B, shegansu B, and gnetin D had significant anti-influenza virus activity in MDCK cells, with IC50 values ranging from 0.67 to 11.99 μg/mL when compared to the positive controls oseltamivir and ribavirin with IC50 values of 0.040 and 5.54 μg/mL, respectively.276 Tellimagrandin I, a tannin from *Coriun canadensis* was found effective against herpes simplex virus type 1 (HSV-1) with an EC50 of 2.6 μM for the direct mode and 5.0 μM for the absorption mode of the plaque reduction assay.277 There are several literatures documenting antiviral agents from other natural sources such as those from mushrooms,278, 279 and from marine natural products.279, 280
Figure 3: Chemical structures of some promising lead compounds
**Figure 3 Cont’d:** Chemical structures of some promising lead compounds

18 Podophyllotoxin
19 Quercetin
20 Reserpine
21 Yatein
22 R=H Sorbifolin
23 R=OH Padalitin
24 Herbacetin
25 Isobavachalcone
26 Helichrysetin
27 Robustaflavone
Table 1: Selected natural compounds and their antiviral mechanisms of action

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Class</th>
<th>Source</th>
<th>Virus</th>
<th>Mechanisms of action</th>
<th>Dose/IC_{50}</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Deoxynojirimycin</td>
<td>Alkaloid</td>
<td>Commelina communis</td>
<td>Hepatitis</td>
<td>Inhibited glycosylation of viral envelope proteins</td>
<td>9.92 μM</td>
<td>55</td>
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<tr>
<td>Aloe-emodin</td>
<td>Anthraquinone</td>
<td>Aloe vera</td>
<td>Influenza A virus</td>
<td>Up-regulated galectin-3 and thioredoxin</td>
<td>0.05 μg/mL</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enterovirus 71 (EV71)</td>
<td>Induced interferon (IFN)</td>
<td>0.14 μg/mL to 0.52 μg/mL</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Japanese encephalitis virus (JEV)</td>
<td>Induced interferon (IFN)</td>
<td>0.50 μg/mL to 1.51 μg/mL</td>
<td>65</td>
</tr>
<tr>
<td>Amentoflavone</td>
<td>Biflavone</td>
<td>Torreya nucifera</td>
<td>SARS-CoV</td>
<td>3CL\textsuperscript{pro} inhibition</td>
<td>8.3 μM</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Herpes viruses (HSV-1, HSV-2)</td>
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<td>17.9 and 48.0 mg/mL</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td>Human immunodeficiency virus (HIV)</td>
<td>Inhibited HIV-1 RT</td>
<td>119 μM</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory syncytial virus (RSV)</td>
<td></td>
<td>5.5 μg/mL</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dengue virus</td>
<td>Inhibited dengue virus NS5 RNA-dependent RNA polymerase</td>
<td>1.3 μM</td>
<td>70</td>
</tr>
<tr>
<td>Apigenin</td>
<td>Flavonoids</td>
<td>Arisaema tortuosum</td>
<td>Herpes virus HSV-2</td>
<td>Inhibited both early and late events of the HSV-2 replication</td>
<td>0.05 μg/mL</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>African swine fever virus (ASFV)</td>
<td>Inhibited ASFV-specific protein synthesis and viral factory formation</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C virus (HCV)</td>
<td>Inhibited maturation of miRNAs and HCV replication</td>
<td>Decreased the expression levels of mature miR122</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Foot-and-mouth disease virus (FMD)</td>
<td>Inhibited FMDV-mediated cytopathogenic effect and FMDV replication</td>
<td>8.593 μg/mL</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enterovirus-71 (EV71)</td>
<td>Disrupted viral RNA association with hnRNPs A1 and A2 proteins</td>
<td>10.3 μM</td>
<td>73</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Flavone glycoside</td>
<td>Scutellaria baicalensis</td>
<td>Dengue virus (DENV)</td>
<td>Inhibited virus replication, extracellular particles and showed anti-adsorption effect</td>
<td>13.5 ± 0.08, 8.74 ± 0.08 and 18.07 ± 0.2 μg/mL respectively</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza virus</td>
<td>Inhibited neuraminidases</td>
<td>43.3 μg/mL</td>
<td>86</td>
</tr>
<tr>
<td>Compound</td>
<td>Class</td>
<td>Source</td>
<td>Targets</td>
<td>Activities and Concentrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>HIV-1</td>
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<td></td>
<td>Inhibited both T cell tropic (X4) and monocyte tropic (R5) HIV-1 Env protein mediated fusion Inhibited the activity of HIV-1 reverse transcriptase</td>
<td>0.5 μg/mL 87,88</td>
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</tr>
<tr>
<td>Enterovirus 71 (EV71)</td>
<td></td>
<td></td>
<td>Inhibited EV71/3D polymerase expression and Fas/Fasl signaling pathways</td>
<td>4.96 μg/mL 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chikungunya virus (CHIKV)</td>
<td></td>
<td></td>
<td>Inhibited viral entry, viral particle attachment, and replicase complexes formation</td>
<td>7 μM, 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV</td>
<td></td>
<td></td>
<td></td>
<td>12.5 to 25 μg/mL 91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betulinic acid</td>
<td>Triterpenoid</td>
<td>Betula pubescens</td>
<td>Herpes simplex virus</td>
<td>Reduced viral cytopathic effect 30 μg/mL 101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1</td>
<td></td>
<td></td>
<td>Inhibited HIV fusion and interfere with a specific step in HIV-1 maturation</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castanospermine</td>
<td>Alkaloid</td>
<td>Castanospermum austral</td>
<td>HIV</td>
<td>Modified glycoprotein 105</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dengue virus</td>
<td>Inhibited infectivity of viral particles 107</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza</td>
<td>Inhibited glucosidase 1 107</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza</td>
<td>Inhibited glycoprotein 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV</td>
<td>Inhibited virus entry at the Env/coreceptor interaction step 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chebulagic acid</td>
<td>Tannin</td>
<td>Terminalia chebula</td>
<td>Herpes simplex virus</td>
<td>Inactivated HSV-1 viral particles 17.02±2.82 μM 114</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Human enterovirus 71</td>
<td>Inhibition of viral replication 12.5 μg/mL 115</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV</td>
<td>Inhibited HIV reverse transcriptase 116</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza</td>
<td>Inhibited neuraminidase 117</td>
<td></td>
<td></td>
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<tr>
<td>Cyanovirin-N</td>
<td>Protein</td>
<td>Nostoc ellipsosporium</td>
<td>HIV-1</td>
<td>Blocked binding of gp120 to cell-associated CD4 122</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C</td>
<td>Binds to viral envelope glycoproteins and blocked the interaction between the envelope protein E2 and CD81 1.6 ± 0.1 nM 125</td>
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<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Influenza</td>
<td>Bound viral hemagglutinin 0.004 to 0.04 μg/mL 126</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ebola virus</td>
<td>Binds to the viral surface glycoprotein 127</td>
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</tr>
<tr>
<td>Natural Product</td>
<td>Peptide Type</td>
<td>Source</td>
<td>Disease Target</td>
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<td>Cyclosporine A</td>
<td>Peptide</td>
<td><em>Hypocladium inflatum gams</em></td>
<td>HIV-1</td>
<td>Disrupted Gag-cyclophilin A interaction</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV-1</td>
<td>Blocked incorporation of HIV-1 envelope glycoprotein into virions</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Hepatitis C virus (HCV)</td>
<td>Cleavage at NS2/NS3 junction</td>
<td>0.15 g/mL</td>
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<td>Hepatitis B</td>
<td>Inhibited viral replication by blocking cytosolic calcium signaling</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Influenza virus</td>
<td>Inhibited the replication through CypA-dependent pathway</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coronavirus HCoV-NL63</td>
<td>Knockdown of cellular Cyclophilin A (CypA/PPIA) gene</td>
<td>0.9-2.0 μM</td>
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<td>Droserone</td>
<td>Naphthoquinone</td>
<td><em>Drosera whittakeri</em></td>
<td>Measles virus</td>
<td>Reduced viral entry</td>
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<td>Emodin</td>
<td>Anthraquinone</td>
<td><em>Rheum Palmatum</em></td>
<td>SARS-CoV</td>
<td>Inhibited ACE2 interaction</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Herpes simplex virus (HSV)</td>
<td>Inhibited nuclease activity of HSV-1 UL12</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Escin</td>
<td>Triterpene saponin</td>
<td><em>Aesculus hippocastanum</em></td>
<td>HIV-1</td>
<td>Anti-HIV-1 protease</td>
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<td>Porcine epidemic diarrhea virus (PEDV)</td>
<td>Inhibited nucleocapsid protein synthesis and viral replication</td>
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<td>SARS-CoV</td>
<td>Inhibited viral replication</td>
<td>6.0 μM</td>
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<td><em>Galanthus nivalis</em> agglutinin (GNA)</td>
<td>Lectins</td>
<td><em>Galanthus nivalis</em></td>
<td>Mouse hepatitis virus</td>
<td>Inhibition of viral fusion</td>
<td>50 mg/L</td>
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<td>Genistein</td>
<td>Isoflavones</td>
<td><em>Genista tinctoria</em></td>
<td>African swine fever virus</td>
<td>Disrupted <em>viral</em> DNA synthesis</td>
<td>164</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Herpes B virus</td>
<td>Prevented plaque formation of Herpes B virus and reduced virus production</td>
<td>33 and 46 μM</td>
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<td>Geraniin</td>
<td>Dehydroellagitannin</td>
<td><em>Geranium carolinianum</em></td>
<td>Hepatitis B virus (HBV)</td>
<td>Inhibited HBsAg and HBeAg</td>
<td>174</td>
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<td></td>
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<td>HSV-1 and HSV-2</td>
<td>suppressed both HSV-1 and HSV-2</td>
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<td></td>
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<td></td>
<td>HIV-1</td>
<td>Inhibited virus uptake and HIV-1 reverse transcriptase</td>
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<td>Glycyrrhizin</td>
<td>Triterpenoid saponin</td>
<td><em>Glycyrrhiza glabra</em></td>
<td>Varicella-zoster virus</td>
<td>Inhibited replication</td>
<td>0.71 mM</td>
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</table>

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Source/Species</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomisin M₁</td>
<td>Ligand</td>
<td>Schisandra rubriflora</td>
<td>Suppressed viral entry and replication, Inhibited release of infectious HCV particles due to its inhibitory effect on phospholipase A2 group 1B (PLA2G1B)</td>
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<tr>
<td>Coronavirus</td>
<td></td>
<td></td>
<td>Inhibited virus adsorption, penetration and replication</td>
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<tr>
<td>Hippeastrum hybrid agglutinin</td>
<td>Lectins</td>
<td>Hippeastrum hybrid</td>
<td>Inhibited virus adsorption, penetration and replication</td>
</tr>
<tr>
<td>Hirsuteneone</td>
<td>Diarylheptanoids</td>
<td>Alnus japonica</td>
<td>Inhibited viral cell-cell transmission</td>
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<tr>
<td>Juglanin</td>
<td>Flavonol</td>
<td>Juglans mandshurica</td>
<td>Inhibited viral cell-cell transmission</td>
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<tr>
<td>Labyrinthopeptin A₁</td>
<td>Peptide</td>
<td>Actinomadura namibiensis</td>
<td>Inhibited viral cell-cell transmission</td>
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<td></td>
<td></td>
<td></td>
<td>Inhibited human respiratory syncytial virus (hRSV)</td>
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<tr>
<td>Luteolin</td>
<td>Flavonoids</td>
<td>Arisaema tortuosum</td>
<td>Inhibited both early and late events of the HSV-2 replication</td>
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<tr>
<td></td>
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<td></td>
<td>Inhibited cell entry</td>
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<tr>
<td>Mucroporin-M1</td>
<td>Peptide</td>
<td>Lychas mucronatus</td>
<td>Reduced HBV DNA replication and inhibited hepatocyte nuclear factor 4α (HNF4α) expression</td>
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<td>Activated MAPK pathway and down-regulated HNF4α</td>
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<tr>
<td>Mycophenolic acid</td>
<td>Phthalides</td>
<td>Penicillium stoloniferum Fungi</td>
<td>Prevented the synthesis and accumulation of viral RNA</td>
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<td>Inhibited viral infectivity</td>
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<td>Activated MAPK pathway and down-regulated HNF4α</td>
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Concluding remarks

The cellular components of the host are used by corona viruses for different physiological processes in their life cycle. These include viral entry, genomic replication and the assembly and budding of virions resulting in considerable pathological damages to the host cells. Thus, any chemical compound that can interrupt any stage of the viral lifecycle would offer potential therapeutic option for the development of antiviral therapies. In this review, we have reported many compounds of natural origin that have demonstrated in vitro or in vivo potential against other viruses that are similar to SARS-CoV-2. Our hope is to promote the continuing research of diverse molecules with antiviral potentials. All the discussed compounds could be exploited either directly as antiviral agents or form templates for such. Furthermore, structurally related compounds could also be tested for their antiviral potentials. These compounds could also be optimized for drug discovery and development as they can potentially assist in the rational design of novel antiviral therapeutics. Modes of efficient delivery and safety profiles in humans could be further investigated.

Conflict of interest

The authors declare no conflict of interest.

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Authors’ Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.
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