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Review Article

Drug Development for the Management of Corona Viruses: Insights from Natural Antiviral Agents

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ABSTRACT

Infection by human Coronaviruses (CoVs) such as HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1generally 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.

Introduction

Coronaviruses (CoVs) are enveloped viruses that cause multiple respiratory and intestinal infections in humans and animals.[1] The term 'coronavirus' refers to the crown-like appearance of CoVs under electron microscope due to spike projections from the membrane.[2] These viruses were first described in the 1960s from patients with respiratory infections like the common cold.[3] 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.[3] CoVs belong to the subfamilies Coronavirinae and Torovirinae of the family Coronaviridae in the order Nidovirales.[4] Based on phylogeny, they are divided into four genera as α-CoV, β-CoV, γ-CoV and δ-CoV.[5] The beta-CoV genus is further subdivided into four lineages (A, B, C, and D)[1] (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.[3] 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).[6]

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The various coronaviruses cause divers infections in human but historically given little attention due to their mild phenotypes. Globally, HCoV 229E, NL63, OC43, and HKU1 are endemic, accounting for 10% to 30% of upper respiratory tract infections in adults.[7] They rarely cause life-threatening pneumonia and bronchiolitis but this can happen in children and immunocompromised patients.[8,9] HCoVs have also been linked with enteric and neurological disorders.[10-12] The first major alert on severe cases of HVoVs came in 2002 when lethal atypical pneumonia due to SARS-CoV was reported in China.[7]

Better understanding of the biology and the pathophysiology of CoVs infections have resulted from several researches conducted in the last two decades, especially on SARS-CoVs and MERS-CoVs. This has in turn driven the search for appropriate drug therapy and vaccine development.

The use of natural products derived from plants, animals or micro-organisms for medicinal purpose precedes the recorded human history. Over the years, humankind has discovered and utilized several chemical products of natural origin. Perhaps due to their chemical and biological diversity, the application of natural products for medicine and health throughout evolution has been significant.[13] It is reported that the single most productive source of lead compounds for drug development is natural product.[14] Newman *et al*., (2002) reported drugs discovered from natural products between 1981 and 2002, with this accounting for 60% and 75% of new drugs respectively in the areas of cancer and infectious disease.[15] Drugs of natural products origin for managing various disorders such as bacterial and fungal infections, cancer, diabetes, dyslipidemia, atopic dermatitis, Alzheimer's disease, tyrosinaemia and Gaucher disease, introduced for use between 2001 and 2005, have also been reported.[16] Other reviews on the importance and re-emergence of natural products in drug discovery are available.[17-21] In the last few years, new technologies that made screening of natural products easier thereby helping to overcome certain limitations in natural products drug discovery have been developed.[16] Also, natural products have contributed specifically

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to antiviral drug discovery.[22] 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.[23] During CoVs infection cycle, the genomic RNA plays a critical role in the initial RNA synthesis and acts as a messenger RNA (mRNA).[3] 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).[24] The pp1a/pp1ab also encodes nonstructural proteins (nsps).[25] 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.[26] 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).[27]

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) proteins a basic RNA-binding protein.[3,28] The polypeptides 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.[29]

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 hemagglutinin esterase (HE) which has similar function as the S protein.[1] Other special proteins include 3a/b protein and 4a/b protein.

The structural proteins S, M, E and N, in addition to facilitating virion assembly, also suppresses host immune response to facilitate viral replication.[30] Viral replication starts with the binding of the spike protein (S) onto the host's cell-surface. This is an important recognition step that initiate virus entry into the host cells and different CoVs utilizes different receptors to achieve this. For instance, aminopeptidase N is used by HCoV-229E;[31] 9-O-acetylated sialic acid by HCoV-OC43 and HCoV-HKU1;[32,33] angiotensin-converting enzyme 2 (ACE2) by SARS-CoV;[34] and HCoV-NL63[35,36] and dipeptidyl peptidase 4 (DPP4) by MERS-CoV.[37] CoVs also use proteases to facilitate entry into host cell. Proteases used include cathepsin L by SARS- and MERS-CoV viruses, transmembrane protease serine 2 (TMPRSS2) and airway trypsin-like protease TMPRSS11D by HCoV-229E and SARS-CoV viruses.[38-40] The replication process begins after successful entry, with the decoding of viral particle and translation of ORF 1a and 1b into polyproteins pp1a and pp1ab, a process facilitated by 3-C-like protease (3CLpro) and papain-like protease (PLpro). The polyproteins are thereafter split into about 15 NSPs, which subsequently form the replication–transcription complex (RTC). Using replicases, the positive genomic RNA is then transcribed to negative-strand template for the synthesis of new genomic RNAs which are further transcribed to form structural and accessory proteins. Chemical compounds capable of interrupting any stage in the replication process would be a good candidate for therapeutic development.

Mechanisms against human corona viruses

Mechanisms directed at combatting human corona virus 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.[41] 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.[42] 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.[43] Translation and protein processing such as by chymotrypsin-like proteinase and papain-like proteinase are also good anti-coronavirus targets.[44]

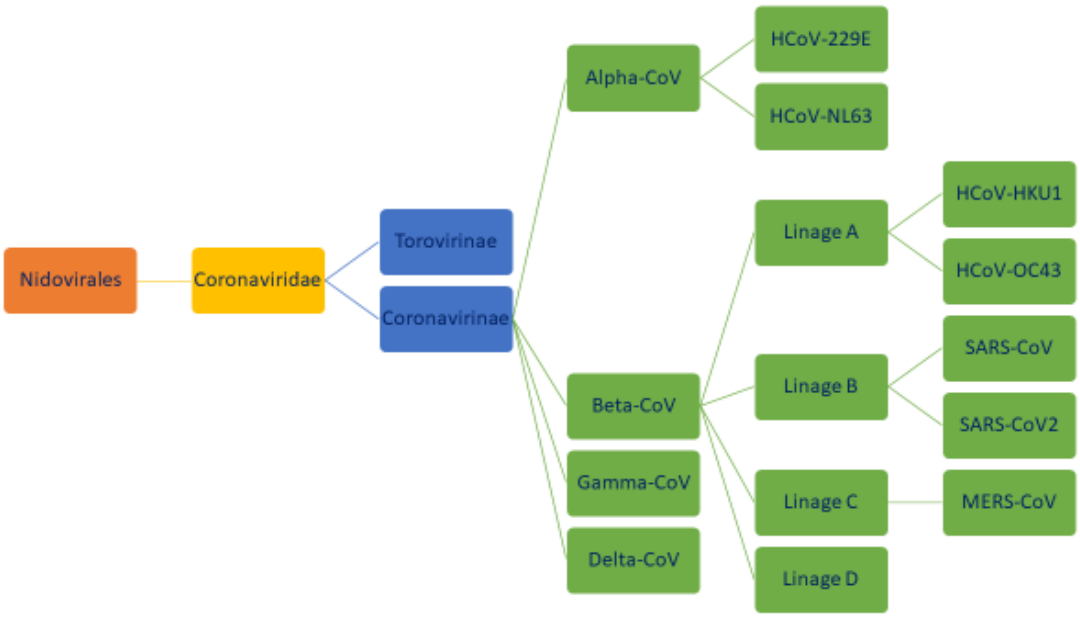

Figure 1: Schematic representation of the human coronaviruses

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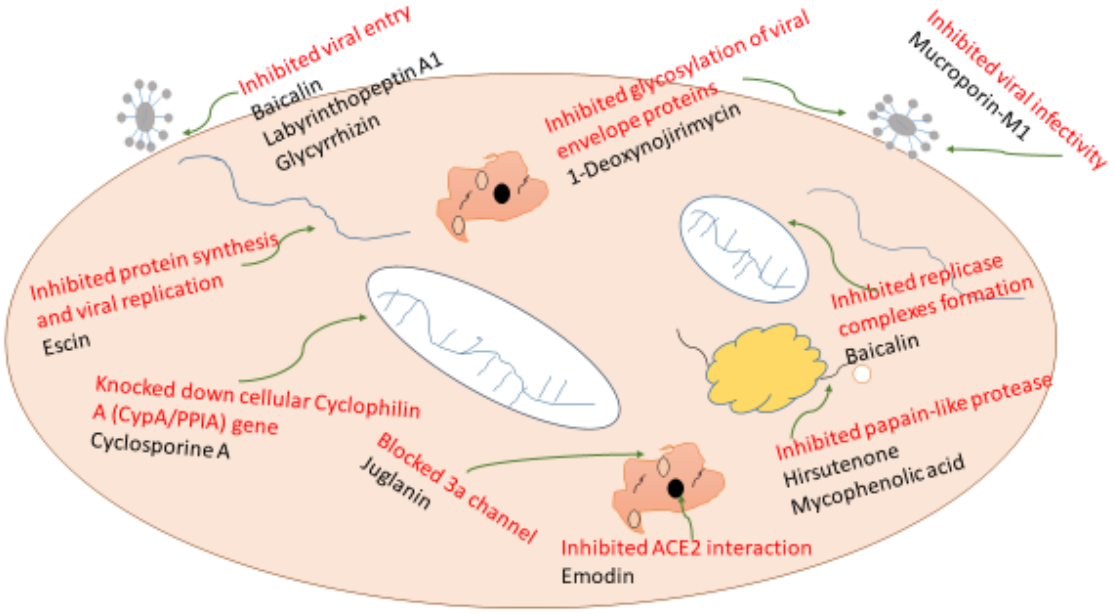

Figure 2: Potential Pharmacologic antiviral targets against SARS-CoV-2

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.[45] 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.[46] In other countries of the world, different therapy combinations have been employed as summarized by Chen *et al*., (2020)[47] 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.[48-51]

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] influenza[56] 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 $Glc_3Man_9GlcNAc_2$, 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 larvicidal[60] and anticancer[61] 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 nuclease activity of HSV-1 UL12 as well as reduced plaque formation with an EC_{50} of 21.5 ± 4.4 mM.[62] The effect of emodin on herpes virus was also confirmed by Xiong *et al*. (2011).[63]

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 IC_{50} 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, STATI phosphorylation of interferon (IFN) stimulation response element (ISRE)-driven promoter, RNA-dependent protein kinase (PKR) and 2′,5′-oligoadenylate 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′-oligoisoadenylate 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*.[66] It is reported to have many biological activities such as anti-inflammatory, anti-oxidative, and anti-diabetic activities.[67] It has also been reported to be active against SARS-CoV by inhibiting SARS-CoV 3CLpro.[66] Amentoflavone (**4**) also showed inhibitory activity against human immunodeficiency virus (HIV)[68] and respiratory syncytial virus (RSV).[69] Other antiviral activities reported for this compound are anti-dengue,[70] anti-influenza and anti-herpes.[71] 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/therapeutic functions.[72] The antiviral effect of apigenin (**5**) has been reported against enterovirus-71 (EV71),[73] hepatitis C virus (HCV),[74] Foot-and-mouth disease virus (FMD),[75] African swine fever virus (ASFV),[76] and herpes virus HSV-2.[77] It has also been implicated as constituent of herbal products used in the management of corona virus.[78,79] In an *in silico* study, it was reported to have moderate binding energy on corona virus.[80] Mechanisms of antiviral action of apigenin include reducing the expression levels of mature MicroRNA122 (miR122) through inhibition of TAR RNA-binding protein (TRBP) phosphorylation,[74] blocking EV71 RNA association with hnRNP A1 and A2 proteins,[73] and inhibition of viral internal ribosome entry site driven translation.[75] *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*.[81,82] Baicalin is associated with several pharmacological activities including antioxidant, antihypertensive, antifungal and anticancer effects.[83] It is also found to be effective in treating cerebral ischemia.[84] The antiviral activity against dengue virus (DENV),[85] influenza virus,[86] HIV-1,[87,88] enterovirus 71 (EV71),[89] chikungunya virus (CHIKV),[90] and SARS-CoV[91] is well established. Liu *et al*., (2008)[92] 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 fRhK4 cell line and against the prototype strains (39849) of SARS-CoV in fRhK4 and Vero-E6 cell lines revealed that it was active. It was also active in the plaque reduction assay with an EC_{50} value of 11 μg/mL.[91] 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.[93]

Betulinic acid

Betulinic acid **(7)** is a triterpenoid found in several plants such as *Betula pubescens*.[94] It has anticancer,[95,96] antimalarial[97] and anti-inflammatory activities.[98] The antiviral efficacy against HIV-1,[99] herpes simplex type I, influenza FPV/Rostock and ECHO 6 viruses,[100] *Herpes simplex* virus[101] have been reported. Several derivatives of betulinic 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.[99] Synthetic derivatives containing nicotinoyl-, methoxycynnamoyl-, alkyne 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*β*,28-di-*O*-nicotinoylbetulin against human papillomavirus type 11 while the 3*β*,28-Dihydroxy-29-norlup-20(30)-yne derivative was active against HCV replicon and the 28-*O*-Methoxycynnamoylbetulin derivative was active against influenza type A virus.[102] 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 *Castanospermum austral*.[103] It is known to inhibits *β*-glucosidase and *β*-glucocerebrosidase.[104] The antiviral effect of castanospermine has been documented against HIV,[105] dengue virus,[106] and influenza.[107] 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 gpl6O, with resultant decreased cell surface expression of the mature envelope glycoprotein gpl20. Also, castanospermine caused defects in steps involved in membrane fusion after binding of CD4 antigen.[105] 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.[106] Several synthetic derivatives with antiviral effect are available.[108] This makes it easier to develop new therapeutics that can inhibit the processing of envelope precursor protein gpl6O 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*.[109] It has been reported as an immunosuppressive,[110] hepatoprotective[111] and *α*-glucosidase inhibitor.[112,113] The compound has satisfactory activity against several viruses including herpes simplex virus,[114] Human enterovirus 71,[115] HIV,[116] and Influenza.[117] 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.[114] Its broad spectrum of activity was demonstrated against human cytomegalovirus (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.[118] Chebulagic ($IC_{50} = 1.41 \pm 0.51$ μg/mL) and chebulinic acids ($IC_{50} = 0.06 \pm 0.002$ 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.[119] Against influenza A virus, chebulagic acid and chebulinic acid inhibited viral replication through inhibiting neuraminidase-mediated viral release.[117] Basically, this compound's broad antiviral 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 ellipsosporium*.[120] It is an elongated, largely *β*-sheet protein that displays internal two-fold pseudosymmetry.[121] Multiple antiviral activities have been associated with this compound. Cyanovirin-N inactivated different HIV-1 strains and other lentiviruses due to its irreversible binding to the viral envelope glycoprotein gp120.[122] Tsai *et al*.,[123] 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.[124] 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 *Hypocladium inflatum gams.*[128] It is known for its immunosuppressant,[129] antimicrobial,[130] anti-psoriasis[131] 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. 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 against 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 virus, 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 human coronavirus HCoV-NL63 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.*[147] The compound has anti-fungal,[148] bactericidal[149] and weak antimalarial[150] properties. It has been reported to reduce measles virus entry considerably suggesting its interaction with viral particles to reduce infectivity.[146] Some synthetic Bis-Naphthoquinones have also been reported effective against Zika virus[151] and HSV-1[152] 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.*[153] The anti-edematous, anti-inflammatory and venotonic properties of *β*-escin have been linked to induction of cholesterol synthesis followed by decreased actin cytoskeleton integrity 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.[154] It also has anticancer activity through intrinsic-mitochondrial apoptosis pathway by arresting G2/M and ROS generation.[155] The antiviral activity of escin has been reported against porcine epidemic diarrhea virus (PEDV),[156] HIV-1[157] and SARS-CoV.[158] Strong cytotoxicity of escins create a challenge for their drug development.[159] However, SAR studies have shown that acylations at C-21 and C-22 with angeloyl or tigloyl groups were important for their cytotoxic effects.[156] Thus, escin derivatives with strong antiviral activities have been reported.[156] 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.*[160] It has been implicated in the treatment of menopausal vasomotor symptoms,[161] cancer,[162] and memory loss[163] 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 virus[169] 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 dehydroellagitannin 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 (HBeAg) 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 liqorice (*Glycyrrhiza glabra, Glycyrrhiza inflata* and *G. uralensis*,) root.[176] It is reported to have several biological activities including antiviral against varicella-zoster virus (VZV),[177] human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 1 (HSV-1),[178] Hepatitis virus (HCV)[179] and coronavirus[180,181] among others. Glycyrrhizin (**11**) is known to affect many cellular signaling pathways[182-184] 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.[185] 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.[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 reaction of NO with 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 response[189] thus acting as host response modulator rather than a simple antiviral agent.[188] Glycyrrhizin is an already approved drug for clinical use as an intravenous medication and it is commercially available.[190] 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.*[191] It has anti-inflammatory[192] and anticancer[193] 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.[194] 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 callicivirus. 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.[195] 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.[196] 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.

Hirsutenone

Hirsutenone (**13**) is a diarylheptanoids obtained from the stem bark of *Alnus japonica*.[197] It has been reported for its anticancer,[198] anti-dermatitis[199] and regulation of osteoclastogenesis.[200] It was found active against SARS-CoV by inhibiting papain-like protease of SARS-CoV.[196] Diarylheptanoids are a broad class of plant structurally divergent phenolics with diverse therapeutic applications.[201] Park *et al*.[197] 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 3CLpro also showed that Hirsutenone had good selectivity towards the coronaviral proteases. Thus, Hirsutenone can be a potential drug target for the treatment of SARS disease.

Juglanin

Juglanin **(14)** is a flavonol isolated from *Juglans mandshurica*[202] and has also been identified in *Polygonum acviculare.*[203] It has been reported to possess anti-inflammatory[204] and anticancer[205] 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. Juglanin (**14**) was effective with an IC_{50} value of 2.3 μM for inhibition of the 3a-mediated current.[206] In an *in silico* experiment against influenza virus, it was shown to have binding specificities to hemagglutinin (H7) and neuraminidase (N9).[207] 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.*[208] Labyrinthopeptin A1 showed broad anti-HIV activity and anti-HSV (herpes simplex virus) activity. It 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.[209] 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, and herpes simplex virus with mechanism of action showing that it induced virolytic effect through binding to the viral membrane lipid phosphatidylethanolamine (PE).[210] Several derivatives are currently available for treating different viral infections,[211] 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.[43] Lectins are known inhibitors of glycosylated viruses like HIV-type 1, cytomegalovirus and human T-cell leukemia virus.[212-214] *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.[215-218] 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,[219] anticancer[220] and anti-inflammatory[221] activities, among others. The antiviral effect against HBV[222] and Herpes virus HSV-2[77] has also been documented. In HepG2.2.15 cells, luteolin inhibited the expression of hepatocyte nuclear factor 4α (HNF4α) and its binding to the HBV promoters and in a HBV replication mouse model, it decreased the levels of HBsAg, HBeAg, HBV DNA replication intermediates, and the HBsAg and HBcAg expression.[222] In a time-of-addition assay, it was shown to interfere with viral replication at the early stage of infection as well as suppressed coat protein I complex expression.[223] Against Japanese encephalitis virus (JEV), luteolin inhibited viral replication in A549 cells with IC_{50} = 4.56 μg/mL and had extracellular virucidal activity on JEV.[224] Luteolin (**15**) inhibited dengue fever virus replication of all four serotypes. It reduced infectious virus particle formation, but not viral RNA synthesis in Huh-7 cells. It also prevented virion maturation process by inhibiting the protease furin responsible for cleaving the pr moiety from prM protein of immature virus particles in the *trans*-Golgi network in the process of producing mature virions.[225] Through a two-step screening platform consisting of reporter virus-based assays and cell viability-based assays, luteolin was shown to exhibit potent inhibition of viral infection against enterovirus 71 and coxsackie virus A16. In the same study, cell viability assay and plaque reduction assay showed that it had an EC_{50} values of about 10 μM. The mechanism of action was described as targeting the post-attachment stage of EV71 and CA16 infection by inhibiting viral RNA replication.[226] In another study, luteolin was reported to profoundly reduce HIV-1 infection in reporter cells and primary lymphocytes 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.[227] 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 reduced virion production.[228] The study concluded that luteolin inhibited EBV reactivation by repressing the promoter activities of Zta (Zp) and Rta (Rp) genes.[228] 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.[229] Mucroporin-M1 has been evaluated for a variety of activities including antibacterial effect.[229] 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 H5N1 viruses were reported with an EC_{50} of 7.15 μg/mL (3.52 μM) and a CC_{50} of 70.46 μg/mL (34.70 μM) against measles virus, an EC_{50} of 14.46 μg/mL (7.12 μM) against SARS-CoV and an EC_{50} of 2.10 μg/mL (1.03 μM) against H5N1 and the mechanism of action proposed to be inhibition of virus infectivity.[230] Using both *in vitro* and *in vivo* studies, Zhao *et al*.[231] established that mucroporin-M1 inhibited hepatitis B virus replication by activating the mitogen-activated protein kinase (MAPK) pathway and down-regulating HNF4α. 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.

Mycophenolic acid

Mycophenolic 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.[232] It is known as an immunosuppressant[233] and is an FDA approved immunosuppressive drug. It also has anti-fungal[234] and antitumor[235] effects. The antiviral effect against some unrelated viruses was reported by Planterose (1969).[236] Its inhibitory effect on Dengue virus was attributed to its ability to prevent the synthesis and accumulation of viral RNA.[237] Smee *et al*.[238] reported its effect against orthopoxviruses. It inhibited hepatitis E virus (HEV) replication through nucleotide depletion.[239] It also inhibited HIV replication by depleting the substrate (guanosine nucleotides) for reverse transcriptase and depletion of the pool of activated CD4+ T lymphocytes.[240] Hepatitis C virus (HCV) replication was shown to be inhibited by mycophenolic acid at 1.0–6.0 μg/mL to approximately 75% through a mechanism independent of guanosine depletion.[241] Mycophenolic acid (**16**) significantly inhibited Japanese encephalitis virus both *in vitro* and *in vivo*,[242] and Avian reoviruses (ARV).[243] Mycophenolic acid inhibited papain-like protease (PLpro) of MERS-CoV.[244]

Niranthin

Niranthin (**17**) is a lignan isolated from plants of the genus *Phyllanthus* like *P. niruri* and *P. amarus*. It has been reported with anti-inflammatory activity.[245] Initial screening revealed that it had anti-hepatitis activity.[246] 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 (HBeAg) with IC_{50} values of 15.6 μM for HBsAg and IC_{50} values of 25.1 μM for HBeAg. It also reduced the serum duck hepatitis B virus (DHBV) DNA, HBsAg, HBeAg, ALT and AST *in vivo*[247] suggesting that niranthin (**17**) acts as an anti-HBV agent through at least two or more targets. Anti-virucidal evaluation against the white spot syndrome virus showed it inactivated the virus.[248] It is thus a potential inhibitor that can be evaluated against SARS-CoV antigen.

Podophyllotoxin

Podophyllotoxin (**18**) is an aryltetralin-type lignan obtained from the resin of *Podophyllum peltatum* L. or *P. emodi*.[249] It has several activities including insecticidal[250] and anticancer[251] activities. Antiviral evaluation on herpes simplex virus type I (HSV/CV-1) and vesicular stomatitis virus infecting fibroblasts of hamster kidney (VSVDHK) showed activity at concentration below 1 μM.[252] Several analogues also showed against herpes simplex virus type II.[253] Chen *et al*.[254] also reported the anti-HIV effect of podophyllotoxin derivatives. Podophyllotoxin and its derivatives could be exploited 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 protective,[255] hypoglycemic,[256] antioxidant[257] and antidiabetic[258] effects. Different flavonoids including quercetin (**19**) were tested for their effect on infectivity and replication of herpes simplex virus type 1 (HSV-I), polio-virus type 1, parainfluenza virus type 3 (Pf-3), and respiratory syncytial virus (RSV). Quercetin (**19**) caused a dose-dependent reduction in the infectivity and intracellular replication of each virus.[259] It also, inhibited HIV-infection by preventing binding of gp120 to CD4.[260] Again, the 4′-OH, 7-OH, C4 keto, and C2-C3 double bond group of flavonoids [91] 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.

Reserpine

Reserpine (**20**) is an indole alkaloid obtained from the roots of *Rauwolfia serpentine* and *Rauwolfia vomitoria*. The compound has anti-arrhythmic,[261] antibacterial,[262] anti-parkinson,[263] anticancer[264] and anti-hypertensive[265] activities, among others. It is an approved drug for the management of high blood pressure and has been reported active against SARS-CoVs.[158] It inhibited viral replication with IC_{50} of 3.4 μM. Six other compounds related to reserpine were also shown to have activities toward SARS-CoV at <100 μM.[158]

Yatein

Yatein, (**21**) a lignan was isolated from *Chamaecyparis obtusa* and tested for it activity against herpes simplex 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.[266] 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.[267] Yatein is a dibenzylbutyrolactone that inhibited HSV-1 alpha gene expression by arresting HSV-1 DNA synthesis and structural protein expression in HeLa cells.[268] This compound and it derivatives can be assessed for effectiveness against coronaviruses.

Others

Other natural products with reported antiviral activity include sorbifolin (**22**) and pedalitin (**23**), two flavonoids from *Pterogyne nitens* proven effective against Hepatitis C virus (HCV).[269] Herbacetin (**24**), rhoifolin and pectolinarin blocked the enzymatic activity of SARS-CoV 3CLpro.[270] Herbacetin, isobavachalcone (**25**), quercetin 3-*β*-d-glucoside, and helichrysetin (**26**) blocked the enzymatic activity of MERS-CoV/3CLpro.[271] Robustaflavone (**27**) inhibited influenza A and influenza B viruses with EC_{50} values of 2.0 μg/mL and 0.2 μg/mL, respectively.[71] Ferruginol, dehydroabieta-7-one, sugiol, 8*β*-hydroxyabieta-9(11),13-dien-12-one, 6,7-dehydroroyleanone, pinusolidic acid, *α*-cadinol, hinokinin, and savinin purified from the ethyl acetate extracts of *Chamaecyparis obtuse*, 3*β*,12-diacetoxyabieta-6,8,11,13-tetraene, cedrane-3*β*,12-diol, and betulonic acid isolated from the ethyl acetate extracts of *Juniperus formosana* along with cryptojaponol and 7*β*-hydroxydeoxycryptojaponol isolated from *Cryptomeria japonica* were evaluated for activity against SARS-CoV. All the compounds inhibited SAR-CoV at concentrations between 3.3 and 10 μM.[272] Gomisin M_1 is a ligand from *Schisandra rubriflora* that had potent anti-HIV activity with EC_{50} value of <0.65 μM.[273] Rubrifloralignan A, from the fruits of *Schisandra rebriflora* is an anti-HIV-1 product with effect on early stage of HIV-1 replication.[274] 1*α*-hydroxybrussonol, a diterpinoid from *Perovskia atriplicifolia* suppressed the replication of hepatitis B virus DNA with selectivity index of 137.7.[275] The anti-influenza virus activity of six stilbenoids from *Gnetum pendulum* showed that isorhapontigenin, gnetupendin B, shegansu B, and gnetin D had significant anti-influenza virus activity in MDCK cells, with IC_{50} values ranging from 0.67 to 11.99 μg/mL when compared to the positive controls oseltamivir and ribavirin with IC_{50} values of 0.040 and 5.54 μg/mL, respectively.[276] Tellimagrandin I, a tannin from *Cornus canadensis* was found effective against herpes simplex virus type 1 (HSV-1) with an EC_{50} 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.[275-283]

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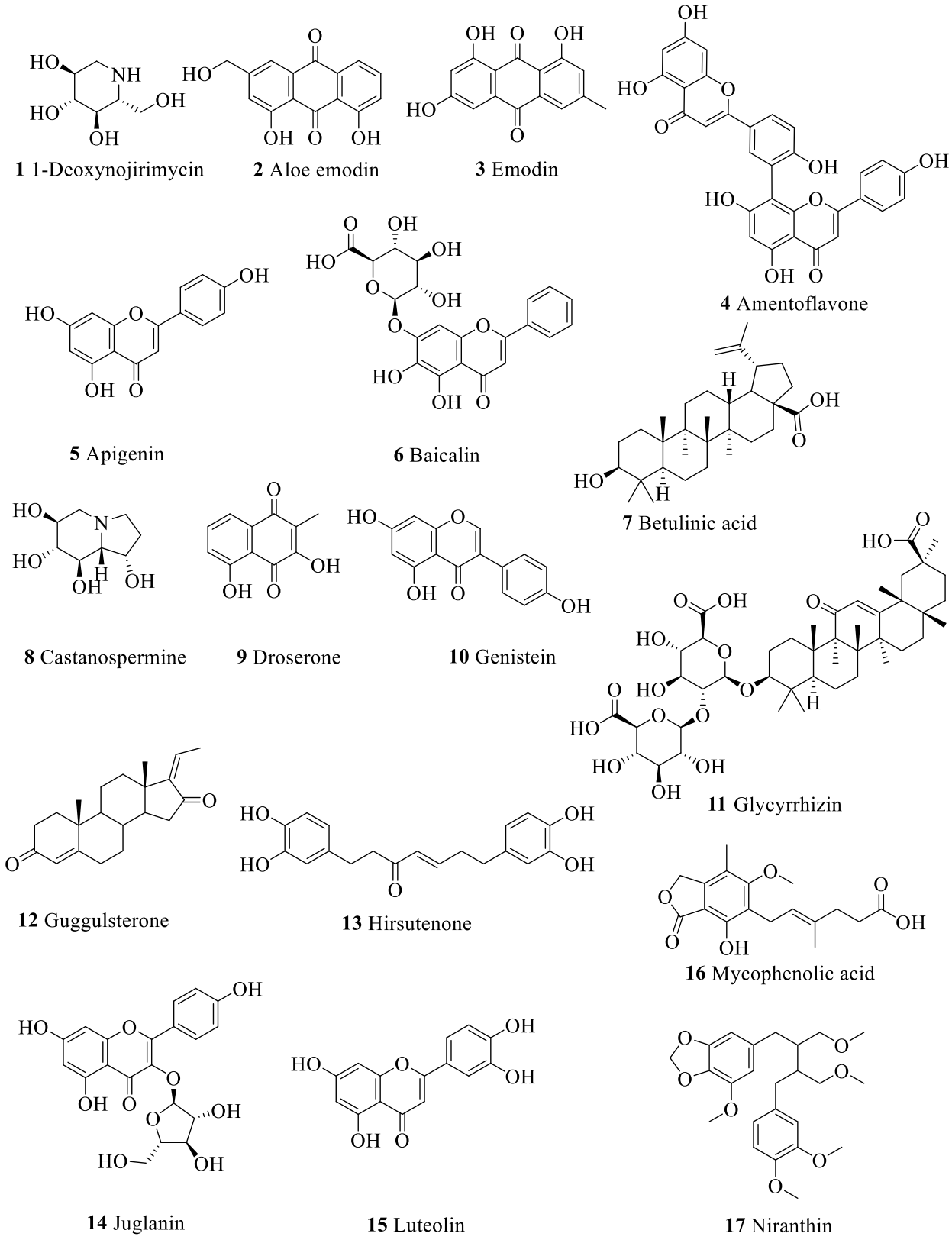

Figure 3: Chemical structures of some promising lead compounds

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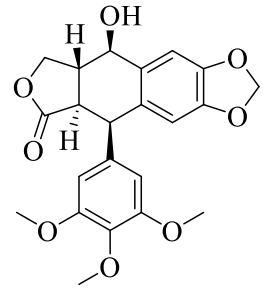
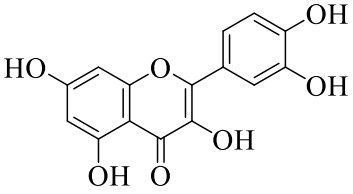


18 Podophyllotoxin



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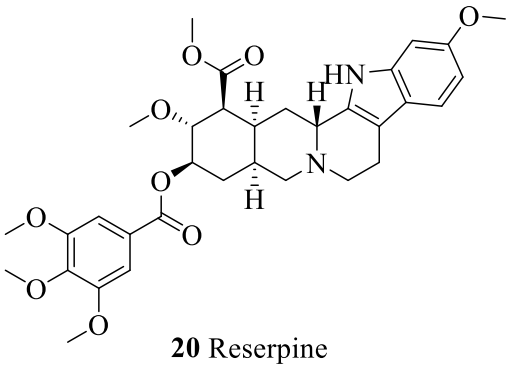
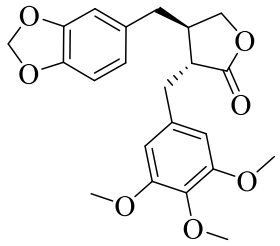
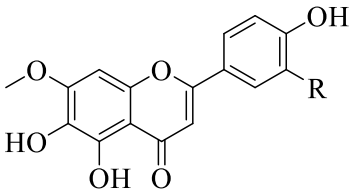


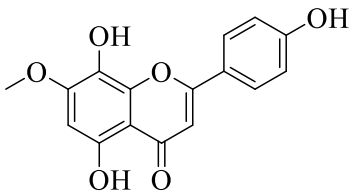
20 Reserpine



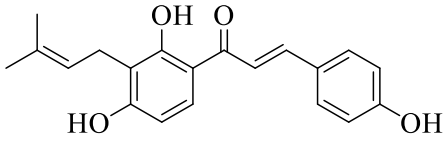
21 Yatein



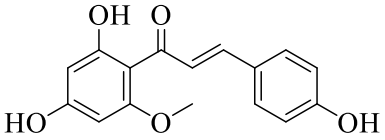
22 R=H Sorbifolin
23 R=OH Padalitin



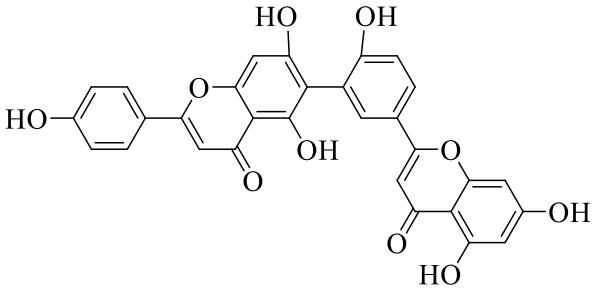
24 Herbacetin



25 Isobavachalcone



26 Helichrysetin



27 Robustaflavone

Figure 3 Cont'd: Chemical structures of some promising lead compounds

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Table 1: Selected natural compounds and their antiviral mechanisms of action

Compounds	Class	Source	Virus	Mechanisms of action	Dose/IC_{50}	References
1-Deoxynojirimycin	Alkaloid	*Commelina communis*	Hepatitis	Inhibited glycosylation of viral envelope proteins	9.92 µM.	55
Aloe-emodin	Anthraquinone	*Aloe vera*	Influenza A virus	Up-regulated galectin-3 and thioredoxin	0.05 µg/mL	64
			Enterovirus 71 (EV71)	Induced interferon (IFN)	0.14 µg/mL to 0.52 µg/mL	65
			Japanese encephalitis virus (JEV)	Induced interferon (IFN)	0.50 µg/mL to 1.51 µg/mL	65
Amentoflavone	Biflavone	*Torreya nucifera*	SARS-CoV	$3CL^{pro}$ inhibition	8.3 µM	66
			Herpes viruses (HSV-1, HSV-2)		17.9 and 48.0 mg/mL	71
			Human immunodeficiency virus (HIV)	Inhibited HIV-1 RT	119 µM	68
			Respiratory syncytial virus (RSV)		5.5 µg/mL	69
			Dengue virus	Inhibited dengue virus NS5 RNA-dependent RNA polymerase	1.3 µM	70
Apigenin	Flavonoids	*Arisaema tortuosum*	Herpes virus HSV-2	Inhibited both early and late events of the HSV-2 replication	0.05 µg/mL	77
			African swine fever virus (ASFV)	Inhibited ASFV-specific protein synthesis and viral factory formation		76
			Hepatitis C virus (HCV)	Inhibited maturation of miRNAs and HCV replication Decreased the expression levels of mature miR122		74
			Foot-and-mouth disease virus(FMD)	Inhibited FMDV-mediated cytopathogenic effect and FMDV replication	8.593 µg/mL	75
			Enterovirus-71 (EV71)	Disrupted viral RNA association with hnRNP A1 and A2 proteins	10.3 µM	73
Baicalin	Flavone glycoside	*Scutellaria baicalensis*	Dengue virus (DENV)	Inhibited virus replication, extracellular particles and showed anti-adsorption effect	13.5 ± 0.08, 8.74 ± 0.08 and 18.07 ± 0.2 µg/mL respectively	85
			Influenza virus	Inhibited neuraminidases	43.3 µg/mL	86

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			HIV-1	Inhibited both T cell tropic (X4) and monocyte tropic (R5) HIV-1 Env protein mediated fusion Inhibited the activity of HIV-1 reverse transcriptase	0.5 μg/mL	87,88
			Enterovirus 71 (EV71)	Inhibited EV71/3D polymerase expression and Fas/FasL signaling pathways	4.96 µg/mL	89
			Chikungunya virus (CHIKV)	Inhibited viral entry, viral particle attachment, and replicase complexes formation	7 µM,	90
			SARS-CoV		12.5 to 25 µg/mL	91
Betulinic acid	Triterpenoid	*Betula pubescens*	*Herpes simplex* virus	Reduced viral cytopathic effect	30 µg/mL	101
			HIV-1	Inhibited HIV fusion and interfere with a specific step in HIV-1 maturation		99
Castanospermine	Alkaloid	*Castanospermum austral*	HIV	Modified glycoprotein		105
			Dengue virus	Inhibited infectivity of viral particles		107
			Influenza	Inhibited glucosidase 1		107
			Influenza	Inhibited glycoprotein		56
			HIV	Inhibited virus entry at the Env/coreceptor interaction step		57
Chebulagic acid	Tannin	*Terminalia chebula*	Herpes simplex virus	Inactivated HSV-1 viral particles	17.02±2.82 µM	114
			Human enterovirus 71	Inhibition of viral replication	12.5 µg/mL	115
			HIV	Inhibited HIV reverse transcriptase		116
			Influenza	Inhibited neuraminidase		117
Cyanovirin-N	Protein	*Nostoc ellipsosporium*	HIV-1	Blocked binding of gp120 to cell-associated CD4		122
			Hepatitis C	Binds to viral envelope glycoproteins and blocked the interaction between the envelope protein E2 and CD81	1.6 ± 0.1 nM	125
			Influenza	Bound viral hemagglutinin	0.004 to 0.04 µg/mL	126
			Ebola virus	Binds to the viral surface glycoprotein		127

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Cyclosporine A	Peptide	*Hypocladium inflatum gams*	HIV-1	Disrupted Gag–cyclophilin A interaction		133
			HIV-1	Blocked incorporation of HIV-1 envelope glycoprotein into virions		134
			Hepatitis C virus (HCV)	Cleavage at NS2/NS3 junction	0.15 g/mL	137
			Hepatitis B	Inhibited viral replication by blocking cytosolic calcium signaling		138
			Influenza virus	Inhibited the replication through CypA-dependent pathway		139
			Coronavirus HCoV-NL63	Knockdown of cellular Cyclophilin A (CypA/PPIA) gene	0.9-2.0 μM	140
Droserone	Naphthoquinone	*Drosera whittakeri*	Measles virus	Reduced viral entry	2μM	146
Emodin	Anthraquinone	*Rheum Palmatum*	SARS-CoV	Inhibited ACE2 interaction		59
			Herpes simplex virus (HSV)	Inhibited nuclease activity of HSV-1 UL12		62
Escin	Triterpene saponin	*Aesculus hippocastanum*	HIV-1	Anti-HIV-1 protease	35 μM	157
			Porcine epidemic diarrhea virus (PEDV)	Inhibited nucleocapsid protein synthesis and viral replication	20 μM	156
			SARS-CoV	Inhibited viral replication	6.0 μM	158
Galanthus nivalis agglutinin (GNA)	Lectins	*Galanthus nivalis*	Mouse hepatitis virus	Inhibition of viral fusion	50 mg/L	284
Genistein	Isoflavones	*Genista tinctoria*	African swine fever *virus*	Disrupted *viral* DNA synthesis		164
			Herpes B virus	Prevented plaque formation of Herpes B virus and reduced virus production	33 and 46 μM	165
Geraniin	Dehydroellagitannin	*Geranium carolinianum*	Hepatitis B virus (HBV)	Inhibited HBsAg and HBeAg		174
			HSV-1 and HSV-2	suppressed both HSV-1 and HSV-2	35.0 μM and18.4 μM	173
			HIV-1	Inhibited virus uptake and HIV-1 reverse transcriptase	0.24 μM	172
Glycyrrhizin	Triterpenoid saponin	*Glycyrrhiza glabra*	Varicella-zoster virus	Inhibited replication	0.71 mM	177

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			Hepatitis virus (HCV)	Suppressed of viral entry and replication, Inhibited the release of infectious HCV particles due to its inhibitory effect on phospholipase A2 group 1B (PLA2G1B)	16.5 µM	179
			Coronavirus	Inhibited virus adsorption, penetration and replication	300 mg/L	180
Gomisin M_1	Ligand	*Schisandra rubriflora*	HIV		<0.65 µM	273
Hippeastrum hybrid agglutinin (HHA)	Lectins	*Hippeastrum hybrid*		Inhibition of viral fusion	50 mg/L	284
Hirsutenone	Diarylheptanoids	*Alnus japonica*	SARS-CoV.	Inhibited papain-like protease of SARS-CoV.	4.1 µM	197
Juglanin	Flavonol	*Juglans mandshurica*	SARS coronavirus	Blocked 3a channel	2.3 µM	206
Labyrinthopeptin A1	Peptide	*Actinomadura namibiensis*	HIV	Inhibited viral cell-cell transmission	0.70–3.3 µM	209
			Herpes	Inhibited viral cell-cell transmission	0.29–2.8 µM	209
			Human respiratory syncytial virus (hRSV)	Inhibited cell entry		285
Luteolin	Flavonoids	*Arisaema tortuosum*	Herpes virus HSV-2	Inhibited both early and late events of the HSV-2 replication	0.41 µg/mL	77
			HBV	Reduced HBV DNA replication and inhibited hepatocyte nuclear factor 4α (HNF4α) expression		222
Mucroporin-M1	Peptide	*Lychas mucronatus*	Measles virus	Inhibited viral infectivity	3.52 µM	230
			SARS-CoV	Inhibited viral infectivity	7.12 µM	230
			Influenza A (H5N1)	Inhibited viral infectivity	1.03 µM	230
			Hepatitis B virus	Activated MAPK pathway and down-regulated HNF4α		231
Mycophenolic acid	Phthalides	*Penicillium stoloniferum Fungi*	Dengue virus	Prevented the synthesis and accumulation of viral RNA	0.3 µM	237
			Hepatitis E virus	Nucleotide depletion		239
			HIV	Depleted guanosine nucleotides		240
			Japanese encephalitis		3.1 g/ml	242
			MERS-CoV	Inhibited papain-like protease (PL^{pro})	222.5–	244

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Niranthin	Lignan	*Phyllanthus niruri*	Hepatitis B virus	Decreased the secretion of HBsAg and HBeAg	247.6 µM 15.6 µM and 25.1 µM	247
Quercetin	Flavonoid	Many plant species	Herpes simplex virus type 1 (HSV-I), polio-virus type 1, parainfluenza virus type 3 (Pf-3), and respiratory syncytial virus (RSV)	Reduced infectivity and intracellular replication		259
			HIV-1	inhibited HIV-infection by preventing binding of gp120 to CD4	20 µg/mL	260
Reserpine	Indole alkaloid	*Rauwolfia serpentine*	SARS-CoVs	Inhibited viral replication	3.4 µM	158
Rubrifloralignan A	Ligand	*Schisandra rebriflora*	HIV	Inhibited early stage of HIV-1 replication		274
Urtica dioica agglutinin (UDA)	Lectins	*Urtica dioica*		Inhibition of viral fusion	50 mg/L	284
Yatein,	Lignan	*Chamaecyparis obtuse*	Herpes simplex virus type 1 (HSV-1).	Inhibited HSV-1 α gene expression	30.6 ± 5.5 µM	266
			EV71	Viral inhibition	10 µg/mL	175

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.

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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