

# A narrative review of herbal preparations against RNA viruses

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## Abstract

**Objective** Although several therapeutics were designed to control infectious diseases, viral infections are still fatal. Currently, evidence extracted from *in vivo*, *in vitro*, and *in silico* studies support the antiviral activity of many herbs scientifically; however, the therapeutic potential of many other herbs is still unknown. Plants and their products may potentially control the propagation of viruses in a variety of conditions.

**Methods** Data were extracted from PubMed, Scopus, Google Scholar, and Science Direct from 1983 to 2020. We gathered a list of plant extracts, phytochemicals, and herbal formulations that can inhibit RNA viral infections, mainly those are originated from the coronaviruses family. We also provided an overview of their inhibitory mechanism of actions.

**Results** Plant families, including Lamiaceae, Asteraceae, and Myrtaceae, contain the highest number of species with anti-coronaviruses activities, respectively.

**Conclusions** It can be suggested that the combination of these antiviral ingredients with each other, any synthetic compound, or already approved drugs or inhibitors can be a novel approach for antiviral therapies.

**Keywords** viruses, coronaviruses, herbal extracts, phytochemicals, essential oils

## Introduction

Viruses are microscopic particles ranging in size from 30 to 300 nm, lacking typical cellular structures. They are not able to reproduce outside the living host cell and are more like a large chemical compound. For this reason, they are also called compulsive intracellular parasites. Viruses can infect hosts ranging from bacteria to animals, plants to humans.<sup>1-3</sup> Viruses rely on host cell surface receptors to enter the cell and employ host cellular machinery to replicate, assemble, and release new virus particles. Each virus has a specific mechanism to infect the host through the attachment of the virus to host cell membrane via binding of molecules of the outer surface of the virion to a receptor molecule on the host cell (protein or carbohydrate); penetration and uncoating of the virus and subsequent release of the virions into host cell; reverse transcription of viral RNA into DNA (i.e., Retroviruses); integration of the viral DNA into host cell genome; use of the cellular system for gene duplication and translation (i.e., human immunodeficiency virus (HIV)), or use of their system to produce mRNA coding for viral proteins (early genes); synthesis and assembly of nucleocapsids (late genes); release of the naked virions by cell lysis. Alternatively, viruses with envelopes can be released by a process known as budding, in which the nucleocapsid is wrapped by the membrane and pinched off<sup>4-8</sup> (Fig. 1).

As of now, viral infections are significant threats to human and animal health, imposing a tremendous economic burden. During the past two decades, the epidemic of Ebola virus, chikungunya virus, Zika virus, Yellow fever, the severe acute respiratory syndrome (SARS) virus and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), influenza,

Nipah and henipaviral diseases, and Lassa fever raised significant challenges for public health authorities all over the world, highlighting the emerge of strategies to predict, prevent, or control the pathogens geographic spread, and the human-to-human transmission.<sup>9</sup> In the 21st century, three members of the  $\beta$ -coronavirus genus caused deadly infections in humans. In 2002, the outbreak of SARS-CoV began in northern China and extended globally. After that, MERS-CoV spread out in the Middle East in 2012, and lately, SARS-CoV-2 (COVID-19) was reported on December 30, 2019, in Wuhan City, Hubei Province, China. SARS is an 80–160 nm single-stranded positive RNA virus surrounded by a coat containing the E2 virus binding protein, the E1 matrix protein, and the nucleocapsid N protein. To date, no proven effective therapeutics or vaccines exist for human coronaviruses infections.<sup>10</sup>

Current treatment options for coronavirus infections include medications such as Lopinavir/Ritonavir, Oseltamivir, Chloroquine, Hydroxychloroquine, Remdesivir, Favipiravir; nucleoside analogs; neuraminidase (NA) inhibitors; peptide (EK1); abidol; RNA synthesis inhibitors (such as TDF, 3TC); anti-inflammatory drugs (such as hormones and other molecules); angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; and Chinese traditional medicine such ShuFengJieDu Capsules and Lianhuaqingwen Capsule. A patent review study offered that proteases inhibitors (since proteases are essential for viruses replication), monoclonal antibodies, and interferons (INFs) are definite targets for coronavirus infection treatment. This study also concluded that traditional formulations containing natural compounds might help to improve symptoms of infection such as fever, cough, sore throat, and shortness of breath.<sup>11,12</sup> A recent

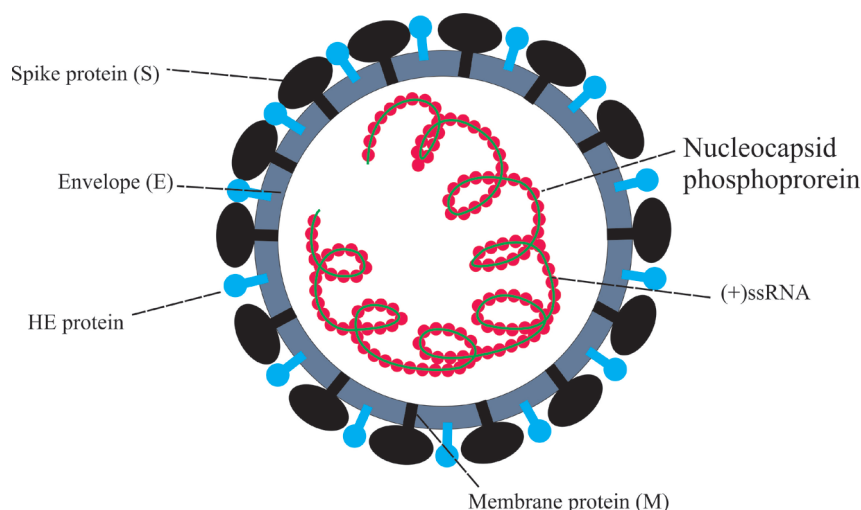


Fig. 1 A schematic model of a coronavirus.

study reported that some natural products such as lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, and 7-methoxycryptopleurine may possess potential antiviral activities at nanomolecular equivalent concentrations.<sup>13</sup> Natural isolates or extracts such as scutellarein, silvestrol, tryptanthrin, saikosaponin B2, lectins such as griffithsin, lycorine and polyphenolics including quercetin, myricetin, caffeic acid, psoralidin and isobavachalcone were also shown to be active against human coronaviruses.<sup>14</sup> Given the significance of natural products, particularly herbal preparations and phytochemicals, on viral infections, we tried to collect a list of plant species/bioactive components or antiviral herbal medicine formulations that are capable of combating viral infections in RNA viruses with emphasize on coronaviruses. We also provided a summary of different types of viruses and the family of coronaviruses.

## Methods

### Study design

Data were extracted from PubMed, Scopus, Google Scholar, and Science Direct, using the keywords “antiviral” OR “coronavirus” OR “RNA virus” OR “herbals” OR “plant species” OR “herbal preparation” OR “herbs” OR “herbal formulation” in the title/summary and the keywords “plant, herb, phytochemistry” in the whole text. The research results were included in the study, regardless of the time limitation. The final articles used in the current review were from 1983 to 2020. 32% of the references were from 2015 until 2020. Two persons independently evaluated studies and non-English and duplicates were excluded. We avoided studies on DNA viruses and focused on RNA viruses, specifically the coronavirus family. We also prioritized our work over studies that examined the antiviral mechanisms of plants and their derivatives.

### Data extraction

A summary of information including the name of plants, essential oil, phytochemical compounds, and herbal formulation, method of study such as *in vitro* or *in vivo*, the model used in the assay, dosage of treatment, and finally the results of the study are presented in two tables.

### Study selection and characteristics

Out of a total of 930 studies, 440 studies were deleted due to irrelevant title and abstract, 186 studies were excluded in repetitive, and 50 non-English studies were left out. In total, 22 studies remained to review the full text. A further 53 studies were discontinued due to the irrelevance of criteria in this study.

### Types of viruses

Viruses only reproduce within individual species. Therefore, to facilitate the study, they are divided into vertebrate viruses, invertebrate viruses, bacterial viruses (bacteriophage), and plant viruses, depending on the type of host. Virus families are classified by the *suffix-viridae*. Today, viruses are classified considering to three major characteristics: nature and structure of the genome, viral symmetry nucleocapsids (icosahedral or helical), and general morphology. Nevertheless, other features are also used to viral classification: size, physiochemical properties; mechanisms of gene expression and virus replication; serological relationships; host and tissue susceptibility; and pathology. Vertebrate viruses are often classified according to their genomic content (DNA or RNA) (Table 1), single- or double-stranded, and linear or annular.<sup>15,16</sup>

### Double-stranded DNA (dsDNA) viruses

There are many viruses with the dsDNA genome that infect mammals. They are divided into seven families: Hepadnaviridae, Polyomaviridae, Papillomaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Asfarviridae. With the exception of the Poxviridae and Asfarviridae families, all families have members that can cause persistent infection in humans or animals. Hepadenoviruses, polyomaviruses, papillomaviruses, and viral herpes are causally linked to human cancers. This suggests that dsDNA viruses have many ways of disrupting and influencing cell division. Many details of their reproduction cycle indicate that they evolved from retroviruses.<sup>17</sup> Genomic content of these viruses enter the host cell nucleus and mimics the genome of the host cell. Typically, the viral genome is replicated from the host cell using a DNA polymerase, and the viral genome is transcribed from the host cell by RNA polymerase. The resulting transcripts are then

Table 1. **Types of viruses, examples and their typical properties.**

Virus type	Example	Properties
DNA viruses	Poxviruses, Herpes, Adenoviruses, Papillomaviruses	Contain mostly double-stranded DNA, a small number single-stranded DNA. DNA viruses enter the cell nucleus and direct the generation of new viruses
RNA viruses	Influenza, Measles, Mumps, Cold, Meningitis, Poliomyelitis, Retroviruses (AIDS, T-cell leukemia), Arenaviruses, Coronaviruses	Contain largely ssRNA. RNA viruses do not enter the cell nucleus (except the influenza virus). RNA retroviruses use the viral reverse transcriptase to make a DNA copy of the viral RNA, which is then integrated into the host genome

ssRNA, single-stranded RNA.

transported to the cytoplasm and are replicated by the host cell ribosomes. Several replicated viral DNA molecules are converted to virions. Virions contain an entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid. Virions use the machinery of host cells to complete their life cycle and target other host cells, initiating new infection cycles.<sup>18</sup>

### Single-stranded DNA (ssDNA) viruses

This type of virus is often identified by the presence of two genes; a gene for viral nucleocapsid protein and another gene as a DNA replication enzyme. Once these viruses enter the cells, viral ssDNA converts to dsDNA using host cell DNA polymerase using the 3' end of viral DNA as the base template for transcription, resulting in the production of viral proteins. Then replicated viral DNA is reconverted into an ssDNA genome, which later might form virions. Parvoviruses in dogs and cats belong to the ssDNA virus family.<sup>19-22</sup>

### (+) Single-stranded RNA or (+) ssRNAs viruses

This class is by far the largest group of viruses (i.e., many common cold viruses and the poliovirus) and consequently has considerable variety in terms of size, structure, organization, and observed replication strategy. ssRNAs are also known as picornaviruses because they have small RNA genomes. The ssRNA genome can act as an mRNA molecule, thus called "+". However, there are several common theme in genome organization, particularly unsegmented and single open reading frame (ORF) genomes, where the proteolytic lysis of a long "polyprotein" leads to mature gene products. Non-segmented genomes with multiple ORFs require two rounds of translation or subgenomic mRNA to express structural and non-structural proteins. According to this situation, there are multi-part genomes, each component has a single ORF. The virus genome in this class range in size from 5 kb (i.e., leviviruses) to 30 kb (i.e., coronaviruses).<sup>23</sup>

### (-) Single-stranded RNA or (-) ssRNAviruses

The negative-strand RNA viruses are a broad group of animal viruses that comprise several important human pathogens, including influenza, measles, mumps, rabies, respiratory syncytial, Ebola, and hantaviruses. All these viruses are enveloped viruses whose genomes is consisted of either one (in paramyxoviruses, rhabdoviruses, filoviruses, and Bornadisease virus) or several (in orthomyxoviruses, bunyaviruses and arenaviruses) RNA segments. The virus carries its RNA-dependent RNA polymerase, which is responsible for the transcription and replication of the viral genome in the infected cell.<sup>24, 25</sup>

### Double-stranded RNA (dsRNA) viruses

Double-stranded RNA (dsRNA) molecules belong to a limited group of viruses such as Reoviruses with 10 different dsRNAs in their genomes.<sup>26</sup> These viruses also contain the RNA replicase enzyme as a part of the virus structure. This enzyme transcribes positive RNA strands and helps the virus to complete the steps of its replication cycle alone, such as rotaviruses.<sup>27, 28</sup>

### (+) ssRNA retroviruses

The retroviruses encompass a large family of infectious agents (Retroviridae) unified by a typical virion structure and mode of replication. Retroviruses genomes may serve as mRNA, consisting of a dimer of identical single-stranded RNA molecules, each 7–10 kb in length. Viruses with genomes higher than 8 kb are those that have other genes in addition to *Gag*, *Pol*, and *Env*. They use an enzyme called reverse transcriptase, giving them the unique property of transcribing their RNA into DNA after entering a cell. Once the virus enters the cell, instead of the RNA (+) strand, the virion RNA is used as a template to create a DNA copy of the viral genome through a viral enzyme called reverse transcriptase. This viral DNA becomes integrated into the host-cell DNA. Such viral DNA is called a "provirus", identical to the genes of host cells. This integrated provirus is transcribed into RNA (+) and is transported to the cytoplasm to be utilized for the synthesis of viral proteins, or as a genome for new viruses. Retroviruses are in effect retrograde because the flow of genetic information is reversed compared with the normal pathway of molecular biosynthesis: DNA to RNA and then to protein. These viruses are referred to as Human Endogenous Retroviruses or HERVs. HIV is a retrovirus and a member of the lentivirus.<sup>29, 30</sup>

Approaches to counter virus infection should be adjusted according to the specific viral characteristics. To this end, today's medicines hit targets that minimize the risk of disease by disrupting the vital functions of the virus. Table 2 provides a summary of current medications with their mechanism of action for viral infections. There are several therapeutic targets for these drugs, which are also used to design new drugs. Considering the side effects of chemical drugs, the search for new drugs with similar properties and fewer side effects could fix a significant part of the health problems area.

### Coronaviruses; structure, genome, and lifecycle

The family Coronaviridae includes the genus *Coronavirus* and *Torovirus*. Coronaviruses belong to the family Coronaviridae, suborder Cornidovirineae, order Nidovirales, and realm Riboviria. Coronaviruses are large enveloped positive-sense, ssRNA viruses of vertebrates by importance in medical and veterinary diseases.<sup>31</sup> The same other RNA viruses,

coronaviruses are highly mutant. However, the mutation rate might be somewhat lower than other RNA viruses because of its genome-encoded exonuclease, enabling the viruses to become more virulent and to extend more efficiently through different hosts.<sup>32</sup> Coronaviruses are likely to have a seasonal distribution and may cause asymptomatic as well as lower and upper respiratory tract infections.<sup>33</sup> It has been reported that human coronaviruses can infect neurons since viral RNA has been detected in the brain of patients with multiple sclerosis.<sup>34</sup> Interest in this family of viruses has increased in recent years due to the identification of a newly emerging coronavirus as the causative agent of SARS and MERS.<sup>35, 36</sup> Until the appearance of SARS in 2003, only four human low-pathogenic; HCoV-OC43, HCoVHKU1, HCoV-NL63, and HCoV-229E, were recognized, of which types 229E and OC43 constitute a significant cause of the common cold and therefore were not high precedence for centralized research.<sup>37-39</sup> Coronaviruses contain three significant proteins in their structure: the very large (200 K) glycoprotein S (spike) is the major inducer of neutralizing antibody, which forms the large (15–20 nm) peplomers in the virus envelope; an unusual transmembrane

protein (M); and an internal phosphorylated nucleocapsid protein (N). Moreover, there is a tiny transmembrane protein E, and some coronaviruses contain another coat protein with hemagglutination and esterase (HE) functions.<sup>40, 41</sup>

Their 30-kb (+) ssRNA is the largest known RNA virus genome with G+C contents varying from 32% to 43%.<sup>42</sup> The viral genome contains distinctive features, including a unique N-terminal fragment within the spike protein. SARS-CoV-2 binds to ACE2 (the angiotensin 2 converting enzyme) via its S protein and enables the virus to penetrate and infect cells. To complete the virus entrance into the cells, the S protein must be enzymatically prepared by a protease, for example, protease TMPRSS2 in the case of SARS-CoV and SARS-CoV-2. TMPRSS2 facilitates the linkage of the virus receptor (S protein) to its cellular ligand (ACE2)<sup>43, 44</sup> (Fig. 1). Since the S glycoprotein is surface-exposed and mediates the virus entry into host cells, also, the ACE2 could mediate SARS-CoV-2 S-mediated entry into cells, they both are the main targets of ongoing vaccine and therapeutic design efforts and for neutralizing polyclonal antibodies upon infection.<sup>45</sup> Within the host cell, the virus undergoes uncoating, and then the genome

Table 2. Antiviral mechanisms of compounds as therapeutic targets in medical applications.

Antiviral mechanism	Target virus (es)	Compounds approved	Selected compounds in development for the indicated target virus	Reference
<b>Virus adsorption inhibitors</b>	HIV, Herpesviruses (HSV), CMV, RSV, and other enveloped viruses	-	Polysulphates, polysulphonates, polycarboxylates, polyoxometalates, chicoric acid, zintevir, cosalane derivatives, negatively charged albumins	51-55
<b>Viral DNA polymerase inhibitors</b>	HSV-1 & -2, VZV, CMV, EBV, HHV-6, -7, -8	Acyclovir, valaciclovir, ganciclovir, valganciclovir, penciclovir, famciclovir, brivudin, foscarnet	Bicyclic furopyrimidine nucleoside analogues, A5021, cyclohexenylguanine	56-58
<b>Reverse transcriptase</b>	HIV	NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir NNRTIs: nevirapine, delavirdine, efavirenz	Emtricitabine, amdoxovir Emvirine, UC781, DPC083, TMC125 (R165335)	59-63
<b>Virus-cell fusion inhibitors</b>	HIV, RSV, and other paramyxoviruses	-	HIV: AMD3100, TAK779 and T20 derivatives	64-66
<b>Acyclic nucleoside phosphonates</b>	DNA viruses (polyoma, papilloma-, herpes-, adeno- and poxviruses), HIV, HBV	CMV: cidofovir HIV: tenofovir	HBV: adefovir	67-69
<b>Viral protease inhibitors</b>	HIV, herpesviruses, rhinoviruses, HCV	HIV: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir	HIV: atazanavir, mozenavir, tipranavir Human rhinovirus: AG7088	70-74
<b>Inhibitors of processes associated with viral RNA synthesis</b>	HIV, HCV	-	-	75
<b>Viral neuraminidase inhibitors</b>	Influenza A and B virus	Zanamivir, oseltamivir	RWJ270201	76-79
<b>IMP dehydrogenase inhibitors</b>	HCV, RSV	Ribavirin	Mycophenolic acid, EICAR, VX497	80-82
<b>S-adenosylhomocysteine hydrolase</b>	(-) RNA hemorrhagic fever viruses (for example, Ebola)	-	-	83, 84

is transcribed and translated. As mentioned earlier, the positive-stranded viral RNA serves as mRNA for the translation of the two large ORFs (ORF 1a and 1b), each coding for the RNA polymerase units, depending on the RNA. Upon cleavage, these proteins convert to the active RNA polymerase, forming a full-length complementary RNA (negative sense). Cytoplasmic membranes are the site of coronavirus replication and transcription. These membranes modulate both continuous and discontinuous RNA synthesis through a viral replica, a large protein complex encoding the 20 kb replicase gene.<sup>46</sup> Based on the genome size, numerous genetic recombination can happen between different but related coronavirus genomes, which is a critical mechanism for the genetic diversity of coronaviruses in nature.<sup>47</sup> During maturation and assembly, protein S is co-translationally inserted into the rough endoplasmic reticulum (RER) and is glycosylated with N-linked glycans. Glycosylation is a crucial stage for protein S function and transportation. Protein S forms trimers before being exported from ER, and then interacts with proteins M and E to translocate to the site of virus assembly. SARS-CoV expresses another structural protein which is called 3a. This protein is associated with both the intracellular and plasma membranes, and can induce programmed cell death (apoptosis). Protein S is crucial for virus entry, but not for its assembly<sup>48-50</sup> (Fig. 2).

### Herbal preparations and antiviral mechanisms

Medicinal herbs, especially those used in folk medicine, have been highly regarded in the treatment of viral diseases because they contain bioactive substances that can be used to produce antiviral drugs with minimal side effects. Several secondary plant metabolites such as essential oils, flavonoids, saponins, tannins, alkaloids, lignans, terpenes, and phenolic acids shown significant antiviral activities against various viruses.<sup>85, 86</sup> Indeed, those elements that interfere with certain stages of viral biosynthesis, for example, the replication cycle, are the best for clinical antiviral approaches. Low concentrations and minimum effects on host cell machinery are the main privileges of these drugs, which ultimately leads to cure of infected

cells. On the other hand, virucidal drugs denature viral structural proteins or glycoproteins, which results in a total loss of the infectivity of the viral particles. The therapeutic approach, as well as herbal derivatives, could apply different strategies to inhibit virus function. It is known that both protein and lipid-protein of capsids must protect the nucleic acid inside the virus from the harmful substances, and facilitate the surface absorption of the virion into the host cell. The invasion of a cell by a viral particle always depends on its specific and close connection to one of the surface components of the host cell's plasma membrane.<sup>87</sup> Some plants use this mechanism to abolish the virus entry into the host cell by blocking their attachments to the cell surface.<sup>88</sup> Most RNA viruses propagate in the cytoplasm because they have all the enzymes needed for in their genome.<sup>89</sup> This step may be a therapeutic target for some herbal compounds due to their inhibitory effects.<sup>90</sup> The HIV protease enzyme is responsible for the proteolytic cleavage between gag and gag-pol precursor polypeptide, which in turn converts them into functional forms and ensures the viral maturation and infectivity. The HIV polymerase inhibitors show their activity at the end of virus replication and therefore interfere with active virus formation functionally.<sup>91, 92</sup> Many active plant compounds act as HIV protease inhibitors are shown in *in-vitro* assays.<sup>93</sup> Besides, the HIV integrase enzyme performs two main functions: the entry of pre-viral complexes into the nuclear pores and then the integration of the viral DNA genome into the host cell chromosome.<sup>94</sup> The effectiveness of some herbs in inhibiting this enzyme has reduced the proliferation of the HIV-1 virus.<sup>95</sup> Some phytochemicals have been studied, and results indicated their efficiency in integrase activity.<sup>96</sup> The influenza virus NA causes the release of the virus from the host cell surface by catalysis a breakdown in the silicic acid attached to glycoprotein and glycolipid.<sup>97, 98</sup> The inhibition of this enzyme can be considered as one of the therapeutic targets in medicinal plant studies.<sup>99</sup> It is well evidenced that many plants contain ribosome-inactivating proteins (RIPs) with N-glycosidase activity that can affect ribosomal function through depurination of large ribosomal rRNAs in infected cell and Inhibition of viral protein synthesis. RIPs

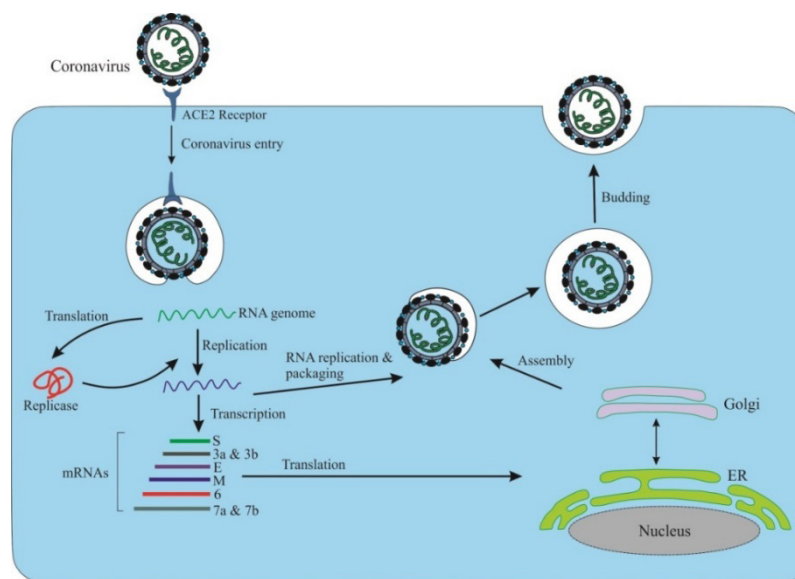


Fig. 2 A viral cycle of a coronavirus in the host cell.

can inhibit viral mRNA and DNA replication. Depurination is defined as inactivation of ribosomes by removal of a specific adenine from the sarcin/ricin (S/R) loop of the large rRNA, thereby inhibiting translation. To date, RIPs were shown effective against HIV, HBV, and HSV. For example, Trichosanthin (*Trichosanthes kirilowii*), PAP (*Pokeweed americana*), GAP31 (*Gelonium multiflorum*) and MAP30 (*Momordica charantia*) have been reported to inhibit HIV-1 replication *in vitro*.<sup>100, 101</sup> In following sections, we prepared a list of herbal preparations, essential oils, and phytochemicals that were able to inhibit the activity of the coronaviruses family.

### Herbal extracts

To date, numerous herbal preparations were investigated against various types of viruses. Table 3 represents plant species, and those were shown valid on coronaviruses.

#### *Morus* spp.

Antiviral properties of the leaves and the stem bark of the mulberry tree (*Morus* spp.) were evaluated in human coronavirus (HCoV 229E) in L-132 cells. It was shown that *Morus* spp. reduced the viral titer and the cytopathogenic effects. The hydroalcoholic extract of the leaves exhibited the highest antiviral activity. The inhibition percentage of viral infectivity ranged from 34% to 36% for the aqueous stem bark extracts and from 37% to 45% for the hydromethanolic stem bark extracts. In comparison, this inhibition ranged from 67% to 100% for the hydromethanolic extracts of leaves.<sup>102</sup>

#### *Echinacea purpurea*

Antiviral potential of *E. purpurea* examined against HCoV 229E and the highly pathogenic MERS- and SARS-CoVs *in vitro*. HCoV-229E was irreversibly inactivated when exposed to Echinaforce (a commercial standardized extract of *E. purpurea*) at an IC<sub>50</sub> of 3.2 µg/ml. Pre-treatment of cell lines had only a marginal effect on virus propagation at 50 µg/ml.<sup>103</sup>

#### *Uvaria angolensis*

The methanolic extract of the stem bark of *U. angolensis* inhibited both the HIV-1 RNase H enzyme and the reverse transcriptase activities with IC<sub>50</sub> values of 1.0 ± 0.2 and 0.62 ± 0.15 µg/mL, respectively. RDS1643 and Efavirenz were considered as control of RNase H inhibitor and reverse transcriptase, respectively. The IC<sub>50</sub> values for RDS1643 were measured as 2.7 ± 0.2 µg/mL.<sup>104</sup>

#### *Pometia pinnata*

Leaf and bark of *P. pinnata* have traditionally been used to treat fever and fester. The ethanolic extracts of *P. pinnata* (Sapindaceae) leaves have shown one of the most potent inhibitory activity against HIV-1 integrase *in vitro* with an IC<sub>50</sub> value of 8.8 µg/mL. In this study, proanthocyanidin A2 was isolated as an anti-HIV-1 integrase compound, with an IC<sub>50</sub> value of 30.1 µM.<sup>95</sup>

#### *Anthemis hyalina*

Antimicrobial activities of different species in the genus of *Anthemis* have been documented. Treating HeLa CEACAM1 cells infected coronavirus MHV-A59 with the ethanoic extract of *Anthemis hyaline* decreased the proliferation and function of this virus. However, this herb has a positive effect on IL-8

secretion and expression of transient receptor potential proteins (TRP) family genes, and its primary role was reducing the viral load.<sup>105</sup>

#### *Phyllanthus amarus*

The hydroalcoholic extract of *P. amarus* leaves inhibited the interaction of HIV-1 envelope gp120 protein with its CD40 cell receptor up to 50%. Inhibition of virus envelope protein gp120 binding to the cellular receptor CD4 was the primary mechanism underlying the blocked virus entry. The extract also showed an inhibitory effect on other enzymes of the virus, such as reverse transcriptase, integrase, and protease.<sup>106</sup>

#### *Glycine max* or Black soybean

An aqueous/ethanol extract of black soybean inhibited respiratory tract viruses such as human adenovirus type 1, coxsackie B1, and influenza A in Vero, HeLa, MDCK, and FL cell lines in a dose-dependent manner. Ethanolic extract from black soybean demonstrated dose-dependent inhibitory activity against human adenovirus type 1 replication. The antiviral index was about 1.5 mg/ml, and significant activity was recorded at 3.5 mg/ml.<sup>107</sup>

#### *Sambucus nigra*

In a placebo-controlled randomized, double-blind study, oral administration of elderberry (*Sambucus nigra*) extract was shown to be an effective, safe, and cost-saving healing agent in influenza patients. In this study, patients received 15 ml of elderberry syrup for 5 days, and they recorded their symptoms on a visual analog scale. Compared with placebo, respiratory influenza symptoms improved 4 days earlier, and their need for medication decreased.<sup>108</sup>

#### *Geranium sanguineum*

*Geranium sanguineum* belonging to Geraniaceae is one of the medicinal plants rich in polyphenols, which reduces infection of various types of influenza viruses (H7N1, H7N7, and H3N2) in chicken embryo fibroblasts, MDCK cell lines and ICR mice (10 mg/kg in mice). n-butanol/ethanol and the ethanol/acetic acid fractions showed the highest antiviral effects *in vitro* and *in vivo*, respectively.<sup>109</sup>

#### *Boehmeria nivea*

*Boehmeria nivea* root extract reduced Hepatitis B virus (HBV) replication *in vitro* (in HepG2 2.2.15 cell). Real-time PCR, Southern blot and Northern blot techniques were used in this study to assay viral gene expression and replication.<sup>110</sup>

#### *Polygonum cuspidatum*

Different extracts of *P. cuspidatum* was shown to inhibit various viruses. This effect was associated with the presence of a class of the chemical group called anthraquinones. Anthraquinones have been reported to possess antiviral and virucidal activities against various types of viruses. Ethanolic extract of *P. cuspidatum* inhibited the HBV replication in a dose-dependent manner in the stable HepG2 2.2.15 hepatoblastoma cell line.<sup>111</sup>

#### *Guazuma ulmifolia*

*G. ulmifolia*, also known as mutamba, has therapeutic effects such as wound healing, antiulcerogenic, hypoglycemic and

Table 3. Medicinal plants investigated against coronaviruses and related viruses.

Scientific name	Family	Mechanism	Herbal product	Type of study	Effective dosage	Cell type/animal model	Virus	Reference
<i>Morus spp.</i>	Moraceae	Inhibition of viral infectivity	Leaves and stem bark extract	<i>In vitro</i>	5 µg/mL	L-132	coronavirus (HCoV 229E)	(102)
<i>Echinacea purpurea</i>	Asteraceae	Virucidal activity	Herbal extract	<i>In vitro</i>	3.2 µg/ml	Huh-7 Vero A9	MERS- and SARS-CoVs	103
<i>Anthemis hyalina</i>	Asteraceae	Decrease virus load and IL-8 decrease TRP genes expression	Ethanol extract	<i>In vitro</i>	-	HeLa ceacami	Coronavirus MHV-A59	105
<i>Sambucus nigra</i>	Adoxaceae	Improve symptoms and overall wellbeing	Herbal extract	A Clinical trial	15 ml of syrup four times a day, for 5 days	-	Influenza	108
<i>Uvaria angolensis</i>	Annonaceae	HIV-1 RNase H enzyme and reverse transcriptase activity	Methanol stem bark extract	<i>In vitro</i>	1.0 ± 0.2 and 0.62 ± 0.15 µg/mL	A549	HIV-1	104
<i>Pometia pinnata</i>	Sapindaceae	Activity against HIV-1 integrase	Ethanol leaves extract	<i>In vitro</i>	8.8 µg/mL	-	HIV-1	95
<i>Boehmeria nivea</i>	Urticaceae	Inhibit HBV DNA secretion into supernatant	Root extract	<i>In vitro</i>	10 mg/L	HepG2.2.2.15 human hepatoblastoma	HBV	110
<i>Polygonum cuspidatum</i>	Polygonaceae	Increase expression of HBsAg decrease HBV DNA in the suspension	Ethanol extract	<i>In vitro</i>	30 µg/ml	HepG2.2.2.15 human hepatoblastoma	HBV	111
<i>Guazuma ulmifolia</i>	Malvaceae	Inhibited replication block the synthesis of viral antigens	Herbal extract	<i>In vitro</i>	5 mg/ml	HEp-2 (human larynx carcinoma) cells	Poliovirus-1 & Bovine Herpesvirus	112
<i>Olea europaea</i>	Oleaceae	Decrease VHSV titers and viral protein accumulation inhibits replication modulate host cell gene expression profile	Leaf extract	<i>In vitro</i>	0.6–1 mg/ml	<i>Epithelioma papulosum</i> cyprinid MT2 cell line	Hemorrhagic septicaemia virus (VHSV) and HIV-1	114, 140
<i>Phyllanthus amarus</i>	Phyllanthaceae	Blocked the interaction of HIV-1 gp120 with CD4 Inhibition of virus entry inhibited key enzymes RT, IN and PR Inhibition of HIV-1 replication after oral application	Herbal extract	<i>In vitro</i> & <i>ex vivo</i>	1 mg/ml <i>in vitro</i> 1200 mg, single dose in human	MT4 cells	HIV-1	106
<i>Trichilia glabra</i>	Meliaceae	Reduction in VSV titer	Leaf methanolic extract	<i>In vitro</i>	0.25 mg/ml	Vero cells	Vesicular stomatitis virus (VSV) and HSV-1	141
<i>Glycine max</i>	Fabaceae	Inhibit virus replication	Herbal extract	<i>In vitro</i>	0.1–5 mg/ml	HeLa cells FL cells MDCK cells Vero cells	Human adenovirus type 1, coxsackie B1 and influenza A	107

<b><i>Azadirachta indica</i></b>	Meliaceae	Inhibit virus replication inhibition of viral RNA replication	Leaf extract	<i>In vitro &amp; in vivo</i>	1.897 mg/ml 120–30 mg/ml	C6/36 cell line Mice	Dengue virus type-2 (DEN-2)	107
<b><i>Eucalyptus camaldulensis</i></b>	Myrtaceae	Virucidal activity	Essential oil Leaves extract	<i>In vitro</i>	0.85±0.15 µg/ml 0.1±0.008 µg/ml 0.3±0.002 µg/ml	Hep-2 MA104 BGM Vero	HSV, varicella zoster, poliovirus, echovirus, Coxsackie B4, rotavirus	124-126
<b><i>Artemisia princeps</i></b>	Asteraceae	Plaque formation inhibitor	Essential oil	<i>In vitro</i>	0.1% (v/v) (essential oil)	RAW 264.7 CRFK	Calicivirus-F9 and MNV-1	127,128
<b><i>Mosla dianthera</i></b>	Lamiaceae	Replication inhibitor decrease of cytokine productions (IFN-γ and IL-4) enhancing antioxidant activities	Essential oil	<i>In vivo</i>	90–360 mg/kg	ICR mice	Influenza A	121
<b><i>Heterothalamus alienus, Buddleja cordobensis</i></b>	Asteraceae & Scrophulariaceae	Virucidal activity	Essential oil	<i>In vitro</i>	CC <sub>50</sub> (ppm): 147.6 ±5.7 and 157.2 ±3.5	Vero	HSV-1, DENV-2, and JUNV	129
<b><i>Coridothymus capitatus, Origanum dictamnus, Salvia fruticosa</i></b>	Lamiaceae	Replication cycle and progeny virus production	Mixes essential oil	<i>In vitro</i>	15 mL/L	HeLa MDCK	H1N1 influenza virus and HRV14 rhinovirus	122
<b><i>Melaleuca alternifolia</i></b>	Myrtaceae	Virucidal activity	Essential oil	<i>In vitro</i>	0.0006 % (v/v)	MDCK	Influenza A subtype H1N1	123
<b><i>Laurus nobilis</i></b>	Lauraceae	IC <sub>50</sub> Replication inhibitory	Essential oil (β-ocimene, 1,8-cineole, α-pinene, and β-pinene)	<i>In vitro</i>	120 mg/ml	Vero	Coronavirus SARS	120
<b><i>Lippia junelliana, Lippia turbinata</i></b>	Verbenaceae & Asteraceae	Virucidal activity	Essential oil	<i>In vitro</i>	VC <sub>50</sub> = 14–20 ppm	Vero	JUNV	130
<b><i>Eupatorium patens</i></b>	Asteraceae	Virucidal activity	Essential oil	<i>In vitro</i>	VC <sub>50</sub> = 150 ppm	Vero	Dengue virus type 2 (DEN-2)	130
<b><i>Cinnamomum zeylanicum, Daucuscarota, Eucalyptus globulus, Rosmarinus officinalis</i></b>	Lauraceae, Apiaceae, Myrtaceae, Lamiaceae	Reduced viral units virion envelope structures	Essential oil blend	<i>In vitro</i>	-	Vero	H1N1 subtype of influenza A virus	131-133
<b><i>Fortunella margarita</i></b>	Rutaceae	Virucidal activity	Fruits and leaves essential oil (α-terpineol)	<i>In vitro</i>	6.77µg/mL (fruits) 38.89 µg/mL (leaves)	MDCK	Influenza virus subtype H5N1	134
<b><i>Melissa officinalis</i></b>	Lamiaceae	Virucidal activity Replication inhibitory	Essential oil	<i>In vitro</i>	0.5-0.1 mg/ml	MDCK	Avian influenza H9N2 subtype	135
<b><i>Pogostemon cablin</i></b>	Lamiaceae	Virucidal activity improving the immune response attenuating systemic inflammatory responses	Essential oil	<i>In vivo</i>	10-80 mg/kg	Mice	H1N1 & H2N2 influenza virus	136-138
<b><i>Trachyspermum ammi</i></b>	Apiaceae	Reduction virus titer Virucidal activity	Essential oil	<i>In vitro</i>	0.5mg/ml	Vero	Japanese encephalitis virus	139
<b><i>Aloe vera (L.)</i></b>	Asphodelaceae	3CL <sup>pro</sup> inhibitory	Herbal extract	<i>In vitro</i>	428 µg/mL	-	SARSCov-2	116



antimicrobial. *G. ulmifoli* extract inhibited poliovirus-1 replication by 26% in HEP-2 cells and restricted the synthesis of viral antigens in the infected cell culture.<sup>112</sup>

### ***Azadirachta indica***

*Azadirachta indica* (Neem) is grown in tropical countries and has been reported to possess anti-inflammatory, antipyretic, and hypoglycemic activities. The aqueous extract of the leaves of *A. indica* inhibited Dengue virus type-2 (DEN-2) *in vitro* C6/36 cell line and *in vivo* (mice).<sup>113</sup>

### ***Olea europaea***

Olive leaf extract inhibited replication of viral hemorrhagic septicaemia virus (VHSV).<sup>114</sup> The extract also inhibited acute infection and cell-to-cell transfer of HIV-1 virus in MT2 cell line.<sup>115</sup>

### ***Aloe vera***

A set of experiments suggested that *A. vera* has potent antiviral activity. *A. vera* contains bioactive virucidal compounds such as anthraquinones. As mentioned, anthraquinones like some antiviral drugs (Lopinavir, ritonavir), alone or in combination with other medications, can target SARS-CoV-2 protease 3CLPro.<sup>116</sup> Acemannan is the predominant acetylated polysaccharide mannan extracted from *A. vera* gel and has been approved by the US FDA for the treatment of HIV-1 in humans. Acemannan inhibits glycosylation of viral proteins and inhibits cell fusion and suppression of virus release.<sup>117</sup>

### **Essential oils**

Essential oils contain a large number of compounds and may target several purposes. However, in most cases, synergistic mechanisms are involved in their antimicrobial activity. Studies have shown essential oils are complex mixtures of lipophilic and volatile secondary metabolites isolated from plants such as monoterpenes (hydrocarbon and oxygenated monoterpenes), sesquiterpenes (hydrocarbon and oxygenated sesquiterpenes), and/or phenylpropanoids that are responsible for a broad biological functions such as antimicrobial, antioxidant, anti-inflammatory, anticancer, cancer chemoprotective, repellent and insecticidal, allelopathic, cytotoxicity, and antiviral activities.<sup>118, 119</sup>

### ***Laurus nobilis***

The essential of the leaves of *L. nobilis* has been shown to have potent antiviral activity against coronavirus SARS. The most important compounds in the essence of this herb include  $\beta$ -ocimene, 1,8-cineole,  $\alpha$ -pinene, and  $\beta$ -pinene. The IC<sub>50</sub> of *L. nobilis* was measured 120 mg/ml with a selective index of 4.2 (SI; TC<sub>50</sub>/IC<sub>50</sub>).<sup>120</sup>

### ***Mosla dianthera***

This herb is used as an aromatic herb in traditional medicine in the treatment of cough, colds, fever, bronchitis, nasal hyperemia, and headache. The effect of the essential oil of this herb on mice infected by influenza A was investigated. It was found that this essence has significant effects, including reducing viral lung titers, inhibiting pneumonia, lowering serum levels of IFN- $\gamma$  and interleukin 4 (IL-4), and enhancing the antioxidant activity in lung tissue of mice infected with influenza A.<sup>121</sup>

### ***Coridothymus capitatus, Origanum dictamnus and Salvia fruticosa***

A mixture of aromatic plant essential oils consisted of *C. capitatus*, *O. dictamnus*, and *S. fruticosa* was tested against the H1N1 influenza virus and HRV14 rhinovirus in HeLa and MDCK cells. It was found that this compound caused a defect in the nucleoprotein trafficking of the virus *in vitro*, thereby, has the potential to be used as an herbal drug against respiratory system viruses such as H1N1 influenza and rhinovirus HRV14.<sup>122</sup>

### ***Melaleuca alternifolia***

The antiviral effect of this essence on the MDCK cell line was investigated using plaque reduction assay. The results of this study confirmed the antiviral activity of the essence of *M. alternifolia* against influenza A subtype H1N1, which was implicated to the presence of terpinen-4-ol, as the essence active ingredient.<sup>123</sup>

### ***Eucalyptus camaldulensis***

The essential oil of *E. camaldulensis* reduced the proliferation of Coxsackie B4, rotavirus, and herpes simplex virus (HSV). Moreover, the methanolic extract of this plant attenuated the activity of HSV, varicella zoster, poliovirus, and echovirus.<sup>124-126</sup>

### ***Artemisia princeps***

The essential oil of *A. princeps* var. *orientalis* and its bioactive components, including Borneol, Athujone, and Camphor, were studied on two noroviruses; MNV-1 and calicivirus-F9 by time-of-addition plaque assays. The *A. princeps* essence at concentrations of 0.1 and 0.01 inhibited the growth of calicivirus-F9 and MNV-1 by 48% and 64% (*v/v*), respectively. Borneol and Camphor showed no antiviral activity, whereas Athujone, the major compound of the essence, strongly and dose-dependently inhibited virus infection.<sup>127, 128</sup>

### ***Heterothalamus alienus and Buddleja cordobensis***

In a study on seven herbs (*Pectis odorata*, *Gaillardia megapotamica*, *Heterothalamus alienus*, *Aloysia triphylla*, *Artemisia mendozana*, *Jungia polita*, *Buddleja cordobensis*) indigenous to the South America, their cellular properties (cytotoxicity) and their inhibitory effects on HSV-1, Dengue Virus Type 2 (DENV-2) (causing Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome), and Junin virus (JUNV) (the cause of Argentine hemorrhagic fever) were evaluated. The strongest association between cytotoxicity and antiviral activities was observed for the essence of *Hetero-thalamus alienus* and *B. cordobensis* against JUNV virus.<sup>129</sup>

### ***Lippia junelliana and Lippia turbinata***

The essential oils of South American species named as *L. junelliana* and *L. turbinata* could temperature- and time-dependently inhibit JUNV in Vero cells *in vitro* (VC<sub>50</sub>: 14–20 ppm).<sup>130</sup>

### ***Eupatorium patens***

The essential oil of the leaves, flowers, and fruits of *E. patens* (Asteraceae), indigenous to South America, potently restrained the DEN-2 replication (VC<sub>50</sub>: 150 ppm). The

main components of the essential oil were D-germacrene;  $\beta$ -caryophyllene; bicyclogermacrene;  $\alpha$ -pinene; caryophyllene oxide.<sup>130</sup>

### ***Cinnamomum zeylanicum*, *Daucus carota*, *Eucalyptus globulus* and *Rosmarinus officinalis***

The blend of essential oil of these herbs inhibited H1N1 subtype of influenza A virus function, probably through interfering the formation of the virus coat and inhibiting its DNA polymerase enzyme. For H1N1, a reduction was greater than 99%.<sup>131-133</sup>

### ***Fortunella margarita***

The essential oil compound of the fruit and leaves of *F. margarita* was found effective against avian influenza virus subtype H5N1 in MDCK cell line, which was associated with the presence of  $\alpha$ -terpineol in its fruit. The fruit essential oil has been shown to be more effective and caused an 80% inhibition of the virus activity.<sup>134</sup>

### ***Melissa officinalis***

The inhibitory effect of the essential oil of *M. officinalis* on the avian influenza H9N2 subtype was investigated in the MDCK cell line. It has been found that this herb has a synergistic effect in inhibiting the H9N2 virus with Noseltamivir. *M. officinalis* can interact with cell surface proteins (i.e., masking the cell surface), thereby blocking the virus binding to cellular receptors.<sup>135</sup>

### ***Pogostemon cablin***

The antiviral activity of the essential oil obtained from *P. cablin* has been demonstrated against H1N1 and H2N2 influenza virus. Oral administration of *P. cablin* essential oil in mice has also been shown to protect against influenza virus infection by enhancing the immune response and decreasing the systemic and pulmonary inflammatory response.<sup>136-138</sup>

### ***Trachyspermum ammi***

The essential oil of *T. mumammi* was found efficient against the Japanese encephalitis virus (JEV) *in vitro*. JEV titration was determined by plaque assay, and the antiviral activity of this plant was measured *in vitro* using a plaque reduction neutralization test. Treatment of Vero cell line with this essential oil in both pre- and post-exposure treatments reduced the virus titers by 80% and 40%, respectively.<sup>139</sup>

## **Herbal active biochemicals**

### **Cinnamaldehyde**

Cinnamaldehyde, an abundant aromatic phenylpropanoid in *Cinnamomi cortex* (*Cinnamomum verum*) has been studied for its potential properties against the influenza virus. The results of reverse transcription (RT-PCR) and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analyses showed that cinnamaldehyde inhibited the synthesis of influenza virus proteins at the post-transcriptional level. In mice infected with influenza virus, inhalation (50 mg in the cage daily) and nasal inoculation (250  $\mu$ g for each rat daily) of this compound over 8 days increased the survival rate from 20% to 100% and 70%, respectively. Importantly, inhalation of

cinnamaldehyde reduced virus titers in the bronchoalveolar lavage on the sixth day after infection<sup>142</sup> (Table 4).

### **5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone**

5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, is extracted from *Psoralea argyrea*. The anti-leishmanial property of this compound has already been proven in the scientific literature. Chymotrypsin virus-like cysteine protease enzyme (3CL<sup>pro</sup>) is an essential factor for the replication cycle of coronavirus, representing a potential target for the treatment of such disease. This compound has a high affinity to the catalytic domain of 3CL<sup>pro</sup> enzyme. It also can bind receptor-binding residues of the 3CL<sup>pro</sup><sup>143, 144</sup> (Table 4).

### **1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucoside**

A compound called 1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucoside, extractable from the aerial parts of *Saxifraga melanocentra*, is responsible for the anti-hepatitis C virus (HCV) effect of the herb. The compound was also a potent inhibitor of the HCV serine protease enzyme<sup>145</sup> (Table 4).

### **Myricitrin and Scutellarin**

Myricitrin can be obtained from a plant called *Myrica cerifera*. It also can bind to and inhibit the catalytic domain of 3CL<sup>pro</sup> enzyme with high affinity. Modeling analysis also showed that Scutellarin or Myricitrin from *Scutellaria baicalensis* could directly link the ATP/ADP binding site of the SARS-CoV virus helicase enzyme (nsP13), thereby preventing direct binding of ATP/ADP to it. In particular, Myricitrin interferes with the ATPase activity of the SARS-CoV protein helicase. It is likely to do so by directly interacting with essential residues of the ATPase domain, such as N265, Y269, and R443<sup>146, 147</sup> (Table 4).

### **Glycyrrhizin and Licorine**

Glycyrrhizin, the bioactive component of Licorice and Licorine from red spider lily (*Lycoris radiata*), exhibited a potent anti-SARS-CoV Corona activity. However, the effective concentration of Glycyrrhizin (EC<sub>50</sub>) for inhibiting viral infection was very high (EC<sub>50</sub> 300 mg/L). Glycyrrhizin was most effective when given both during and after the adsorption period<sup>148, 149</sup> (Table 4).

### **Quercetin**

Quercetin is the most abundant dietary plant pigment flavonoid (i.e., in onion and garlic). It was reported that this compound inhibited the activity of 3CL<sup>pro</sup> of SARS-CoV with a FRET method. Its shown quercetin has low toxicity to the cells *in vitro*. Their MERS-CoV 3CL<sup>pro</sup> inhibitory activity is lower than their corresponding compounds at 40  $\mu$ M<sup>150</sup> (Table 4).

### **Baicalein**

*Scutellaria baicalensis* is one of the genus that may use as a source of this flavonoid. Ethanolic extract of *S. baicalensis* inhibited SARS-CoV-2 3CL<sup>pro</sup> activity *in vitro* and the replication of SARS-CoV-2 in Vero cells with an EC<sub>50</sub> of 0.74  $\mu$ g/ml. Baicalein strongly inhibited SARS-CoV-2 3CL<sup>pro</sup> activity with an IC<sub>50</sub> of 0.39  $\mu$ M<sup>151</sup> (Table 4).

Table 4. Antiviral phytochemicals effective on RNA viruses.

Compound	Source	Herbal family	Virucidal target	Type of study	Effective dosage	Cell type/animal model	Virus	Reference
Myricitrin	<i>Myrica cerifera</i>	Myricaceae	3CLpro inhibitory (a necessary protease for viral growth)	3D structure simulation	-	-	SARS-CoV-2	146
Scutellarin	<i>Scutellaria baicalensis</i>	Lamiaceae	Helicase (nsP13) inhibitory	<i>in vitro</i>	0.86 ± 0.48 μM	MCF10A	SARS-CoV-2	147
Glycyrrhizin and Licorine	Lycorisradiate	Amaryllidaceae	Inhibit CPE (virus-induced cytopathic effect) replication inhibitor	<i>in vitro</i>	MTS assay 15.07 ± 1.2 nM 300 mg/L	Vero	SARS-CoV-2	148, 149
Cinnamaldehyde	Cinnamomi cortex	Myricaceae	Survival rate (in vivo) protein synthesis (in vitro)	<i>In vivo &amp; in vitro</i>	<sup>1</sup> inhalation (50 mg/cage/day) <sup>2</sup> inoculation (250 μg/mouse/day) 20–200 μM	ICR female mice MDCK	Influenza A (H1N1 subtype)	142
5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	<i>Psoralea argyrea</i>	Fabaceae	Virucidal activity	<i>in vitro</i>	7.1 μM	Vero	Coronavirus	143, 144
Quercetin	-	-	3CL <sup>pro</sup> inhibitory	<i>in vitro</i>	40 μM	<i>E. coli</i> BL21	SARS-CoV	150
Baicalensis	<i>Scutellaria baicalensis</i>	Lamiaceae	3CL <sup>pro</sup> inhibitory	<i>in vitro</i>	0.39 μM	Vero	SARS-CoV-2	151
Sennoside A	Rheum palmatum L. and Rheum officinale Baill.	Polygonaceae	Reverse Transcriptase RNase H RT-associated functions Integrase	<i>in vitro</i>	2–5 μM	Jurkat	HIV-1	152
Tetra-O-galloyl-β-D-glucose	Chinese herbs	-	Virucidal activity	<i>in vitro</i>	4.5 M	Vero	SARS-CoV	153
Luteolin	Onopordum illyricum L.	Asteraceae	RNase H RT-associated	<i>in vitro</i>	12.8 μM	Jurkat	HIV-1	154
Tryptanthrin	Strobilanthes cusia	Acanthaceae	Inhibits early and late stages of replication, by blocking viral RNA synthesis and papain-like protease 2 activity	<i>in vitro</i>	1.52 μM	LLC-MK2	Coronavirus NL63	155
Tellimagrandin	<i>Eugenia caryophyllata</i> ,	Myrtaceae	Virus-Cell Fusion	<i>in vitro</i>	16.12 ± 1.98 mg/ml	syncytia	HIV-1	159
Globoidnan A	<i>Eucalyptus globoida</i>	Myrtaceae	HIV-1 integrase activity	<i>in vitro</i>	0.64 μM	HuT78 T-cell	HIV-1	160
Ginkgolic acid	Chinese herbal medicines	-	inhibited HIV protease activity	<i>in vitro</i>	31.2 μg/ml	Jurkat cells	HIV-1	93
Kaempferol derivatives	-	-	Block the 3a channel proteins	<i>in vitro</i>	2.3 μM	Xenopus oocyte	coronavirus	156
Saikosaponins	-	-	Absorption and penetration of the virus	<i>in vitro</i>	25 mmol/L	MRC-5	coronavirus	158
1,2,3,4,6-penta-O-galloyl-β-D-glucoside	<i>Saxifraga melanocentra</i>	Saxifragas	Inhibits NS3 serine protease	<i>In vitro</i>	0.1–0.001 mg/ml	Cos7 cells	Hepatitis C virus	145
Artesunate	<i>Artemisia annua</i>	Asteraceae	Inhibition of HIV-1 replication	<i>In vitro</i>	600 nM	-	HIV-1	157

### Sennoside A

Sennoside A from dried roots of *Rheum palmatum* L. and *Rheum officinale* Baill is HIV-1 RT inhibitor effective phytochemical on both HIV-1 Reverse Transcriptase and RNase H RT-associated functions in biochemical assays. Besides, Sennoside A affected the HIV-1 integrase activity *in vitro* and HIV-1 replication in Jurkat cell line. Sennoside A inhibited both HIV-1 RT-associated functions with IC<sub>50</sub> values of 2–5 μM range.<sup>152</sup> (Table 4).

### Tetra-O-galloyl-β-D-glucose

This small molecule from Chinese herbs exhibited prominent anti-SARS-CoV activity with a EC<sub>50</sub> concentration of 4.5 M in Vero E6 cells<sup>153</sup> (Table 4).

### Luteolin

Among seven compounds isolated from *Onopordum illyricum* L., Luteolin was the most effective on HIV-1 RNase H RT-associated function in a low concentration without cytotoxicity (IC<sub>50</sub> of 12.8 μM)<sup>154</sup> (Table 4).

### Tryptanthrin

The antiviral activity of Tryptanthrin isolated from *Strobilanthes cusia* was investigated against coronavirus NL63 in LLC-MK2 cell line. Tryptanthrin effectively inhibited the cytopathic effect and virus yield (IC<sub>50</sub> = 1.52 μM) in HCoV-NL63-infected cells. This molecule prevented the early and late stages of HCoV-NL63 replication, mainly by blocking the viral RNA genome synthesis and papain-like protease 2 activity<sup>155</sup> (Table 4).

### Kaempferol derivatives

These phytochemicals have a potency to block the 3a channel proteins of coronaviruses. The YxxΦ domain of 3a channel is a protein internalization signal which is involved in clathrin-mediated endocytosis, therefore its involved in virus cell entry. In a research study, using *Xenopus* oocyte for heterologous expression and applied voltage-clamp techniques, the glycoside juglanin (carrying an arabinose residue) was found as the most effective kaempferol derivatives with an IC<sub>50</sub> value of 2.3 μM for Inhibition of the 3a-mediated current<sup>156</sup> (Table 4).

### Artesunate

Bioingredients of *Artemisia annua* can play potential protective roles against infections by viruses, specifically HSV-1, HBV, HCV, bovine viral diarrhea virus, and Epstein-Barr virus. It was demonstrated that 10 days administration of artesunate (a semi-synthetic derivative of artemisinin used to treat malaria) at 600 nM inhibited HIV-1 replication<sup>157</sup> (Table 4).

### Saikosaponins

Among saikosaponins (A, B2, C, and D) tested on coronavirus 229E in human fetal lung fibroblasts, saikosaponin B2 demonstrated a potent anticoronaviral activity at a concentration of 25 mmol/L. Although, the mode of action of this compound possibly involved interference in the early stage of viral replication such as absorption and penetration of the virus<sup>158</sup> (Table 4).

### Tellimagrandin

Initially, the interaction between the HIV envelope glycoprotein gp120 and the cell membrane protein CD4 results in

virus-cell fusion. Out of isolated compounds from *Eugenia caryophyllata*, tellimagrandin significantly inhibited the virus-cell fusion and syncytia formation in HIV-1 with an IC<sub>50</sub> value of 16.12±1.98 mg/ml<sup>159</sup> (Table 4).

### Ginkgolic acid

In Jurkat cells, ginkgolic acid (31.2 μg/ml) isolated from Ginkgo leaves, inhibited the HIV protease activity by 60% in a dose-dependent manner. Moreover, ginkgolic acid treatment (50 and 100 μg/ml) effectively inhibited the HIV infection at day 7 dose-dependently<sup>93</sup> (Table 4).

### Globoidnan A

It was reported that Globoidnan A, a lignan obtainable from *Eucalyptus globoidea*, can interfere with HIV-1 integrase activity. This compound was found to inhibit the combined 3' processing and strand transfer activity of HIV integrase with an IC<sub>50</sub> = 0.64 μM<sup>160</sup> (Table 4).

## Antiviral herbal medicine formulations

### KangBingDu

KangBingDu (KBD) is a Chinese traditional medicinal formula in form of a classic oral liquid that has been modified based on the traditional Chinese “BaiHutang” and “QingWenBaiDuYin” medicine formulations. KBD is often used to improve the clinical symptoms of viral diseases, especially the influenza virus. KBD is composed of *Radix isatidis*, *Rhizoma phragmitis*, *Radix rehmanniae*, *Radix curcumae*, *Rhizoma anemarrhenae*, *Rhizoma acori tatarinowii*, *Herba pogostemonis*, *Fructus forsythiae* and *Gypsum fibrosum*. KBD significantly reduced the sensitivity of male Kunming mice to influenza viruses, which is evidenced by reduced mortality, decreased inflammation, and inhibited viral replication in the pulmonary system. In A549 cells, administration of KBD increased the protein expression of MAVS (mitochondrial antiviral signaling protein) and the levels of IFN-β protein and interferon-induced transmembrane-3 protein, resulting in inhibition of viral infection. It was shown that (R, S)-Goitrine, Mangiferine, Forsythine, and Forsythoside A were other active ingredients of KBD against the influenza virus. The mitochondrial antiviral signaling pathway was introduced as the primary mechanism of action of KBD.<sup>161</sup>

### Maxingshigan–yinqiaosan

In a prospective RCT, the efficacy and safety of Oseltamivir and a traditional Chinese mixture named “Maxingshigan–Yinqiaosan” in treatment of uncomplicated influenza H1N1 subtype were compared. Maxingshigan–yinqiaosan consisted of 12 herbs: Zhimahuang (honey-fried *Herba Ephedrae*); Zhimu (*Rhizoma Anemarrhenae*); Qinghao (*Herba Artemisiae Annuae*); Shigao (*Gypsum Fibrosum*); Yinhuo (*Flos Lonicerae Japonicae*); Huangqin (*Radix Scutellariae*); Chaoxingren (stir-baked Semen *Armeniacae Amarum*); Lianqiao (*Fructus Forsythiae*); Bohe (*Fructus Forsythiae*); Zhebeimu (*Bulbus Fritillariae Thunbergii*); Niubangzi (*Fructus Arctii Tosum*); and Gancao (*Radix Et Rhizoma Glycyrrhizae*). Clinical interventions and control were given for 5 days with Oseltamivir, 75 mg twice daily; Maxingshigan–yinqiaosan, 200 mL 4 times daily. Oseltamivir and Maxingshigan–yinqiaosan, alone or together, reduced time of fever resolution in patients with H1N1 influenza.<sup>162</sup>

### Sheng Jiang San

Sheng Jiang San (SJS) is a Chinese multi-herbal formulation made of four herbs consist of *Rhei Radix et Rhizoma*, *Bombyx Batryticatus*, *Cicadae Periostracum*, and *Curcumae Longae Rhizoma*. The inhibitory effect of SJS against different strains of influenza virus A/WSN/33 (H1N1) on MDCK cells was examined. The IC<sub>50</sub> of SJS was lower than 35 µg/ml against H1N1. SJS at 2 mg/ml inhibited the NA activity up to 80%. This enzyme cleaves terminal neuraminic acid residues of glycan structures on the surface of the infected cell, thereby facilitating the release and spread of viruses progeny to reach the surrounding uninfected cells. The IC<sub>50</sub> of Oseltamivir acid was 250 µM against Neuraminidase. To evaluate the efficacy of SJS in the influenza virus, infected BALB/c mice were employed as *in vivo* model. Oral administration of 1 g/kg/day of SJS for 7 days, exhibited 50% protection of infected mice from H1N1 symptoms. SJS also significantly down-regulated tumor necrosis factor (TNF-α) and up-regulated IL-2 of influenza virus-induced mice.<sup>163</sup>

### Lianhuaqingwen

Lianhuaqingwen (LH) is another Chinese plant medicine composed of 13 herbs with positive impact on SARS-CoV-2 by inhibiting viral replication. A research study revealed that LH significantly inhibited SARS-CoV-2 replication in Vero E6 cells (600 µg/mL) and markedly reduced mRNA transcription of pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10).<sup>164</sup> In addition, LH in the form of capsule (4 capsules, thrice daily for 14 days) in patients who were suffering Covid-19 conferred therapeutic effects by improving the recovery rate of symptoms, shortening recovery time, and improving the recovery of chest radiologic abnormalities.<sup>165</sup>

### San Wu Huangqin Decoction

San Wu Huangqin Decoction (SWHD) is a Chinese compound formulation consists of *Sophora flavescens*, *Scutellaria baicalensis*, and *Rehmannia glutinosa*. This herbal formulation could effectively inhibit the influenza A/PR/8/34 (H1N1) virus at all steps of virus replication *in vitro*. The RNA expression of four H1N1 target viral proteins (hemagglutinin, NA, NP nucleoprotein, and matrix-2) was significantly down-regulated in MDCK cells. *In vivo*, SWHD at 23.40 and 11.70 g/kg significantly attenuated clinical symptoms, reduced mortality, and increased the survival time of infected animals. SWHD mediated the pulmonary index, viral titer, pathological changes in lung tissue, and expression of the main IFV proteins.<sup>166</sup>

### Kabasura Kudineer

Cresset Flare is a software that used for molecular docking studies against the spike protein SARS-CoV-2. *In silico* molecular docking assay, examining pharmacokinetics parameters, have shown that six plant species in *Kabasura Kudineer* formula (*Sida acuta*, *Adhatoda vasica*, *Andrographis paniculata*, *Tinospora Cordifolia*, *Costus speciosus*, *Plectranthus ambonicus*) have potential to directly suppress the SARS-CoV-2 spike protein.<sup>167</sup>

### Poly-herbal gel

The anti-HIV activity of an aqueous gel formula containing ethanolic extract of the heartwood of *Acacia catechu*, leaves of *Lagerstroemia speciosa*, and fruits of *Aegle marmelos*,

*Phyllanthus emblica*, and *Terminalia chebula* was examined against CXCR4 tropic and CCR5 tropic viruses. The gel inhibited viral activity with IC<sub>50</sub> values of 58.17 ± 4.4 and 63.54 ± 6.8 µg/ml for CXCR4 and CCR5, respectively. CXCR4 and CCR5 are two of several chemokine receptors used by the HIV to infect T CD4+ lymphocytes. Furthermore, this gel could inhibit three key enzymes of the HIV-1 reverse transcriptase, protease, and integrase enzymes significantly.<sup>168</sup>

### Qing Fei Pai Du Tang

Qing Fei Pai Du Tang (QFPDT) is a Chinese medicinal preparation consisting of 21 plants derivation of 5 conventional formula. Some studies have reported the QFPDT inhibitory effect of QFPDT on COVID-19. By several mechanisms, QFPDT could prevent the progression of mild COVID-19 cases and shorten the average duration of symptoms and hospitalization. Necessary scientific studies, supported by network pharmacology, reviewed the possible therapeutic targets of QFPDT and its constituents, including *Ephedra sinica*, *Bupleurum chinense*, *Pogostemon cablin*, *Cinnamomum cassia*, and *Scutellaria baicalensis*. Their findings indicated that main herbs of QFPDT have antiviral effects via different mechanisms including direct effect on virus replication and autophagy; regulation of host pathways like Toll-like receptors, RIG-1-like helicases, AMP-activated protein kinase, phosphatidyl inositol-3-kinase/protein kinase B or extracellular regulated kinase 1/2/mitogen-activated protein kinase signal pathways; elevation of the human defense system via T and B cell functions, and free radical scavenging activities by enhancing antioxidant enzymes. QFPDT also modulated inflammation conditions through suppression of inflammatory-related genes, signal pathways and cytokines.<sup>169</sup>

### Chai-Ling

Chai-Ling decoction (CLD), derived from a modification of two decoctions, include Xiao-Chai-Hu (XCH) and Wu-Ling-San (WLS) decoction, has been used to treat early-stage of COVID-19. The possible mechanisms of CLD in COVID-19 were preliminarily investigated, relying on network pharmacology and molecular docking method. CLD might reduce the inflammatory response and improve lung damages of COVID-19 through interleukin 17 signaling, T helper cell 17 differentiation, tumor necrosis factor signaling, and hypoxia-inducible factor-1 signaling. Besides, molecular docking assay indicated that beta-sitosterol, kaempferol, and stigmasterol were the primary three components in CLD with the highest affinity to SARS-CoV-2 and ACE2.<sup>170</sup>

### San Yao San

San Yao San Fang (SYSF) was shown effective in patients with COVID-19. The synergy of SYSF and Western interventions improved the recovery rate of COVID-19 symptoms such as fever, cough, and fatigue, and other symptoms such as headache, gastrointestinal symptoms, myalgia, dyspnoea, and chest tightness.<sup>171</sup>

### Conclusion

Throughout history, humans have been dependent on plant/natural sources for the treatment of various infections. Over the last few decades, hundreds of plant and herb species were shown to have potential antiviral activities, which

were attributed to a variety of active phytochemicals including flavonoids, terpenoids, lignans, sulphides, polyphenolics, coumarins, saponins, furyl compounds, alkaloids, polyines, thiophenes, proteins, peptides, and some essential oils. Plant extracts or substances derived from plants possess their antiviral effects through inhibition of viral replication and by deterring the activity of viral reproduction or interacting with vital viral proteins that are associated with virulence.<sup>172</sup> Their ability to act as bioreactors and production of vaccines under plant platforms are another advantage of plant systems to induce mucosal or long-term immunity against viral infection. Very recently, it was proposed that highly polar glycosylated compounds and polyphenols are more effective antiviral substances, particularly when being administered orally.<sup>13</sup> In our study, we gathered information about plant extracts, essential oils, and phytochemicals that are favorable for life-threatening coronaviruses diseases and can be potential candidates for further development of antivirals. We found those plant families,

including Lamiaceae, Asteraceae, and Myrtaceae contain the highest number of species with anti-coronaviruses activities, respectively. It can be suggested that the combination of these antiviral ingredients with each other, any synthetic compound, or already FDA-approved drugs or inhibitors can be a novel approach for antiviral therapies. Evaluation of efficacy and adverse effects of herbal medicines for the treatment of viral infection is warranted. Recent findings exhibited that a combination of herbal therapy with modern medicines significantly improved the total effective rate and syndrome score of cough, fever, dry, and sore throat, and fatigue in COVID-19 patients, signifying the advantage of herbal therapy for viral infections.<sup>173</sup>

## Conflict of Interest

None

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