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REVIEW

Leveraging knowledge of Asian herbal medicine and its active compounds as COVID-19 treatment and prevention

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Abstract

The outbreak of COVID-19 disease has led to a search for effective vaccines or drugs. However, insufficient vaccine supplies to meet global demand and no effective approved prescribed drugs for COVID-19 have led some people to consider the use of alternative or complementary medicines, such as traditional herbal medicine. Medicinal plants have various therapeutic properties that depend on the active compounds they contain. Obviously, herbal medicine has had an essential role in treatment and prevention during COVID-19 outbreak, especially in Asian cultures. Hence, we reviewed the uses of herbal medicine in Asian cultures and described the prominent families and species that are sources of antiviral agents against COVID-19 on the basis of case reports, community surveys, and guidelines available in the literature databases. Antiviral efficacy as determined in laboratory testing was assessed, and several promising active compounds with their molecular targets in cell models against SARS-CoV-2 viral infection will be discussed. Our review findings revealed the highly frequent use of Lamiaceae family members, *Zingiber officinale*, and *Glycyrrhiza* spp. as medicinal sources for treatment of COVID-19. In addition, several plant bioactive compounds derived from traditional herbal medicine, including andrographolide, panduratin A, baicalein, digoxin, and digitoxin, have shown potent SARS-CoV-2 antiviral activity as compared with some repurposed FDA-approved drugs. These commonly used plants and promising compounds are recommended for further exploration of their safety and efficacy against COVID-19.

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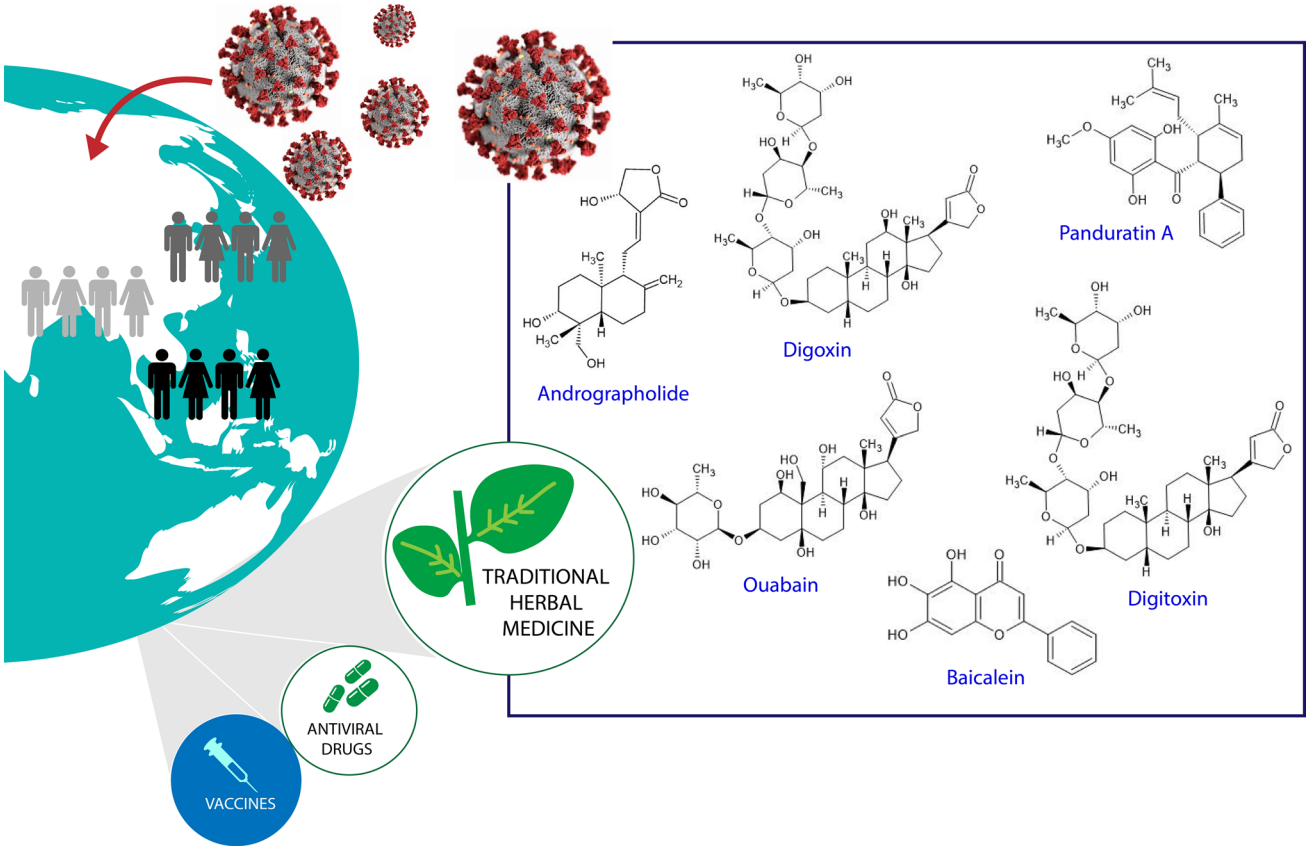
Graphic abstract



Keywords COVID-19 · Asian · Herbal medicine · Plant bioactive compounds · Treatment · Prevention

Background

An outbreak of coronavirus 19 (COVID-19) disease caused by the beta-coronavirus, severe acute respiratory syndrome 2 (SARS-CoV-2), was first reported in late December 2019 in Wuhan, China and continued to rapidly spread worldwide. The angiotensin-converting enzyme 2 (ACE2) receptor, which is known to be an entry point of SARS-CoV-2, is widely presented on lung alveolar cells but also can be found in other organs' cells, such as the upper esophagus, small intestine, colon, bile, heart, kidney, and bladder; hence, this virus can attack various organs and cause damage [1, 2]. Penetration by SARS-CoV-2 stimulates the immune response leading to production of various cytokines, which generates a cytokines storm that triggers disease symptoms. Depending on the cytokines produced, COVID-19 symptoms can be mild, moderate, or severe [2]. Severe disease is characterized by progressive lung damage, over-inflammation, pulmonary tissue edema, vascular leakage, coagulation, and endotheliitis (vascular inflammation). The cytokine storms in the most severely affected COVID-19 patients are very destructive and cause endothelial dysfunction, inflammation, and vasodilatation of pulmonary capillaries. Furthermore, this process triggers alveolar disfunction, acute respiratory distress syndrome with hypoxic respiratory, and multiple-organ failure, resulting in death [3, 4].

A global effort to develop effective vaccines or therapeutic drugs for COVID-19 disease is urgently needed for combating the pandemic. Hence, several approaches have been adopted, including drug repurposing and vaccine development. In drug repurposing, various existing drugs, such as chloroquine, hydroxychloroquine, ivermectin, camostat mesylate, lopinavir, ritonavir, remdesivir, and favipiravir, have been tested in clinical trials [5]. In vaccine development, numerous pharmaceutical/academic developers have developed COVID-19 vaccine candidates using various platforms, such as live-attenuated virus (e.g., Codagenix [6]), inactivated virus (e.g., Sinovac [7], Sinopharm [8]); mRNA (e.g., Pfizer [9] Moderna [10], ChulaCov19 [11], and Curevac [12]); DNA (e.g., COVIGEN [13], Inovio

[14]); non-replicating viral vectors (e.g., AstraZeneca [15], Johnson & Johnson [16]); and protein sub-units (e.g., Novavax[17]), and conducted clinical trials [18]. The World Health Organization (WHO) has approved several vaccines for emergency use, including AZD1222/AstraZeneca, Janssen/Johnson & Johnson mRNA 1273/Moderna, Sinopharm, and Sinovac-CoronaVac, since 2020 [19]. The rapid transmission of COVID-19 disease along with insufficient vaccine supplies for health care workers and the absence of specific and effective prescribed drug treatments for COVID-19 patients [20] have led to some people taking herbal medicines for prevention or treatment of this disease.

Herbal medicine has been used in complementary medicine in various cultures for at least 1000 years and still has an important role in health care systems currently. The extensive use of plant sources of medicines with proven therapeutic ability for treating various diseases has led to more plant-based drug discoveries of numerous effective drugs such as vincristine, vinblastine, paclitaxel, and camptothecin (Fig. 1) [21]. Promising compounds, such as psoralens, guggulsterons, piperidines, phyllanthins, picrosides, curcuminoids, withanolides, steroidal lactones, and glycosides, have been discovered from traditional Ayuverdic medicine [22]. In addition, the discovery of the potent antimalarial drug, artemisinin (Fig. 1), has been attributed to the historical use of the plant *Artemisia annua* in Traditional Chinese Medicine (TCM) [23].

The perception that many herbal medicines have shown promising efficacy, safety, accessibility, environmental friendliness, and affordability has led to increased attention on traditional medicines in recent years. The efficacy of traditional herbal medicines for treating various diseases is due to the pharmacological activity of the active compounds in the plants [24]. Obviously, herbal medicine also plays essentially for prevention and treatment of COVID-19 disease in various cultures. Herbal medicines may act directly or indirectly by attacking the virus, viral–host interaction, signaling pathways, host receptors, molecular targets, immune system, and microenvironments. In TCM, herbal medicines alone or in combination with modern synthetic drugs are prescribed for COVID-19 patients [4]. The Qingfei Paidu decoction, which contains several herbs, has been used for treatment of COVID-19 patients in China [24]. Lianhua–Qingwen, Shufeng Jiedu, Huoxiang Zhengqi, and Jinhua Qinggan herbal formulas also have been used in COVID-19 treatment in TCM [25]. Herbal medicines are widely used, mostly in China and other Asian countries, such as Japan, Korea, Thailand, Vietnam, India, Bangladesh, and Indonesia. Accordingly, the aim of this review article was to describe various medicinal plants used in COVID-19 prevention and treatment from various countries in Asia as obtained from a literature search and discuss the efficacy results from laboratory testing. Additionally, the antiviral activities of

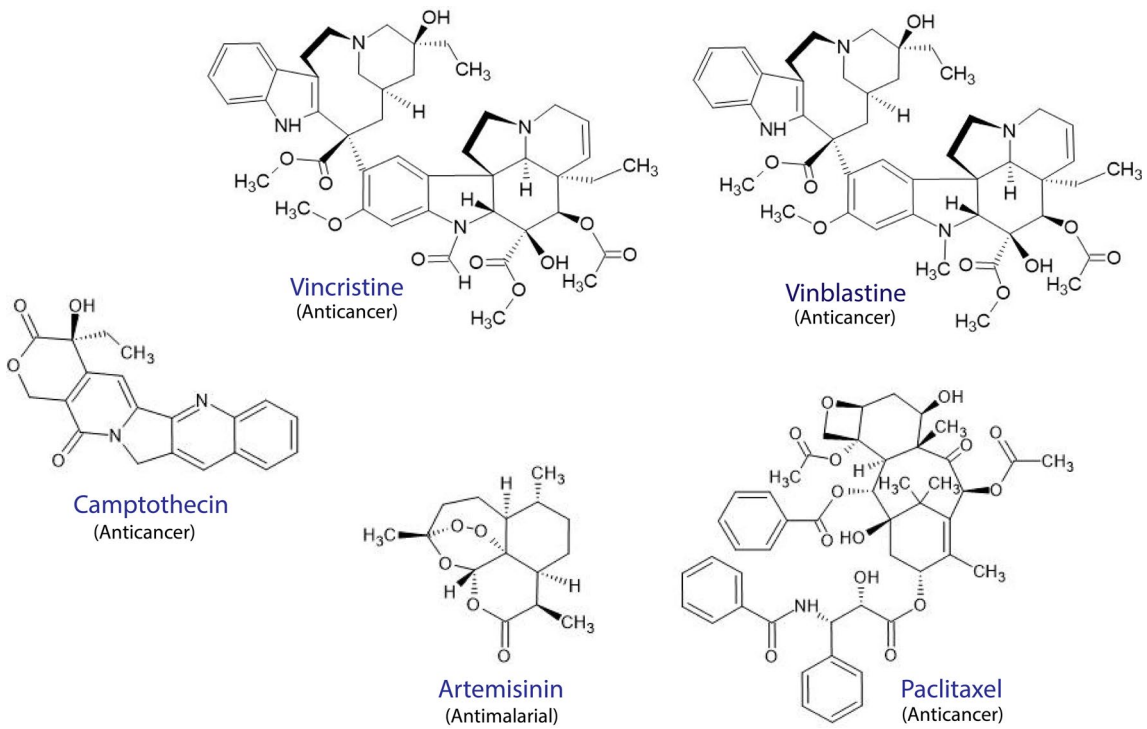


Fig. 1 Several effective modern drugs derived from traditional herbal medicine

natural products isolated from medicinal plants against SARS-CoV-2 are discussed.

Use of traditional herbal medicine during the COVID-19 pandemic and its antiviral activity against SARS-CoV-2

The plants identified as having been used for treatment and prevention of COVID-19 diseases were extracted from literature searches of the ScienceDirect, PubMed, Scopus, and Google Scholar databases from 28th May 2021 until 20th August 2021. Plant data were retrieved from published articles about community surveys, case reports, and relevant articles that described the use of herbal medicines in Asian communities during the COVID-19 pandemic for both prevention and treatment (Tables 1, 2). The species and families of plant taxa were confirmed and verified using World Flora Online database (http://www.worldfloraonline.org/), a specified plant species database maintained by the Royal Botanic Gardens and Kew and Missouri Botanical Gardens. A number of 91 plant taxa were obtained after extracting the data and then further analyzed to determine the most frequently used families and species for treatment and prevention of COVID-19.

Based on the analysis of medicinal plants used in the communities across several countries in Asia, our findings showed that the Lamiaceae family of medicinal plants was the most frequently used for prevention and treatment of COVID-19 during pandemic (Fig. 2). In addition, our findings revealed that *Zingiber officinale* was the most frequently used species followed by *Glycyrrhiza* spp. and *Ocimum sanctum* (Fig. 3).

Z. officinale (ginger) has been shown to be the most frequently used species in herbal medicine in communities across the countries studied. The crude extract of this herb reportedly exhibited antiviral activity against SARS-CoV-2 in a Vero E6 cell model, with IC_{50} of 29.19 μM. The main phenolic compound in ginger, 6-gingerol, only showed an IC_{50} of ≤ 100 μM [26], which suggests that the efficacy of *Z. officinale* may depend on mechanisms that do not involve 6-gingerol for suppressing COVID-19 symptoms, do not directly attack the virus, or that is synergistic with other herbs to achieve a better therapeutic effect. *Z. officinale* is a spice in which gingerols and shogaol are the active compounds thought to provide health benefits. This herb possesses a range of medicinal benefits, including antiviral activity against feline calicivirus, human respiratory syncytial virus, influenza A, and H9N2, and its activity for stimulating tumor necrosis factor alpha (TNF-α) is postulated as a first-line defense for virus infection [27].

Along with ginger, *Glycyrrhiza* spp. is a frequently used medicinal plant for COVID-19 treatment. This herb is mostly included in various formulas in TCM for COVID-19 treatment, such as Ma Xing Shi Gan, Da Yuan Yin, and Lianhua–Qingwen. The Lianhua–Qingwen formula contains various herbs, including *Glycyrrhiza uralensis*, and reportedly exhibits inhibitory activity against SARS-CoV-2 (Table 2). On the other hand, the aqueous extract of *Glycyrrhiza glabra* root reportedly exhibits inhibitory activity against SARS-CoV-2 infected Vero E6 cells. The extract has shown antiviral effects at 2 mg/ml, which is lower than its toxic concentration. Glycyrrhizin, as a triterpenoid glycoside, has also shown viral blocking ability at 0.5 mg/ml and 1 mg/ml in the pre-entry and post-entry conditions, respectively. In addition, no cytotoxic effect has been found at ≤ 4 mg/ml. The half-maximal effective concentration (EC_{50}) of this compound reportedly is 0.44 mg/ml. Glycyrrhizin has also been shown to significantly reduce the SARS-CoV-2 RNA level [28]. An in silico study showed that this compound binds to the ACE2 receptor, which possibly blocks viral entry [29].

Molecular drug targets for COVID-19

SARS-CoV-2 is a novel coronavirus that belongs to the Coronavirinae family. Coronaviruses are RNA viruses that have a spherically shaped envelope 100–160 nm in diameter. The genome size is 27–32 kb. The 3′ end of the genome encodes structural proteins, such as envelope (E), spike glycoprotein (S), nucleocapsid (N), and membrane glycoprotein (M), and the 5′ end encodes polyproteins involved in replication and transcription [20]. SARS-CoV-2 can enter the host cell via various receptors, such as ACE2, aminopeptidase N (APN), and dipeptidyl peptidase 4 (DPP4). Hence, these three receptors are promising targets for treatment of COVID-19 infection. ACE2 is known to be prevalent in alveolar cells. In addition, males are known to express higher levels of ACE2 than females. The expression of ACE2 can be increased by binding of the S protein of SARS-CoV-2 to ACE2. On the other hand, DPP4 mediates entry of the virus into the host cell via directed cell–cell fusion, whereas APN promotes cross-species transmission of SARS-CoV-2, which is involved in receptor binding [30].

The ACE2 receptor, S protein, RNA-dependent RNA polymerase (RdRp), papain-like protease (PL^{pro}), and 3-chymotrypsin-like protease ($3CL^{pro}$ or main protease (M^{pro})) are known to be potential targets for COVID-19 drugs because these biomaterials are essential for viral invasion of the host cell [4]. SARS-CoV-2 invades the host cell by binding of its S protein to the ACE2 receptor of the host cell followed by S protein cleavage by transmembrane serine protease 2 (TMPRSS2). Next, genomic RNA is released into the host cell cytoplasm and undergoes translation of polyprotein (ppa1/ab), which is cleaved further by viral M^{pro} and PL^{pro} into non-structural protein (nsp). The nsp protein then interacts with RdRp for building the replication–transcription

Table 1 Herbal medicines used during the COVID-19 pandemic based on guidelines, community surveys, and case reports

Family	Species	Country origin	References
Amaryllidaceae	*Allium sativum*	Vietnam	[51]
Apiaceae	*Centella asiatica*	Vietnam	[51]
Apiaceae	*Saposhnikovia divaricata*	China	[52]
Apiaceae	*Glehnia* spp.	China	[52]
Araliaceae	*Panax ginseng*	Vietnam	[51]
Asparagaceae	*Ophiopogon* spp.	China	[52]
Brassicaceae	*Isatis indigotica*	China	[52]
Campanulaceae	*Platycodon grandiflorus*	China	[52]
Caprifoliaceae	*Lonicera japonicae*	China	[52]
Compositae	*Artemisia vulgaris*	Vietnam	[51]
Compositae	*Cynara cardunculus*	Vietnam	[51]
Compositae	*Atractylodes macrocephalae*	China	[52]
Compositae	*Atractylodes* spp.	China	[52]
Compositae	*Eupatorium* spp.	China	[52]
Cucurbitaceae	*Citrullus lanatus*	Bangladesh	[53]
Dryopteridaceae	*Cyrtomium fortune*	China	[52]
Lamiaceae	*Perilla frutescens*	Vietnam	[51]
Lamiaceae	*Plectranthus amboinicus*	Vietnam	[51]
Lamiaceae	*Elsholtzia ciliata*	Vietnam	[51]
Lamiaceae	*Ocimum tenuiflorum*	India	[54]
Lamiaceae	*Vitex negundo*	Bangladesh	[53]
Lamiaceae	*Pogostemon cablin*	China	[52]
Lamiaceae	*Perilla* spp.	China	[52]
Leguminosae	*Glycyrrhiza* spp.	Vietnam	[51]
Leguminosae	*Astragalus* spp.	China	[52]
Leguminosae	*Glycyrrhiza* spp.	China	[52]
Menispermaceae	*Tinospora cordifolia*	India	[54]
Moraceae	*Morus alba*	China	[52]
Oleaceae	*Forsythia suspensa*	China	[52]
Phyllanthaceae	*Emblica officinalis*	India	[54]
Piperaceae	*Piper lolot*	Vietnam	[51]
Poaceae	*Phragmites communis*	China	[52]
Poaceae	*Coix lacryma-jobi*	China	[52]
Ranunculaceae	*Nigella sativa*	Bangladesh	[53]
Rutaceae	*Citrus reticulata*	China	[52]
Saururaceae	*Houttuynia cordata*	Vietnam	[51]
Xanthorrhoeaceae	*Aloe vera*	Vietnam	[51]
Zingiberaceae	*Zingiber officinale*	Vietnam	[51]
Zingiberaceae	*Curcuma longa*	India	[54]

complex. After entering the cell, with RdRp, the virus takes over genetic reproduction to produce new viral RNA. Cleaved glycoproteins by virus proteases (PL^{pro} and M^{pro}) are then produced, and the viral material is assembled so that it can synthesize new viral particles to further infect other host cells [4, 31, 32].

ACE2 is also the proposed drug target for preventing SARS-CoV-2 infection. This enzyme is a transmembrane protein, localized in alveolar epithelial cells, vascular endothelial cells, small intestine epithelial cells, and renal tubular epithelial cells. ACE2 functions by cleaving the C-terminal amino acid residue of angiotensin II (Ang II), which maintains the balance of generated Ang II. Furthermore, ACE2 is known to be the receptor for S proteins of SARS-Cov-2; hence, inhibition of this enzyme may be a drug target for preventing SARS-CoV-2 infection [2, 33]. The expressed S protein of SARS-CoV-2 functions by binding to the ACE2 receptor. Infection by this virus can be through two pathways: endocytic and direct fusion. In the endocytic pathway, cleavage of S proteins is mediated by

Table 2 Use of formulated herbal medicines for prevention and treatment during the COVID-19 pandemic from community case reports and its antiviral activity against SARS-CoV-2

Formula	Country origin	Family	Species	Usage report in community	References	Antiviral activity against SARS-CoV-2	References
Lianhua-Qingwen	China	Oleaceae	*Forsythia suspensa*	Yes	[1]	In an in vitro model using infected Vero E6 cell lines with SARS-CoV-2, an herbal formula inactivated virus replication, altered virus morphology, and reduced pro-inflammatory cytokines	[1, 55, 56]
		Caprifoliaceae	*Lonicera japonica*				
		Ephedraceae	*Ephedra sinica*				
		Dryopteridaceae	*Dryopteris crassirhizoma*				
		Rosaceae	*Prunus armeniaca*				
		Crassulaceae	*Rhodiola rosea*				
		Polygonaceae	*Rheum palmatum*				
		Saururaceae	*Houttuynia cordata*				
		Brassicaceae	*Isatis indigotica*				
		Lamiaceae	*Pogostemon cablin*				
		Lamiaceae	*Mentha haplocalyx*				
		Leguminosae	*Glycyrrhiza uralensis*				
Pudilan Xiaoyan Oral Liquid (PDL)	China	Brassicaceae	*Isatis indigotica*	N/D	–	Inhibit SARS-CoV-2 replication in Vero E6 cells with EC_{50} 1.078 mg/ml and in vivo study with hACE2 mice model infected SARS-CoV-2 revealed that this formula is able to relieve symptoms of pneumonia, chronic obstructive pulmonary disease, and asthma	[1, 57]
		Compositae	*Taraxacum mongolicum*				
		Lamiaceae	*Scutellaria baicalensis*				
		Papaveraceae	*Corydalis bungeana*				
Shuanghuanglian	China	Caprifoliaceae	*Lonicera japonica*	N/D	–	Inhibit SARS-CoV-2 in Vero E6 cells, with an EC_{50} 0.93 µl/ml	[45]
		Lamiaceae	*Scutellaria baicalensis*				
		Oleaceae	*Forsythia suspense*				
Ma Xing Shi Gan	China	Rosaceae	*Prunus armeniaca*	Yes	[58]	N/D	–
		Leguminosae	*Glycyrrhiza* spp.				
		Ephedraceae	*Ephedra* sp.				
Da Yuan Yin	China	Magnoliaceae	*Magnolia officinalis*	Yes	[58]	N/D	–
		Arecaceae	*Areca catechu*				
		Zingiberaceae	*Amomum tsao-ko*				
		Lamiaceae	*Scutellaria baicalensis*				
		Leguminosae	*Glycyrrhiza uralensis*				
		Asparagaceae	*Anemarrhena asphodeloides*				
		Dioscoreaceae	*Dioscorea polystachya*				
Qing Fei Pai Du	China	Ephedraceae	*Ephedra* sp.	Yes	[1, 58]	N/D	–
		Araceae	*Pinellia ternata*				
		Zingiberaceae	*Zingiber officinale*				
		Rutaceae	*Citrus aurantium*				
Yu Ping Feng San	China	Leguminosae	*Astragalus membranaceus*	Yes	[1, 58]	N/D	–
		Compositae	*Atractylodes macrocephala*				
		Apiaceae	*Saposhnikovia divaricata*				

Table 2 (continued)

Formula	Country origin	Family	Species	Usage report in community	References	Antiviral activity against SARS-CoV-2	References
Ayush Kwath	India	Lamiaceae	*Ocimum sanctum*	Yes	[59]	N/D	–
		Lauraceae	*Cinnamomum zeylanicum*				
		Zingiberaceae	*Zingiber officinale*				
		Piperaceae	*Piper nigrum*				
N/D	Bangladesh	Zingiberaceae	*Zingiber officinale*	Yes	[60]	N/D	–
		Myrtaceae	*Syzygium aromaticum*				
		Lauraceae	*Cinnamomum verum*				
N/D	Bangladesh	Zingiberaceae	*Zingiber officinale*	Yes	[60]	N/D	–
		Myrtaceae	*Syzygium aromaticum*				
		Lauraceae	*Cinnamomum verum*				
		Lamiaceae	*Ocimum sanctum*				
		Theaceae	*Camellia sinensis*				
N/D	Bangladesh	Zingiberaceae	*Zingiber officinale*	Yes	[60]	N/D	–
		Theaceae	*Camellia sinensis*				
N/D	Bangladesh	Lamiaceae	*Ocimum sanctum*	Yes	[53]	N/D	–
		Piperaceae	*Piper nigrum*				
N/D	Bangladesh	Zingiberaceae	*Zingiber officinale*	Yes	[53]	N/D	–
		Rutaceae	*Citrus limon*				
N/D	Bangladesh	Lamiaceae	*Ocimum sanctum*	Yes	[53]	N/D	–
		Lamiaceae	*Vitex negundo*				
		Rutaceae	*Citrus limon*				
		Zingberaceae	*Zingiber officinale*				
		Ranunculaceae	*Nigella sativa*				

cathepsin B/L in lysosomes. On the other hand, virus entry via direct fusion is mediated by TMPRSS2 for cleavage of S proteins. The cleavage of S viral protein by these two mediators is a critical factor that enables RNA viruses to enter the cytosol of host cells. Hence, these two proteases and the ACE2 receptor determine the susceptibility to SARS-CoV-2 infection [31, 34]. On the other hand, M^{pro}/$3CL^{pro}$ have essential roles in the viral polyprotein maturation process [1]. $3CL^{pro}$ is known to be the main drug target of coronaviruses, mainly inhibits replication of SARS-CoV-2, and is required for viral replication through cleavage of viral polyproteins to undergo the life cycle. Hence, $3CL^{pro}$ is a target of antiviral drugs [35].

Identified medicinal plants and their active compounds against SARS-CoV-2

Various medicinal plants and isolated compounds have been tested against SARS-CoV-2 and revealed some promising activities based on in vitro and in cell studies (Tables 3, 4). Several crude drugs derived from mostly Asian herbs have been tested for anti-SARS-CoV-2 activity in some infected cells and protein targets.

Antiviral drugs or therapy for SARS-CoV-2 can be achieved by targeting the virus itself or enhancing immunity, which may help to suppress viral replication. Inhibition of viral replication may be through a mechanism that blocks the virus from entering human cells (preventing binding of the virus' S protein to the ACE2 receptor) or by attacking the viral enzymes that are essential for its replication. In addition, the drug can act as an inhibitor of various structural proteins, such as M^{pro}, PL^{pro}, helicase, serine protease, and RdRp [2]. Severe COVID-19 patients also may be treated by blocking the cytokine storm through suppression of pro-inflammatory cytokines. In severe COVID-19 patients, the cytokine storm occurs in response to significantly elevated levels of the inflammatory cytokines, such as interleukin (IL)-6, IL-7, IL8, IL9, IL-10, IL-1B, IL-1Ra, granulocyte macrophage colony-stimulating factor, fibroblast growth factor, IFN-γ, TNF-α, platelet-derived growth factor, monocyte chemoattractant protein, macrophage inflammatory protein 1-α, and vascular endothelial growth factor [4].

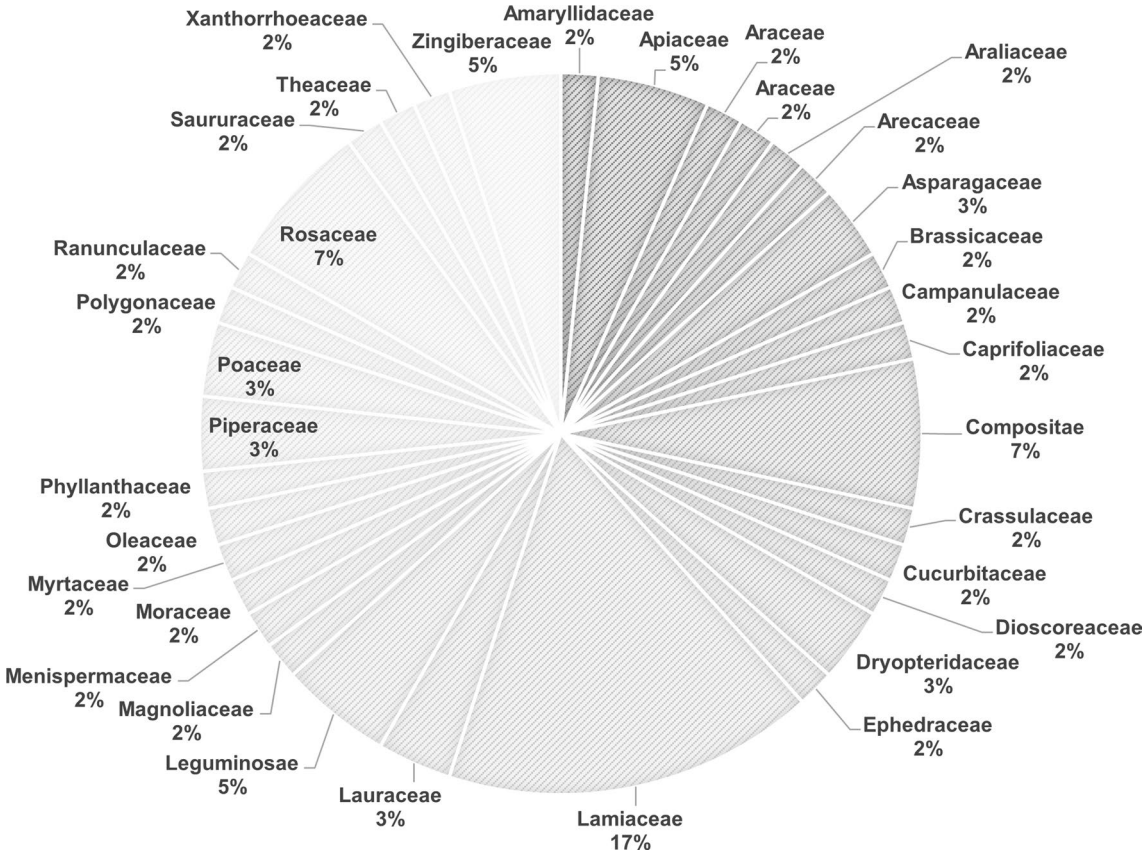


Fig. 2 Frequently used families of medicinal herbs for prevention and treatment of COVID-19

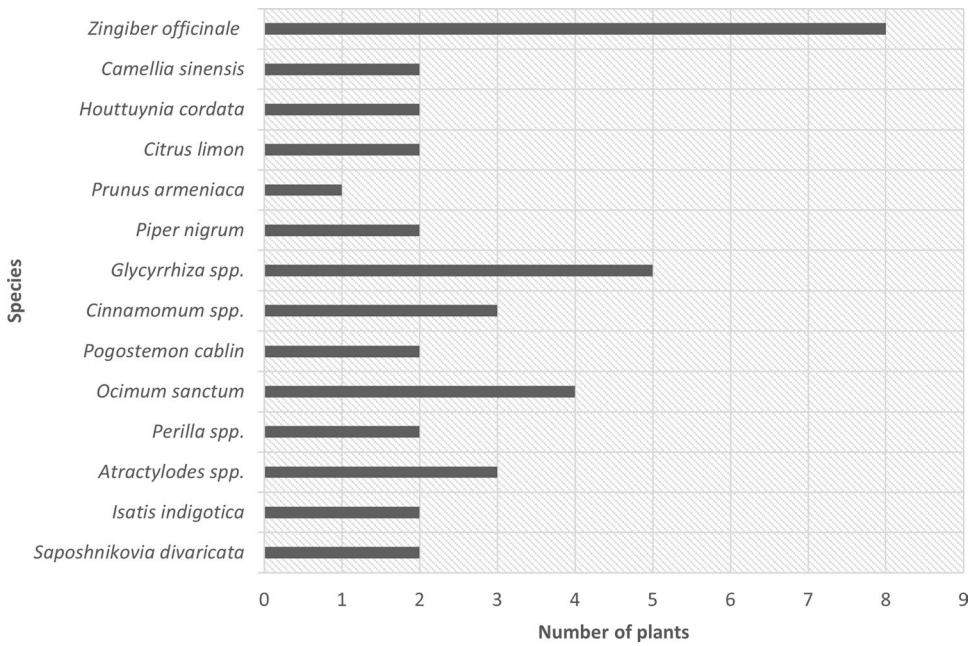


Fig. 3 Frequently used species in herbal medicines against COVID-19

Numerous existing drugs have been repurposed for treating COVID-19 disease, such as chloroquine, remdesivir, favipiravir, and umifenovir [30]. However, currently there is no effective treatment that has been approved by regulators [36]. Chloroquine, an antimalarial drug, possesses antiviral activity, including against coronaviruses, and has been

Table 3 Anti-SARS-CoV-2 activity of medicinal plants (crude drugs)

Origin	Species	Family	IC_{50} (μg/ml)	EC_{50} (μg/ml)	Experimental result	References
Thailand	*Andrographis paniculata*	Acanthaceae	0.036	–	SARS-CoV-2 infected Calu-3 cells	[37]
Thailand	*Andrographis paniculata*	Acanthaceae	68.06	–	SARS-CoV-2 infected Vero E6 cells	[52]
China	*Scutellaria baicalensis*	Lamiaceae	–	0.74	SARS-CoV-2 infected Vero cells	[43]
Korea	*Platycodon grandiflorum*	Campanulaceae	5,010	–	In vitro study using $ACE2^+$ cells using H1299 cell	[34]
Thailand	*Boesenbergia rotunda*	Zingiberaceae	3.62	–	SARS-CoV-2 infected Vero E6 cells	[26]
India	*Camellia sinensis*	Theaceae	8.9 ± 0.5	–	SARS-CoV-2 M^{pro}/$3CL^{pro}$	[61]
India	*Terminalia chebula*	Combretaceae	8.8 ± 0.5	–	SARS- CoV-2 M^{pro}/$3CL^{pro}$	[61]
Thailand	*Zingiber officinale*	Zingiberaceae	29.19	–	SARS-CoV-2 infected Vero E6 cells	[26]
Germany	*Glycyrrhiza glabra*	Fabaceae	–	–	Blocking SARS-CoV-2 replication at pre-entry stage in infected Vero E6 cells at 0.5 mg/ml	[28]
China	*Reynoutria sachalinensis*	Polygonaceae	4.013	–	SARS-CoV-2 M^{pro}/$3CL^{pro}$	[62]
China	*Reynoutria japonica*	Polygonaceae	7.877	–	SARS-CoV-2 M^{pro}/$3CL^{pro}$	[62]
China	*Lycoris radiata*	Amaryllidaceae	–	2.4 ± 0.2	SARS-CoV infected Vero E6 cells	[63]
China	*Artemisia annua*	Compositae	–	34.5 ± 2.6	SARS-CoV infected Vero E6 cells	[63]
China	*Pyrrosia lingua*	Polypodiaceae	–	43.2 ± 14.1	SARS-CoV infected Vero E6 cells	[63]
China	*Lindera aggregata*	Lauraceae	–	88.2 ± 7.7	SARS-CoV infected Vero E6 cells	[63]

considered as a possible antiviral drug for SARS-CoV-2 and been tested against COVID-19 in China. Chloroquine can block cathepsin by increasing lysosomal pH and modulating pro-inflammatory cytokines, including TNF-α and IL-6. However, the failure of this drug in a clinical trial was attributed to its inability to block TMPRSS2-mediated viral entry [30, 34]. Remdesivir, an antiviral drug for Ebola and Marburg virus also has been tested in a clinical trial due to its ability to attack coronaviruses by inhibiting RdRp. The influenza drug, favipiravir, can terminate incorporation of viral RNA into the host cell. Umifemovir/Arbidol, which are influenza A and B drugs, also have been reported to block viral fusion into host cell membranes [30]. Additionally, lopinavir reportedly blocks $3CL^{pro}$ of the virus, whereas both camostat mesylate and nafamostat reportedly inhibit viral entry and act as TMPRSS2 inhibitors. Chloroquine and hydroxychloroquine have also shown inhibition of viral entry [32].

The present review focuses on compounds isolated from medicinal plants against SARS-CoV-2 shown to be active in vitro and in cell studies (Table 4), and several compounds show promising antiviral activity as compared with several FDA-approved drugs as mentioned above (Figs. 4, 5). Among the other tested compounds, andrographolide has shown promising potency (IC_{50} of 0.034 μM, against SARS-CoV-2-infected Calu-3 cells). Andrographolide is a major active compound isolated from *Andrographis paniculata* that has been used for a long time in Thai traditional medicine for diarrhea, common cold, fever, and viral infections. This bicyclic diterpene lactone exhibits various pharmacological properties, such as antioxidant, anticancer, anti-inflammatory, antimicrobial, cardiovascular protection, hepatoprotection, and immunomodulatory. Andrographolide has shown broad-spectrum antiviral activity against various viral infections, such as influenza, hepatitis, HIV, chikungunya, herpes, and HPV. Based on an in vitro assay, the extract and its active compound exhibited anti-SARS-CoV-2 activity. In an enzyme-based assay, andrographolide inhibited M^{pro} (the SARS-CoV-2 main protease), with an IC_{50} of 15 μM, possibly through formation of a covalent bond with the active site at the Cys145 amino acid residue. It is postulated that this compound would attack the virus through multiple pathways, including viral entry, replication, protein synthesis, and protein expression. Andrographolide has also shown binding affinity with the S protein and the ACE2 receptor, hence, it may inhibit viral entry. This compound is thought to be more potent in the late phase of the SARS-CoV-2 life cycle than in genome replication and protein expression [37–40]. The 50% cytotoxic concentration (CC_{50}) of this compound to various normal cell lines from various organs, including liver, kidney, intestine, lung, and brain (HepG-2/imHC, HK-2, Caco-2, Calu-3, and SH-SY5Y, respectively), ranges from 13.2 to 81.5 μM [37].

A prenylated cyclohexenyl chalcone, panduratin A, exhibited potent antiviral activity against SARS-CoV-2 in both pre-entry and post-infection. This compound has been isolated from a fingerroot of *Boesenbergia rotunda* that is commonly used in Southeast Asia and China as a culinarily spice. The rhizome has various pharmacological properties, such as antibacterial, antitumor, anti-allergic, and antioxidant. Panduratin A, as a major active compound, has shown antiviral activity against HIV [41] and

Table 4 Anti-SARS-CoV-2 activity of active compounds isolated from medicinal plants

Plant origin	Compound	Plant	Family	IC_{50} (μM)	EC_{50} (μM)	Model	References
Thailand	6-Gingerol	*Zingiber officinale*	Zingiberaceae	1.38	–	SARS-CoV-2 NP mAb Plaque reduction assay in Vero cells	[26]
Thailand	6-Gingerol	*Zingiber officinale*	Zingiberaceae	> 100	–	SARS-CoV-2 infected Vero E6 cells	[26]
Thailand	Andrographolide	*Andrographis paniculata*	Acanthaceae	0.034	–	SARS-CoV-2 in Calu-3 cells	[37]
Thailand	Andrographolide	*Andrographis paniculata*	Acanthaceae	6.58	–	SARS-CoV-2 infected Vero E6 cells	[52]
Thailand	Andrographolide	*Andrographis paniculata*	Acanthaceae	0.28	–	NP mAb SARS-CoV-2	[26]
Asia	Artemisinin	*Artemisia annua*	Compositae	–	64.45 ± 2.58	SARS-CoV-2 infected Vero E6 cells	[64]
China	Baicalein	*Scutellaria baicalensis*	Lamiaceae	0.39	–	SARS-CoV-2 infected Vero cells	[43]
China	Baicalein	*Scutellaria baicalensis*	Lamiaceae	0.94 ± 0.20 (in vitro $3CL^{pro}$)	2.94 ± 1.19 (in Vero E6 cells)	SARS-CoV-2 infected Vero E6 and in vitro assay against SARS-CoV-2 $M^{pro}/3CL^{pro}$	[45]
	Baicalin			6.41 ± 0.95 (in vitro $3CL^{pro}$)	27.87 ± 0.04 (in Vero E6 cells)	SARS-CoV-2 infected Vero E6 and in vitro assay against SARS-CoV-2 $M^{pro}/3CL^{pro}$	
Korea	Cannabidiol	*Cannabis sativa*	Cannabaceae	7.91	–	SARS-CoV-2 infected Vero cells	[65]
Asia	Cepharanthine	*Stephania cephalanta*	Menispermaceae	4.47	–	SARS-CoV-2 infected Vero cells	[47]
China	Chlorogenic acid	*Lonicera japonica*	Caprifoliaceae	39.48 ± 5.51	–	SARS-CoV-2 $M^{pro}/3CL^{pro}$	[45]
N/D	Digitoxin	*Digitalis purpurea*	Plantaginaceae	0.23	–	SARS-CoV-2 infected Vero cells based on cytopathic effect	[47]
N/D	Digoxin	*Digitalis purpurea*	Plantaginaceae	0.19	–	SARS-CoV-2 infected Vero cells based on cytopathic effect	[47]
Asia	Epigallocatechin gallate (EGCG)	*Camellia sinensis*	Theaceae	16.53	–	In vitro assay against SARS-CoV-2 $M^{pro}/3CL^{pro}$	[35]
Germany	Glycyrrhizin	*Glycyrrhiza glabra*	Fabaceae	–	53.46	SARS-CoV-2 infected Vero E6 cells	[28]

Table 4 (continued)

Plant origin	Compound	Plant	Family	IC_{50} (μM)	EC_{50} (μM)	Model	References
Asia	Myricetin	*Myrica rubra*	Myricaceae	0.22	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[33]
N/D	Osajin	*Maclura pomifera*	Moraceae	3.87	–	SARS-CoV-2 infected Vero cells	[47]
N/D	Ouabain	*Acokanthera ouabaio*	Apocynaceae	0.024	–	SARS-CoV-2 infected Vero E6 cells	[48]
Thailand	Panduratin A	*Boesenbergia rotunda*	Zingiberaceae	0.81	–	SARS-CoV-2 infected Vero E6 cells by IFA assay	[26]
				2.04	–	SARS-CoV-2 infected Calu-3 cells by IFA assay	
				0.53	–	SARS-CoV-2 NP mAb plaque reduction assay in Calu-3 cells	
				0.078	–	SARS-CoV-2 NP mAb plaque reduction assay in Vero cells	
China	Phillyrin	*Forsythia suspensa*	Oleaceae	1.13	–	SARS-CoV-2 infected Vero E6 cells	[66]
Korea	Platycodin D	*Platycodon grandiflorum*	Campanulaceae	0.69	–	In vitro study using $ACE2^{+}$ cells using H1299 cells	[34]
N/D	Quercetin	N/D		4.48	–	Inhibition of rhACE2 (recombinant human) in vitro	[33]
China	Scutellarein	*Erigeron karvinskianus*	Compositae	5.80	–	SARS-CoV-2 in vitro	[1]
Asia	Tetandrine	*Stephania tetrandra*	Menispermaceae	3	–	SARS-CoV-2 infected Vero cells	[47]
Korea	Tetrahydrocannabinol	*Cannabis sativa*	Cannabaceae	10.25	–	SARS-CoV-2 infected Vero cells	[65]
Asia	Theaflavin	*Camellia sinensis*	Theaceae	14.95	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[35]
Asia	Allicin	*Allium sativum*	Amaryllidaceae	–	–	Sub-lethal effect at 50–75 μM with SARS-CoV-2 infected Vero E6 cell	[67]
N/D	Betulinic acid	*Olea europaea*	Oleaceae	10	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[68]

Table 4 (continued)

Plant origin	Compound	Plant	Family	IC_{50} (μM)	EC_{50} (μM)	Model	References
N/D	Betulin	*Olea europaea*	Oleaceae	89.67	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[68]
N/D	Ursolic acid	*Olea europaea*	Oleaceae	12.57	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[68]
N/D	Maslinic acid	*Olea europaea*	Oleaceae	3.22	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[68]
Egypt	Cnicin	*Cnicus benedictus*	Compositae	3.12	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Arctiin	*Cnicus benedictus*	Compositae	> 150	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Sitogluside	*Cnicus benedictus*	Compositae	> 150	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Nortracheloside	*Cnicus benedictus*	Compositae	> 150	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Apigenin 7-O-glucoside	*Cnicus benedictus*	Compositae	> 200	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Luteolin	*Cnicus benedictus*	Compositae	> 300	–	SARS-CoV-2 infected Vero E6 cells	[69]
Egypt	Astragalin	*Cnicus benedictus*	Compositae	> 200	–	SARS-CoV-2 infected Vero E6 cells	[69]
China	Vanicoside A	*Reynoutria sachalinensis*	Polygonaceae	1.364	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[62]
China	Vanicoside B	*Reynoutria sachalinensis*	Polygonaceae	1.639	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[62]
China	Kobophenol A	*Caragana sinica*	Leguminosae	–	71.6	SARS-CoV-2 infected Vero E6 cells	[70]
China	Dihydromyricetin	*Ampelopsis grossedentata*	Vitaceae	4.91	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[71]
China	Isodihydromyricetin	*Ampelopsis grossedentata*	Vitaceae	3.73	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[71]
China	Taxifolin	*Ampelopsis grossedentata*	Vitaceae	72.27	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[71]

Table 4 (continued)

Plant origin	Compound	Plant	Family	IC_{50} (μM)	EC_{50} (μM)	Model	References
China	Ebselen	*Ampelopsis grossedentata*	Vitaceae	2.62	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[71]
China	Resveratrol	N/D	N/D	–	4.48	SARS-CoV-2 infected Vero cells	[72]
N/D	Hopeaphenol	N/D	N/D	42.5	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[73]
N/D	Vaticanol B	N/D	N/D	47.6	–	In vitro assay against SARS-CoV-2 M^{pro}/$3CL^{pro}$	[73]

Dengue virus [42]. The study showed that the antiviral activity against SARS-CoV-2 was superior to the FDA-approved drug, hydroxychloroquine. The value of cytotoxicity against the normal Vero E6 cell line was 14.71 μM [26]. However, molecular targets for this compound have not been well explored.

Baicalin and baicalein, active compounds isolated from *Scutellaria baicalensis*, are used in TCM for treatment of respiratory disorders, heat clearing, detoxification, fire purging, and viral diseases, including hepatitis. The herb has shown antitumor, antimicrobial, anti-inflammatory, and broad-spectrum antiviral activity against various viruses, such as Zika, HIV, DENV, and H1N1. Baicalin and baicalein have shown inhibitory activity against the $3CL^{pro}$ main protease of SARS-CoV-2, with IC_{50} values of 6.41 μM and 0.94 μM, respectively. The anti-SARS-CoV-2 activity of baicalein has been shown to be superior to that of baicalin [43, 44]. In a cell assay model using SARS-Co-2-infected Vero E6 cells, baicalein exhibited IC_{50} and EC_{50} values of 0.39 and 2.94 μM, respectively. The CC_{50} of baicalein against Vero E6 cells was > 200 μM, which is categorized as low cytotoxicity. Baicalein reportedly has closed activity with chloroquine, with an EC_{50} of 2.71 μM [43, 45]. This compound reportedly inhibited viral replication by blocking $3CL^{pro}$ via in an in vitro study, and a molecular docking study showed that the 6-OH and 7-OH of its structure interacted with a carbonyl group of Leu141 and an amide group of Gly143 of $3CL^{pro}$, respectively [43]. In addition, baicalein also has been reported to inhibit the RdRp SARS-CoV-2 in an in vitro assay. In the subsequent molecular docking study, inhibition was not predicted on the active site of the enzyme since it is not an analog of a nucleoside. An in silico study showed that the compound had binding affinities with the Asn705 and His133 residues of RdRp on the palm subdomain and nucleotidyltransferase, respectively [46].

Furthermore, cardiac glycosides, including digoxin, digitoxin, and ouabain, also have shown good properties for treating COVID-19 disease. Cardiac glycosides, molecules that contain a steroid moiety, a 5–6C lactone ring, and a sugar moiety, have been suggested as promising treatments for COVID-19 by targeting NA^+/K^+-ATPase (NKA). Some cardiac glycosides have shown antiviral activity through inhibition of NKA and activation of tyrosine kinase (Src). Src regulates nuclear factor kappa B (NFkB), which is the important transcription factor for SARS-CoV-2 [36].

Digoxin and digitoxin, FDA-approved drugs for cardiovascular diseases, are isolated from *Digitalis purpurea* and reported to have activity against SARS-CoV-2-infected Vero cells based on their cytopathic effect, with IC_{50} values of 0.19 μM and 0.23 μM, respectively. The evaluation of cytotoxicity is measured at a $CC_{50} > 50$ μM for both compounds [47]. Another report with a different assay showed inhibitory activity of digoxin against SARS-CoV-2-infected Vero cells (human isolate BetaCoV/Korea), with an IC_{50} of 0.043 μM and a $CC_{50} > 10$ μM. The IC_{50} of digoxin has been shown to be tenfold higher than those of chloroquine and remdesivir, which have IC_{50} values of 0.526 μM and 1.57 μM, respectively. Digoxin also inhibited viral mRNA expression, protein expression, and viral copy number. Furthermore, the inhibition of mRNA expression of digoxin was superior to those of remdesivir and chloroquine. However, digoxin reportedly is not effective in the viral entry stage. Digoxin appears to act as a viral RNA synthesis inhibitor [48]. On the other hand, digitoxin can suppress the levels of cytokines, including TNFα, M1P2, IFNγ, MCP1, and GRO/KC in an influenza-infected rat lung model. This finding implied that digitoxin may be able to block the cytokine storm caused by the elevated levels of pro-inflammatory cytokines during coronavirus infection. Digitoxin was reported as one of the top-ten pro-inflammatory cytokine inhibitors among 2800

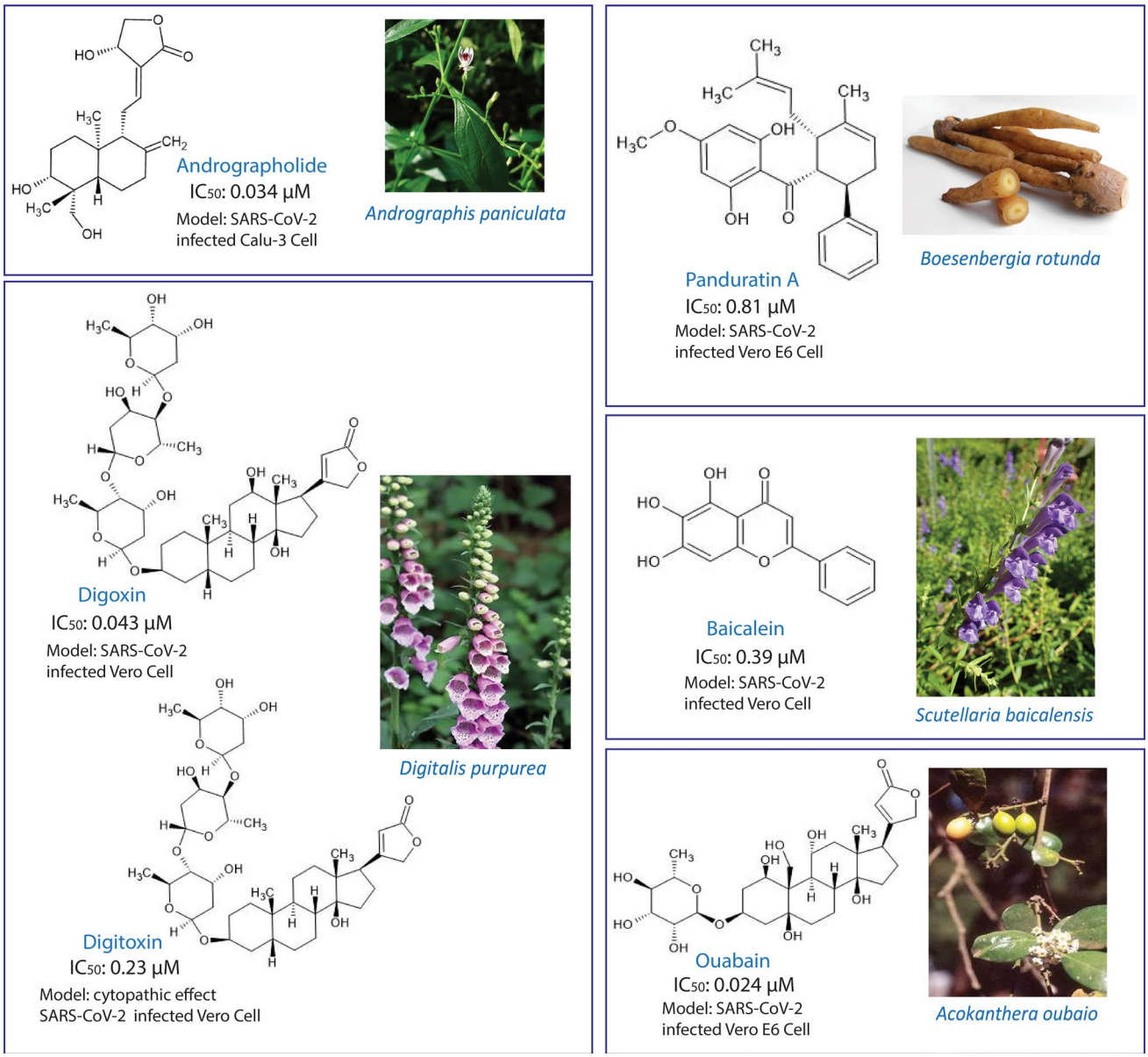


Fig. 4 Promising natural product isolated from medicinal plants as an antiviral drug against SARS-CoV-2 in a cell model

FDA-approved drugs by suppressing TNFα-activated NFkB. Furthermore, compared with digoxin, digitoxin has an affinity to the SARS-CoV-2 spike pseudo-typed VSV in human lung cells and hence is able to block ACE2-S binding for viral entry. Digoxin is postulated to act as an inhibitor at the intracellular level of the host cell rather than at the entry stage [49, 50].

On the other hand, ouabain reportedly showed the antiviral activity against SARS-CoV-2-infected Vero cells, with an IC_{50} of 0.024 μM and a $CC_{50} > 416.66$ μM. The IC_{50} of ouabain is reported to be superior to those of chloroquine and remdesivir. This compound also exhibited inhibition of viral copy number, mRNA, and protein expression. It has been postulated that ouabain inhibits at the viral entry stage by blocking Src-mediated endocytosis [48]. Furthermore, another study reported that the blocking ability of ouabain occurred via binding to the S protein of SARS-CoV-2, so it also may block viral penetration into human lung cells [50].

Conclusion

Herbal medicine has been applied in the treatment of COVID-19 disease in various Asian cultures. Several medicinal plants from both single- and multiple-component herbal medicines have been found to have antiviral

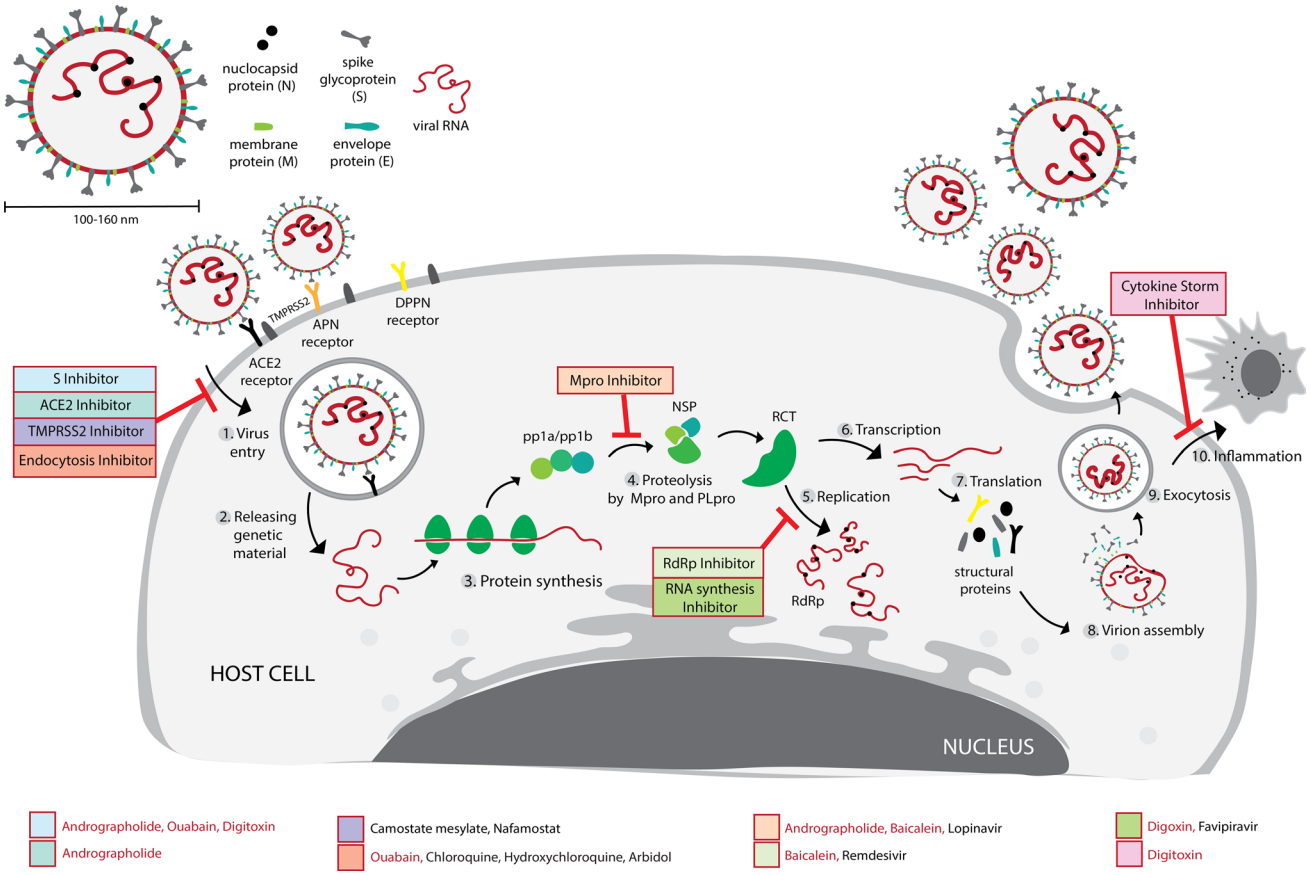


Fig. 5 Summary of the antiviral activity in cell targets of selected isolated active compounds from medicinal plants (highlighted in red) and FDA-approved drugs/antiviral agents against SARS-CoV-2 (highlighted in black)

properties against SARS-CoV-2 in cell-based assays and in vitro studies against various molecular targets, which implies some degree of efficacy for these traditional medicines. Our review showed that the Lamiaceae family was the most frequently used plant family in the treatment and prevention of COVID-19, which suggests that it is a promising source of antiviral agents. In addition, a direct approach using testing of isolated compounds from medicinal plants against SARS-CoV-2 also revealed some promising antiviral activity when compared with repurposed FDA-approved drugs (e.g., digoxin, digitoxin, panduratin A, and andrographolide). These Lamiaceae family members and the isolated compounds discussed in the review warrant further investigations for their activities against coronaviruses, including SAR-CoV-2.

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Author contributions AP and DL designed the study. AP initiated the concept and idea, supervised it, provided input, and revised the manuscript. DL collected, curated, analyzed the data, and wrote the draft of the manuscript. All authors made equal contributions, have read the manuscript, and agreed on the final form for submission.

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Declarations

Conflict of interest Authors declared there is no competing of interest.

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