Promising medicinal plants as a starting point for clinical research into therapies for COVID-19: A literature review

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Review

Abstract

Background: The world community continues to tackle the life-threatening Coronavirus infection which has spread across the world. In times of pandemic, it is to be expected that people turn to those medicinal plants (MPs) commonly used to protect themselves against disease.

Methods: To meet our objectives, we examined all documented findings about the antiviral activity of MPs as well as some other essential compounds, which may act as future research targets for treating Coronavirus (COVID-19). For this purpose, a range of electronic databases have been reviewed up until 15 November 2021: Medline via PubMed, Google Scholar, ScienceDirect and Scopus. Data on MPs that demonstrated one or more of these three actions were recorded, including the extraction method and plant part used, the chemical compounds present, the mechanism of action and the type of study. The compounds in some of these MPs responsible for these activities have also been discussed in the literature.

Results: The following findings were obtained: 41 MPs with antiviral activities and 19 phytocompounds under clinical trials. The secondary metabolites with direct or indirect antiviral activity are mainly flavonoids, tannins, phenols, polysaccharides, terpenes, lectins, alkaloids and steroids.

Conclusions: These informative data could constitute a starting point for further studies to validate antiviral activities in vivo, as well as meaningful efficacy in humans, for potential therapeutic agents for COVID-19

Keywords: Medicinal plants; Antiviral activity, Phytocompounds; Secondary metabolites, COVID-19 Therapy

Background

In December 2019, a new coronavirus was identified belonging to the Coronaviridae family, originating from China. This highly contagious virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Indeed, this coronavirus has affected 220 countries and territories around the world (Worldometer 2021). Coronavirus diseases manifests in several different ways with various symptoms including those associated with the common cold, a severe acute respiratory syndrome, Middle East respiratory syndrome (Davenne *et al.* 2020) and anosmia (Moein *et al.* 2020). The global community has already faced the prospect that this coronavirus will spread across the world and become endemic (CDC 2020).

Today, SARS-CoV-2 continues to spread globally, resulting in associated morbidity, increased mortality producing a significant strain on health care resources (Cohen *et al.* 2021). Several preventive protocols, mainly vaccines, were proposed and some of them have been authorized accompanied by extensive vaccination campaigns. Although there has been approval of antivirals such as remdesivir, there is still an important need for effective antiviral therapies given the potential for this coronavirus to develop new strains.

Like any previous global health crisis, it is normal for certain communities to turn to traditional treatments and practices as an alternative of defensive measures during a pandemic. These treatments may include the use of compounds from medicinal plants (MPs), some of which are already known for their antiviral properties. it's necessary to strick a balance between the great popularity of these practices in some countries, where many people believe in the power of these MPs, and the support of conventional scientific evaluation.

MPs are the oldest form of health care known to mankind and they are used for various ailments such as hypertension, diabetes, cancer, and viral infections. They contain a multitude of bioactive substances that can operate on several diverse targets and signaling pathways, leading to significant outcomes in treating viral infections. In general, the postulated benefit of using MPs in viral infections is correlated to effects on the immune system and the inflammatory effects of some MPs (Vellingiri *et al.* 2020). Such antiviral effects of MPs may play a significant role at different stages of viral growth (Akram *et al.* 2018). Moghadamtousi *et al.* propose that unlike synthetic antiviral drugs, MPs can provide basic raw ingredients for synthesizing potentially important antiviral drugs (Moghadamtousi *et al.* 2015). For this particular pandemic, social media reported that some "alternative" remedies (such as MPs) can prevent infection with COVID-19 or that herbal therapies and teas or infusions can treat infection caused by the virus. Unfortunately, there is no scientific evidence that any of these alternative remedies can prevent or cure the illness caused by COVID-19. More worryingly, some of them may not be safe for consumers. In these conditions, data are scanty regarding which MPs or which mixtures of MPs to use, what the formulation or the constituents should be, what the effective dosage is, and whether these MPs have any side effects.
This paper aims to review the data contained in publicly available literature on the antiviral effect of medicinal plants. Selected data derived from MPs and their compounds could constitute interesting and potentially useful targets for research for therapies for COVID-19.

Materials and Methods

Data Source and Conditions

The search for literature data involved a variety of the online bibliographical databases: Medline via PubMed, Google Scholar, ScienceDirect and Scopus. This selective review used the following search terms: medicinal plants, antiviral activity, antiviral compounds, COVID-19 therapy. From the electronic databases mentioned above, MPs traditionally used that possessed antiviral activity were identified based on specifying the Latin name (Family), extraction method and plant part used, chemical compounds, mechanism of action and type of study all which helped guide us to judge the quality of the study conducted and the information provided. The mechanisms of action of these compounds against the different types of viruses have also been specified. The main active ingredients within some MPs responsible for these activities have also been discussed through data obtained in the literature.

The period covered by the literature data search was open-ended. In addition, there was no language restriction for literature searches that were conducted up until 15 November 2021.

Data Analysis

All data were extracted, fully read, analyzed and validated in the sense that authors checked and selected only articles related to the aim of the study and meeting the following inclusion criteria: ability to access pdf versions of the articles; availability of experimental and clinical studies; articles with high impact factor when information is cited more than once; articles published in relation to and during the period of the COVID-19 pandemic. Only references which report particular and useful data were retained.

When pharmacological and clinical studies were reviewed, the authors have assessed the quality of the studies regarding ethics, scientific standards as well as quality of these articles to extract and discuss only important and promising data. This is because in the context of COVID-19, it is essential not to raise expectations based on primary and theoretical research. Therefore, we prioritized medicinal plant compounds with antiviral activity based on information from clinical studies.

Use of other Ttols

Structures of all the phytomolecules of this article were drawn with the free Chemdraw software (https://chemdrawdirect.perkinelmer.cloud/js/sample/index.html#).

Results and Discussions

A flowchart of the separate analytic steps for MPs that had antiviral activity, and the resulting sets of data which were analyzed, are shown in Figure 1.

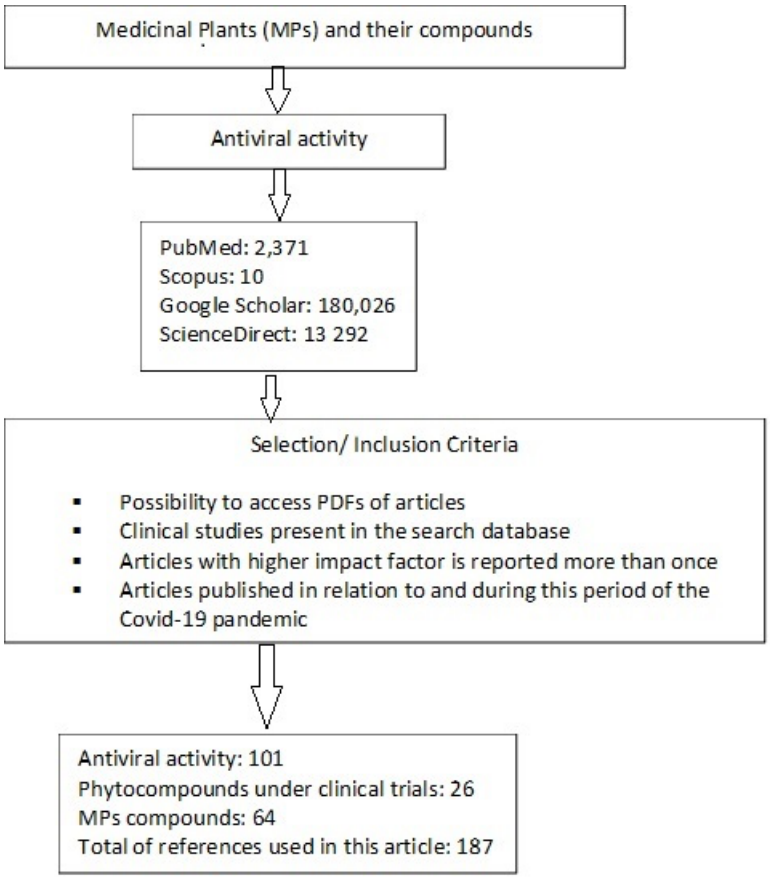

Figure 1. Flowchart of the separate analytic steps for medicinal plants that had antiviral, anti-inflammatory and strengthening of the immune system activities and the resulting sets that were analyzed.

In this literature study, we have identified 41 MPs with antiviral activities (Table 1). It emerges from this literature study that most data are from experimental studies (97.6%) examining antiviral activity with only very few data from clinical studies (2.4%). Additionally, Table 2 includes a list of 17 phytoconstituents that have been investigated in clinical trials and are being evaluated in medical practice.

Antiviral activity of MPs

Antiviral activity can manifest itself through multiple pathways ranging from direct antiviral activity to other indirect antiviral actions such as antibacterial, immune or inflammatory actions. Hence, we found it difficult in our analysis to make these specific distinctions. The role of MPs in combating viral diseases is still limited with an only a few examples such as in the case of coronavirus. Because there are no effective medicines available, now is the right time to highlight existing data to advance research based on natural compounds to treat diseases such as COVID-19. The mechanism of antiviral potential of MPs varies depending on the type of virus. Some phytochemical substances target the viral envelope or membrane proteins; others inhibit the formation of the viral genome or stop attachment of the virus to the host cellular system for reproduction while some destroy enzymes necessary for viral encoding (Ruwali *et al.* 2013).

Table 1. Latin name (Family), Extraction method & plant part used, Chemical compounds, Mecanism of action and Type of study of Medicinal plants with antiviral activity.

Latin name (Family)	Plant part used	Extraction method	Chemical compounds	Mechanism of action	Type of study	Virus	References
Allium sativum L. *(*Liliaceae)	Aged powder, red bulbe, pods	Decoction, Oil	Ajoenes, **Alliin**, **Allicin**, vinyldithiins, sulfides, diallyl trisulfide.	Blocking viral entry into host cells and inhibiting viral RNA polymerase, reverse transcriptase, DNA synthesis and IEG1 transcription through downregulating (ERK)/(MAPK).	A, C	HCMV, influenza A, influenza B, HPIV3, HRV2, HSV, Coxsackie viruses	Arora *et al.* 2011, Chavan *et al.* 2016 , El-Saber Batiha *et al.* 2020, Guo *et al.* 1993, Lawson & Wang 2001, Rouf *et al.* 2020, Tsai *et al.* 1985
Agrimonia pilosa Ledeb. (Rosaceae)	Whole plant	Ethanol extract	Polyphenols, catechin	High plaque reduction on host cells against influenza type A and B viruses, direct contact with virus particles and inhibition of endosome and lysosome acidification for the virus uncoating process.	A, B	Influenza A, Influenza B	Denaro *et al.* 2019, Shin *et al.* 2010
Aloe vera (L.) Burm.f. *(*Liliaceae)	Leaves	2% DMSO gel solution	**Anthraquinone derivatives: aloe-emodin**, emodin, chrysophanol, Vitamins, minerals, enzymes, polysaccharides, polyphenols, sterols, indoles, phenolic and organic acids, acemannans, polymannans, C-glycosides, anthrones	Inhibition of influenza A virus replication by up regulating galectin-3 expression and the expression of antiviral genes IFN-β, IFN-γ, PKR and 2'5',-OAS in infected cells.	B	influenza A	Li *et al.* 2014, Rezazadeh *et al.* 2016
Artemisia afra Jacq. ex Willd. (Asteraceae)	Leaves	Hexane extract, Maceration	**Sesquiterpenes: Artemisinin**, terpenoids, alkaloids, tannins, saponins and cardiac glycosides, phenols, flavonoids.	Inhibition the central regulatory processes of viral-infected cells (NF-κB or Sp1-dependent pathways), thus blocking the host-cell–type and metabolic requirements for viral replication.	A, B, C	HCMV, HSV-1, EBV, HBV, HCV, BVDV, SARS-CoV-2	Efferth *et al.* 2008, Kane *et al.* 2019, Kshirsagar & Rao 2021, Li *et al.* 2020
Artemisia annua L. (Asteraceae)	Leaves	Dichlorometh ane extract	Sesquiterpene lactones: **Artemisinin,** artesunate, coumarin, flavones, phenolic compounds .	Inhibition of the central regulatory processes of viral-infected cells (NF-κB or Sp1-dependent pathways), thus blocking the host-cell–type and metabolic requirements for viral replication.	A, B, C	HCMV, HSV-1, EBV, HBV, HCV, BVDV, SARS-CoV-2	Alesaeidi & Miraj 2016, Chekem & Wierucki 2006, Efferth *et al.* 2008, Kshirsagar

							& Rao 2021, Li *et al.* 2020
Astragalus membranaceus (Fisch.) Bunge (Fabaceae)	Roots	Aqueous and methanol extracts	Astragaloside I, Formononetin-7-O-b-D-glucoside, 3'hydroxyl-formononetin-7-O-b-D-glucoside.	Inhibition of virus on cell proliferation and blocking effect of influenza after infection, increased the SOD activity and reduced the MDA content.	A,B	Influenza	Ganjhu *et al.* 2015, Khan *et al.* 2019, Liang *et al.* 2019
Azadirachta indica A. Juss. (Meliaceae)	Leaves, seeds, bark	Aqueous extract	**Polysaccharides**, Terpene, nimbin, nimbinin, nimbidin, **Azadirachtin**, β-sitosterol.	Inhibition action the initial stage of viral replication and possible interaction with conserved residues of nucleoprotein.	A, B	PV1, Influenza	Ahmad *et al.* 2016, Arora *et al.* 2011, Ganguli 1994, Parida *et al.* 2002
Camellia sinensis (L.) Kuntze (Theaceae)	Leaves	Infusion	Myricetin 3-O- beta-D-glucopyranoside, **Catechin derivatives**: epigallocatechin-3-gallate, epicatechin, epicatechin-3-gallate, epigallocatechin polyphenolic compounds and catechins.	Inhibition effect of three major types of human influenza viruses and avian influenza virus by stopping the adsorption of the viruses on red blood cell.	A, B	3 types human influenza viruses, AIV	Arora *et al.* 2011, Song *et al.* 2007
Chrysanthemum indicum L. (Asteraceae)	Flowers	Infusion	**Polysaccharide**, Glycoside, **phosphorylated chrysanthemin**, glucose, cyanidin; stachydrine, oil and vitamin A, α-terpineol, cis-sabinol, thujone, camphor, chlorogenic acid, luteolin-7-glucoside, linarin, luteolin and acacetin, α-terpineol, cis-sabinol, thujone, camphor.	Inhibition of the virus gene replication.	A, B	H1N1 (swine flu)	Arora *et al.* 2011, Poletto *et al.* 2020
Cinnamomum cassia (L.) Presl (Lauraceae)	Twigs	Supercritical fluid extract, ethanol extract	Flavonoid, Phenylpropanoids, cinnamaldehyde, **cinnamaldehyde**, cinnamic acid, 2-methoxy cinnamic acid, coumarin, cinnamic alcohol, and 2-methoxy cinnamaldehyde.	Inhibiting influenza virus growth. Preventing the viral entrance to inhibit the cytopathic effect of RSV.	A, B	Influenza, RSV	Hayashi *et al.* 2007, Ji *et al.* 2015, Liu et al, 2013, Liu *et al.* 2020, Wang *et al.* 2009, Zhou *et al.* 2017
Cinnamomum verum J.Presl (Lauraceae)	Leaf	Methanolic extract	Polyphenols, Cinnamaldehyde, gum, tannin, mannitol	Prevention the entry of the virus in the host cell	A, B	H1N1 (swine flu)	Arora *et al.* 2011, Mathew & Abraham 2006

Crocus Sativus L. (Iridaceae)	Flowers	Water extract, Infusion	**Crocin, picrocin**, Safranal, non-volatile (carotenoids, lycopene, and α and β carotenes), aromatic compounds, vitamins: riboflavin and thiamine	Inhibition the virus entry by suppression of penetration virions into Vero cells and disturbance of virus replication	A, B	HIV-1, HSV-1	Dar *et al.* 2017, Soleymani *et al.* 2018
Echinacea purpurea (L.) Moench (Asteraceae)	Stems, leaves, barks	Aqueous, ethanol and ethyl acetate soluble fractions	Alklamides, Cichoric acid, ethanol and ethyl acetate, polysaccharide and cichoric acid	Inactivation of influenza viruses with similar membrane structures suggesting possible membrane target for the antiviral ingredients	B	Influenza	Vimalanathan *et al.* 2005
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae)	Roots and bark	Ethanol extract	3α, 2β-2-(3′-Hydroxy-4′-methoxy-phenyl)-1-(4″-hydroxy-5″-methoxyphenyl)-1-oxo-3-propanol, 1,6-Bis-(3,5-dimethoxy-4-hydroxyphenyl) hexane-1,6-dione, 1-(3-hoxy-4-hydroxyphenyl)-6-(3,5-dimethoxy-4-hydroxyphenyl) hexane-1,6-dione/ syringin, caffeic acid, isofraxidin, sesamin, oleanolic acid Coniferyl aldehyde and afzelin.	Inhibition the productive replication of all viruses which belong to the RNA type human viruses like rhinovirus, RSV and influenza A virus in cell cultures.	B	Rhinovirus, RSV, Influenza A	Aicher & Wozniewski 1998, Glatthaar-Saalmuller *et al.* 2001, Madabushi *et al.* 2006, Salah Fatnassi *et al.* 2013
Eupatorium perfoliatum L. (Asteraceae)	Aerial part, flowers	Hydroalcoholi c extract	Eupafolin, Chlorogenic acid, Rutin, Isoqurcitrin, Trifolin, Astragalin, 3,5,-O-Caffeoyl quinic acid, flavonoid glycosides, caffeoyl quinic acids.	Inhibition the growth of influenza A virus by blocking attachment of the virus and by interfering with virus-induced hemagglutination.	B	Influenza A	Derksena *et al.* 2016
Geranium sanguineum L. (Geraniaceae)	Flowers	Methanolic ethanolic, polyphenolic extracts	Polyphenols, Caffeic acid.	Reducing the expression of hemagglutinin protein on the surface of cells infectious virus of influenza A yield and plaque, inhibition of formation Synthesis proteins of the virus, the action was directed against an early stage of infection.	B	influenza A	Serkedjieva & Hay 1998, Sokmena *et al.* 2005
Ginkgo biloba L. (Ginkgoaceae)	Fruits, leaves	Powder extract	Flavonoid glycosides and terpenoids: ginkgolides, bilobalides.	Inhibitory effect of the plant extract was observed against influenza A (H1N1 and H3N2) and influenza B viruses when Hemagglutination inhibition assays revealed that the extract interferes with the interaction between influenza viruses and erythrocytes.	A, B	influenza A (H1N1), H3N2, influenza B	Arora *et al.* 2011, Haruyama & Nagata 2013

Glycine max (L.) Merr. (Fabaceae)	Seeds	Methanol extract	Phenolic acids, flavonoids, **isoflavones: genistein**, **saponins: soyasaponin I and II**, phytosterols, sphingolipids, oleic, linoleic, linolenic, **7S-peptides**, **β-conglycinin**, arachidic acids, behenic, lignoceric acids, **palmitic acid**, **myristic acid**.	Inhibition of virus penetration and protein synthesis involving a virucidal effect.	B	HSV-1, HCMV, influenza, HIV1, FCV (surrogate of Human Norovirus)	Alghamdi *et al.* 2017, Hayashi *et al.* 1997, Matemu *et al.* 2011, Sakai & Kogiso 2008
Glycyrrhiza glabra L. (Fabaceae, Papilionaceae)	Rhizome roots	Aqueous extract	**Glycyrrhizic acid,** Triterpene, Saponins, liqcoumarine, glabrocoumarone, sweet tasting compound anethole ("trans"-1-methoxy-4-(prop-1-enyl) benzene), Glucosides, Liquiritin, Isoliquiritin.	Inhibition of virus replication, Inhibition of adsorption and penetration of the virus during the early steps of the replicative cycle.	A, B	HBV, HCV, HSV, influenza A virus pneumonia, HIV, SARS related coronavirus	Cinatl *et al.* 2003, Curreli *et al.* 2005, Fiore *et al.* 2008
Hypericum perforatum L. (Hypericaceae)	Leaves	Ethyl acetate extract	**Hypericin**, pseudohypericin, hyperoside, quercitrin, quercetin.	Reducing the relative messenger ribonucleic acid mRNA expression and virus titer of infectious bronchitis virus in the trachea and kidney in vivo.	B	Bronchitis virus	Chen *et al.* 2019
Jatropha multifida L. (Euphorbiaceae)	Stem	Aqueous ethanol extract	**Lathyrane-type diterpenoids, jatrophane-type diterpenoids**, coumarino-type lignoids, multifidone, multifidanol, multifidenol, podcarpic acid, totarol.	Inhibition of both viral infection and growth.	A, B	Influenza	Das *et al.* 2008, Das *et al.* 2009, Das *et al.* 2010, Denaro *et al.* 2019, Mohan *et al.* 2020, Shoji *et al.* 2017
Justicia adhatoda L. (Acanthaceae)	Whole plant	Aqueous and methanolic extracts, powder	Phenols, Tanins, Saponins, flavonoids, Alkaloids.	Interfering with influenza type B virus protein envelope and inhibit the infection by blocking the virus attachment and by inhibition of viral hemmaglutinin protein.	A, B	Influenza B	Amber *et al.* 2017, Denaro *et al.* 2019, Chavan & Chowdhary 2014
Melaleuca alternifolia	Leaves	Essential oil, infusion	Terpene hydrocarbons: **terpinen-4-ol**, **terpinolene**, 1,8-cineole, γ Terpinene, α -Terpinene, p-Cymene, α –pinene, **α –**	Inhibition of the viral replication by interference with an early step of the viral replicative cycle.	A, B	Influenza A	Bishop 1995, Garozzo *et al.* 2009, Garozzo *et*

(Maiden & Betche) Cheel (Myrtaceae)			**Terpineol**, Aromadendrene, δ-Cadinene, Limonene, β-phellandrene, Globulol, Myrcene, α –thujene.				*al.* 2011, Shah & Baghel 2017
Melissa officinalis L. (Lamiaceae)	Leaves	Hydroalcoholic extract, essential oil, infusion	Citronellal, linalool, geraniol, β-caryophyllene-oxide.	Destructive effect on the virus and the internal mechanisms of the cell could reduce the virus of influenza A by suppressing effect on the growth of the virus, also was able to suppress the propagation of the H9N2 through direct interaction with the virus particles.	B	Influenza A	Jalali *et al.* 2016
Mimosa pudica L. (Fabaceae)	Leaves and twigs	Methanol, ethanol extracts	Alkaloid : Mimosine, Adrenalin, Crocetin dimethyl Easter, tannin, d-xylose, d-glucuronic acid, green yellow fatty oil, tubuline, phytohormone turgorines, 4-α-(b-D-glucopyranosyl-6-sulphate) gallic acid, terpenoids, flavonoids, glycosides, alkaloids, quinines, phenols, tannins, saponins, coumarins.	Inhibition of viral replication and prevention about of cytopathic effects development.	B	MuV	Gandhiraja *et al.* 2009, Joseph *et al.* 2013, Malayan *et al.* 2013
Nerium Oleander L. (Apocynaceae)	Whole plant, leaves	Aqueous extract, maceration	**Digitoxigenine,** Limonene, α-Pinene, **β-Phellandren,** terpinene-4-ol, Sabinene, Neriine, Oleandrin.	Reducing the infectivity of virus produced from infected cells and Reduced expression of the envelope protein gp120, the sole determinant of virus infectivity, suggesting a novel mechanism underlying the impaired infectivity.	B	HIV, HSV-1, HSV-2	Aanouz *et al.* 2020, Boff *et al.* 2019, Singh *et al.* 2013
Olea europaea L. (Oleaceae)	Fruits	Virgin olive oil, leaf extract	Phenolic compounds: **oleuropein**, hydroxytyrosol, oleic acid, squalene.	Blocking Cell-to-cell transmission of HIV and HIV replication.	A, B	HIV virus	Lee-Huang *et al.* 2003, Omar, 2010
Origanum vulgare L. (Lamiaceae)	Leaves	Methanol extract, infusion, maceration, decoction: essential oil	**Carvacrol**, thymol, Caryophyllene, spathulenol, germacrene-D, α-terpineol, linoleic acid, phenolic compounds: caffeoylquinic acids, flavans and flavone C-glycosides.	Inactivating MNV and H1N1 influenza by acting directly on the viral capsid and subsequently the RNA.	A, B	MNV, Influenza A	Gilling *et al.* 2014, Şahin *et al.* 2004, Vimalanathan & Hudson 2012, Zhang *et al.* 2014

Panax ginseng C.A.Mey. (Araliaceae)	Roots	Infusion and decoction extracts	Ginsenosides, triterpenoïdes, gintonin, L-arabinose: D-galactose: L-rhamnose: D-galacturonic acid: D-glucuronic acid, hexuronic acid, ginsenan PA, ginsenan PB.	Inhibition of the virus replication.	B	RSV	Ang *et al.* 2020, Lee *et al.* 2014, Tomoda *et al.* 1993
Plumbago indica L. (Plumbaginaceae)	Roots	Maceration, methanolic and ethanolic extracts	**Plumbagin**: 2-methyl-5-hydroxy-1,4-naphthoquinone, flavonoid, tanins, carbohydrates, alkaloids, phenols.	Inhibition of viral nucleoprotein synthesis and polymerase activity.	B	Influenza A	Chavan *et al.* 2016
Sambucus ebulus L. (Adoxaceae, Caprifoliaceae)	Leaves	Essential oil	Steriods, tannic acids, glycoside compounds, ebulin, caffeic acid, and cardiac glycosides, chlorogenic acid, free fatty acids: palmitic acid, alkanes, β-bisabolene, germacrene D, geranyl acetate and α-cubebene, Lectins: ebulitin and ebulin derivatives.	Inhibition of enveloped viruses and agglutinating virus particles or preventing their penetration to cells by blocking virus receptor sites.	A, B	Influenza, enveloped viruses	Bliah 1987, Ganjhu *et al.* 2015, Kaya *et al.* 2019
Sambucus nigra L. (Adoxaceae, Caprifoliaceae)	Flowers	Water extract	Flavonoids, agglutinins.	Attacking the entry of influenza virus in the host cells to prevent the pathogenesis and stop the infection by competitive inhibition of the virus attachment and endocytosis.	A, B	Influenza	Akram *et al.* 2018, Bliah 1987, Denaro *et al.* 2019
*Schefflera heptaphylla (*L.) Frodin (Araliaceae, Scarabaeoidea)	Leaves	Infusion	**Frodin, caffeoylquinic acids: 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 3-O-caffeoylquinic acid,** Saponin, Triterpenoids, 3alpha-hydroxylup-20[29]-ene-23,28-dioic acid and 3-epi-betulinic acid 3-O-sulfate.	Inhibition of virus-cell fusion in the early stage, and the inhibition of cell-cell fusion at the end of the virus replication cycle.	A, B	H1N1 (swine flu)	Arora *et al.* 2011, Li *et al.* 2007, Valcheva Kuzmanova & Belcheva 2006
Scutellaria baicalensis Georgi (Lamiaceae)	Roots	Aqueous and ethanol extracts	5,7,4'-trihydroxy-8-methoxyflavone (F36), **baicalin**.	Reducing of influenza virus replication by inhibiting the fusion of the virus with endosome and lysosome membrane.	A, B	Influenza	Nagai *et al.* 1995, Shi *et al.* 2016
Sophora flavescens Aiton (Fabaceae)	Roots	Methanol, ethanol extracts	Quinolizidine, matrine : alkaloids, flavesines, alopecurine B, 7,11-dehydro-oxymatrine, 10-oxy-5,6-dehydromatrine, 10-oxysophoridine, piperidine, **kuraridin**.	Antiviral activity against HBV and direct inhibition of reovirus attachment, inhibition of viral replication by inhibiting hemagglutination, blocked binding of viral sigma 1 protein.	A, B	HBV, Reovirus	Kwon *et al.* 2015b, Zhang *et al.* 2018

Syzygium aromaticum (L.) Merr. & L.M.Perry (Myrtaceae)	Flower buds	Aqueous extracts	**Eugenol**, Beta-Caryophyllene, 2-propanediol, eugenol acetate, galic acid, eugeniin.	Inhibition viral DNA synthesis by inhibition of viral DNA polymerase.	B	HSV, FCV (surrogate of Human Norovirus)	Aboubakr *et al.* 2016, Benencia & Courreges 2000, Kurokawa *et al.* 1998
Taraxacum officinale (L.) Weber ex F.H.Wigg. (Compositae)	Leaves	Methanolic extracts	Taraxine, luteolin, caffeoylquinic acids, quercertin diclycosides.	Inhibition of viral nucleoprotein synthesis and polymerase activity and have inhibitory effects on dengue virus serotype 2 replication.	B	DENV-2	Flores-Ocelotl *et al.* 2018, He *et al.* 2011
Thymus capitatus (L.) Hoffmanns. & Link (Lamiaceae)	Leaves	Essential oil, infusion	carvacrol, thymol, p-cymène, eugenol, α-pinène, β-myrcène.	Inhibition of the adsorption and penetration of the virus into the cell and inhibition of its replication within the cell.	B	HSV1, ECV11, ADV	Salah-Fatnassi *et al.* 2010
Thymus vulgaris L. (Lamiaceae)	Leaves	Hydrosol extract, infusion	Carvacrol, thymol, p-cymene, γ-terpinene, alpha-Thujene, alpha-Pinene, beta-Pinene, beta-Myrcene, alpha-Phellandrene, D-Limonene, beta-Phellandrene, Terpineol, Caryophyllene, Terpinen-4-ol, Cyclohexene, 1-methyl-4-(5-methyl-1-methylene-4-hexenyl).	Operating during pre-entry and post-entry steps of the virus and possible direct effects by inhibition on the principal external proteins of the influenza virus called hemagglutinin and Neuraminidase.	A, B	Influenza	Borugă *et al.* 2014, Kaewprom *et al.* 2017
Urtica dioica L. (Urticaceae)	Whole plant	Methanolic extracts	Phenolics compounds: chlorogenic and 2-O-caffeoylmalic acid, **Flavonoids (quercetin-3-Orutinoside, kaempherol-3-O-rutinoside)**, Anthocyanins, carvacrol, carvon; naphthalene, (E)-anethol, hexahydrofarnesyl acetone, (E)-geranyl acetone, (E)-β-ionone, phytol.	Inhibitory effect DENV-2 replication.	B	DENV-2	Flores-Ocelotl *et al.* 2018, Gül *et al.* 2012, Pinelli *et al.* 2008
Zingiber officinale Roscoe (Zingiberaceae)	Roots rhizome	Decoction	Vanillyl ketones: gingerol, paradol, shogaols, zingerone, camphene, p-cineole, zingiberene.	Inhibition of viral replication inside the HCV-infected cells and have strong anti-influenza virus type A activity by inhibiting attachment of the virus to the cell.	A, B	Influenza A	Abd El-Wahab *et al.* 2009, Park & Lee 2005

Legend:

Type of study: A = Literature review; B = Experimental study; C = Clinical study.

Abbreviations. ADV: Adenovirus; AIV: Avian influenza virus, BD: Bovine dermis; BVDV: bovine viral diarrhea virus; CDV: Canine Distemper Virus; CRFK: Crandell feline kidney Cell; DADS: Diallyl disulfide; DATS: Diallyl trisulfide; DENV-2: Dengue virus serotype 2; DMSO: dimethylsulfoxyd; ECV11: Echovirus 11; ERK: extracellular-signal-regulated kinase; EBV: Epstein-Barr virus; FCV: feline calicivirus; HCMV: Human Cytomegalovirus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEP-2: Human larynx epidermoid carcinoma cells; HIV1: human immunodeficiency virus type 1; HPIV3: Human parainfluenza virus type 3; HRV2: human Rhinovirus type 2; HSV-1: herpes simplex virus type 1; IEG1: Immediate-early gene 1; LSDV: Lumpy Skin Disease Virus; MAPK: mitogen activated protein kinase; MDA: Malondialdehyde; MDCK cells: Madin-Darby canine kidney cell line; MDCK: Madin-Darby canine kidney; MNV: murine norovirus; Mumps Virus : MuV; PV1: Poliovirus type1; SARS-CoV-2: respiratory syndrome coronavirus 2; RSV: respiratory syncytial virus; SOD: Superoxide Dismutase.

Secondary metabolites with direct or indirect antiviral activity

Flavonoids and flavones

The antiviral activity of flavonoid derivatives has been shown to be directed towards a multitude of viruses (HSV, HIV, Coxsackie B virus, coronavirus, cytomegalovirus, poliomyelitis virus, rhinovirus, rotavirus, poliovirus and sindbis virus) (De Bruyne *et al.* 1999). It has been verified that the antiviral activity of flavonols against HSV-1 exceeded that of flavones (Berrin *et al.* 2011, Fritz *et al.* 2007). Luteoforol (Figure 2), a pure compound of *Hypericum connatum* Lam. (Hypercaceae), which is used in southern Brazil in the treatment of acute herpetic gingivostomatitis, was very active at reducing the viral titer of HSV-1 DNA viral strains KOS and VR733 (ATCC), at a concentration of 0.625 mg/ml (Fritz *et al.* 2007).

Table 2. List of repurposed phytoconstituants under clinical trial against COVID-19. Phytoconstituant, Plant source (Family), Type of trial, Targeted Virus/Purpose, Stage of development/outcomes, References

Phytoconstituant	**Plant source (Family)**	**Type of trial**	**Targeted Virus/Purpose**	**Stage of development/outcomes**	**References**
Artemisinin-piperaquine (AP)	*Artemisia annua* (Asteraceae)	NRCT	SARS-CoV-2	In patients with mild-to-moderate COVID-19, the time to reach undetectable SARS-CoV-2 was significantly shorter in the AP group	Li *et al.* 2020
Acai palm berry extract	*Euterpe oleracea* (Arecaceae)	CT Phase II	SARS-CoV-2	7-point ordinal symptom scale, need for mechanical ventilation, need for hospitalization	NCT04404218, 2020
Aged garlic extract	*Allium sativum* (Amaryllidaceae)	RCT	Flu virus	Reduction of severity of cold and flu illness, days of symptom exists, number of incidences and work/school missed as well the role of specific innate-like lymphocytes (γδ-T cell and NK cell) and antioxidant parameters	Nantz *et al.* 2012; Percival, 2016 ; Rouf *et al.* 2020
Alklamides, Cichoric acid	*Echinacea purpurea* (Asteraceae)	CT Phase IV	HIV SARS-CoV2	- Illustrate the interaction between the anti-retroviral drug, darunavir, and *Echinacea purpurea* in HIV-1 infected patients - Estimate the potential of different Echinacea formulations (head-to-head) to reduce concentration infectivity and shedding of SARS-CoV-2 under *in vivo* conditions	Mólto *et al.* 2010; NCT04999098, 2021
Black seed oil	*Nigella sativa* (Ranunculaceae)	CT Phase II, CT Phase III (RCT)	Coronavirus Infection SARS-CoV2	Determination of proportion of patients who are clinically recovered, normalization of chest radiograph, rate of complications	NCT04401202, 2020; NCT04347382, 2020
Colchicine	*Colchicum autumnale* (Colchicaceae)	CT Phase III randomized, double-blind,	COVID-19 Coronavirus Infection	Colchicine alleviated the risk of death and hospitalization 21% more in the treatment group than in the placebo group	NCT04322682, 2020; Montreal Heart Institute, 2020

		placebo-controlled clinical trial		Another promising outcome of this statistically significant clinical trial was a decline in hospitalizations of 25%, the use of mechanical ventilation by 50%, and mortality by 44% among 4,159 patients who were tested positive for corona infection in nasopharyngeal PCR tests	
(+)-Calanolide A	*Calophyllum lanigerum* (Clusiaceae)	CT Phase I	HIV	Successfully passed the clinical trial	Creagh et al., 2001
Chloroquine diphosphate, hydroxychloroquine	*Cinchona officinalis* (Rubiaceae)		SARS-CoV-2	Daily dose of 600mg of hydroxychloroquine along with azithromycin significantly reduced virus load after six days of inclusion. A higher dosage of chloroquine diphosphate along with azithromycin in critically ill patients especially suffering from cardio disorders has been reported to be unsafe	Borba et al., 2020; Gautret et al., 2020;
Cannabidiol	*Cannabis sativa* (Cannabaceae)	CT Phase I, CT Phase II	SARS-CoV-2	Evaluation of the impact of Cannabidiol on the cytokine profile with severe and critically COVID-19 infected people along with safety and efficacy profile	NCT04731116, 2020
Medicinal cannabis	*Cannabis sativa* (Cannabaceae)	CT Phase II	SARS-CoV-2	Treatment of COVID-19, treatment of symptoms	NCT03944447, 2020
Licorice extract (Glycyrrhizin)	*Glycyrrhiza glabra* (Fabaceae)	Not applicable	SARS-CoV-2	Increased number of people recovering from COVID-19	NCT04487964, 2020; Armanini et al., 2020
Escin	*Aesculus hippocastanum* (Sapindaceae)	CT Phase II, CT Phase III	Coronavirus Infections	Determination of mortality rate, the differences in oxygen intake methods, time of hospitalization (days), time of hospitalization in intensive care units, pulmonary function	NCT04322344, 2020
Kuntze extract (P2Et)	*Caesalpinia spinosa* (Fabaceae)	CT Phase II, CT Phase III	COVID-19	The efficacy of P2Et in reducing the length of hospital stay of patients with clinical suspicion or confirmed case of COVID-19	NCT04410510, 2020
Resveratrol	*Veratrum album* (Liliaceae)	Not applicable	SARS-CoV2	There was a trend towards reduction in death in patients receiving resveratrol-copper	Mittra et al., 2020

Standardized elderberry extract	*Sambucus nigra* (Adoxaceae)	RCT	Influenza A, Influenza B, RSV, AdV	Improvement in clinical symptoms. No adverse effects	Kong, 2009; Tiralongo et al. 2016; Hawkins et al. 2019
Quercetin	Not available	RCT	SARS-CoV-2	No conspicuous outcome has been published	NCT04377 789, 2020
Triptolide woldifiion	*Tripterygium wilfordii* (Celastraceae)	CT Phase III, RCT	HIV-1	All patients were explored for 18 months in terms of the clinical features, drugs side-effects, and immunological and viral response, and the HIV-1 reservoir	Li, 2014

Abbreviations. AdV: Adenoviruses; COVID-19: COronaVirus Disease 2019; CT: Clinical trial; HBV: Hepatitis B Virus; HIV1: human immunodeficiency virus type 1; NRCT: Non-randomized clinical trials; RCT: Randomized clinical trials; RSV: Respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Particularly promising flavonoids in virology such as luteolin, kaempferol, quercetin and apigenin should be explored further (Figure 2). In this regard, *Artemisia annua* L. (Asteraceae) plays a special role in China in the fight against coronavirus because it is administered alone and not mixed with other plants (Van der Kooyn and Sullivan, 2013). *In vitro, Artemisia annua* L. has been shown to exhibit, with *Lycoris radiata* (L'Hér.) Herb., *Pyrrosia lingua* (Thunb.) Farw. and *Lindera aggregata* (Sims) Kosterm., significant inhibition of SARS-CoV (Li *et al.* 2005). In addition, very recent studies on SARS-CoV-2 confirm the potential of *Artemisia annua* L. in the fight against the epidemic. A study attempted to simulate numerically the chemical inhibition of test molecules on the main protease of SARS-CoV-2. Among the molecules with the greatest potential for inhibition, four are among the active ingredients found in *Artemisia annua* L. namely luteolin, kaempferol, quercetin and apigenin (Smith & Smith 2020, Vincent *et al.* 2005). *Artemisia annua* L. is used to treat fevers and respiratory syndromes and its antiviral properties are now demonstrated. These recent results support the rationale for the administration of *Artemisia annua* L. as a treatment supplement in the fight against COVID-19.

However, it is important to point out that twenty-nine case reports of hepatotoxicity in relation with the use of the extract of *Artemisia annua* L. in grapeseed oil which were collected via the New Zealand pharmacovigilance system. The assessment of the case reports using the Bradford Hill guidelines for causal inference, has concluded that there was a safety signal of a positive causal association between the *Artemisia annua* L. extract and hepatotoxicity sufficient for an alert to be communicated and further investigations are needed (Savage *et al.* 2019).

This should draw the attention of researchers to the importance of the toxicological study of these compounds in parallel with their antiviral effect and also of the studies of possible interactions between these promising natural compounds and conventional drugs prescribed for viral diseases including COVID-19. In addition, we cannot claim that compounds like kaempferol or quercetin are of any therapeutic benefit. While they show promise in terms of *in vitro* effects, there is absolutely no evidence that this is of any clinical therapeutic relevance. Additional well-targeted studies based on the mechanism of action of these substances in virology are required.

Quantitative Real-time Polymerase Chain Reaction (qRT-PCR) results have revealed flavonoids from *Berberis lycium* Royle. (Berberidaceae) root that naturally grows in all regions of the Himalayas and in regions of Pakistan, Nepal, Bangladesh, Afghanistan, and India. In these countries, this plant is used to treat liver disorders and has shown a significant ability in reducing or even stopping proliferation of hepatitis C virus (HCV) virus and (Yousaf *et al.* 2018).

Kaempferol is a polyphenol, which is richly present in many plants such as *Achillea millefolium* L.*, Leptocarpha rivularis* DC. and *Urtica dioica* L. that has anti-inflammatory properties (Alam *et al.* 2020). Moreover, Kaempferol isolated from *Rhodiola rosea* L. (Crassulaceae) root has been reported to have *in vitro* anti-influenza A virus activity, namely against H1N1 and H9N2 (Jeong *et al.* 2009). Indeed, Kaempferol at 30.2 to 99.1 µM induced activity against H1N1 and 18.5 to 133.6 µM against H9N2-induced cytopathic effect (Jeong *et al.* 2009).

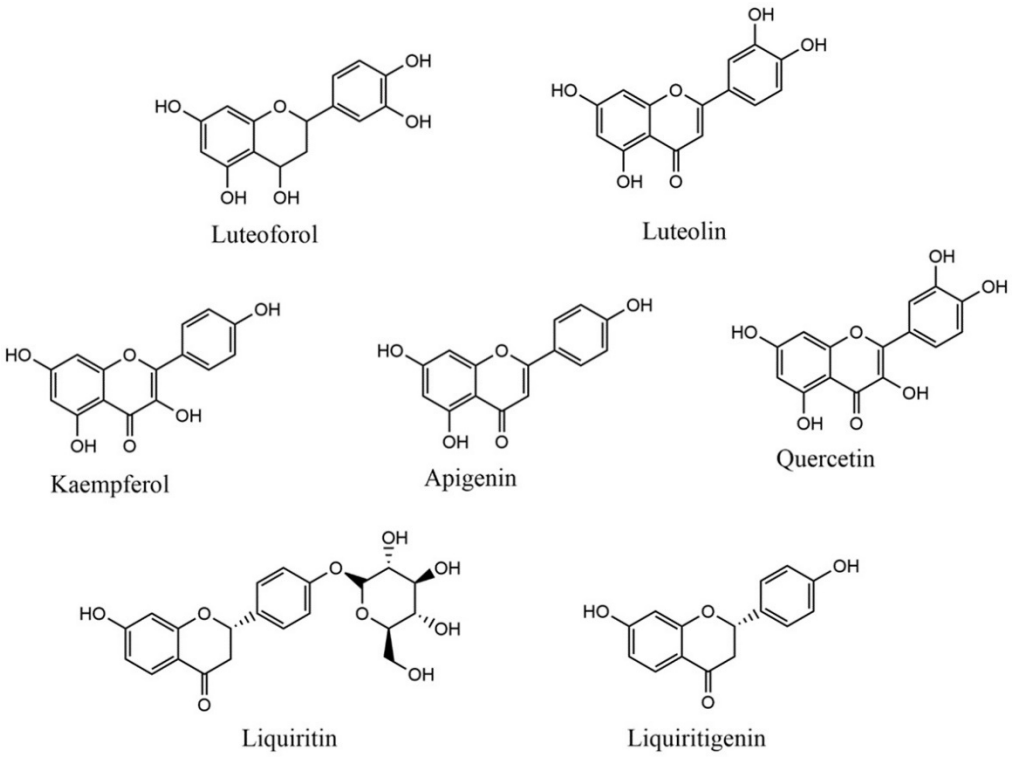

Figure 2. Chemical structure of flavonoids and flavones, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Two other interesting medicinal plants with antiviral activities are *Radix glycyrrhizae* (the rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Batalin. or *Glycyrrhiza glabra* L., Leguminosae) and *Radix astragali* (the root of *Astragalus mongholicus Bge.*, Leguminosae). The flavones of *Radix glycyrrhizae*, represented by liquiritin and liquiritigenin, were the most reported compounds isolated from this medicinal plant (Ming *et al.* 2018) and the main active constituents of *Radix astragali* include flavonoids and saponins (Ma *et al.* 2002).

Until now, most papers on MPs and COVID-19 are from Asian countries. It is important to keep in mind that all concerned plants are almost never used on their own but as part of a formulation containing several ingredients that act together (Ang *et al.* 2020, Wang *et al.* 2020b). This impairs our ability to reach clear and measurable judgements or even evaluate data on the effect of a specific plant in isolation. Despite that we should still think about the possibility of enhanced activity of different antiviral compounds together rather than one type of compound alone. On that point, the WHO commissioned a study in 2004 on the complementarity between conventional treatment and traditional Chinese medicine in the treatment of SARS-CoV (WHO 2004). This study underlines that, under certain conditions, conventional treatment composed of antivirals may be more effective when there is a complementary treatment based on MPs.

A meta-analysis of flavonoids with antiviral potential against coronavirus, showed that rhafolin from the leaves of *Ficus* (Moraceae) and *Hordeum vulgare* L. should be considered in the development of phytomedicines for the treatment of coronaviruses (Sawikowska 2020). Rhafolin has a flavonoid skeleton even though it belongs to the group of phenolic structures. For this reason, we mentioned this compound in this section on medicinal plants with secondary metabolites of interest.

Tannins

By mean of an *in vitro* study, it has been demonstrated that *Punica granatum* L. (Punicaceae) with its effective pericarp tannin, affects HSV-2. The mechanism of this effect was explained by the way this specific tannin inhibits HSV-2 replication, kills and blocks the absorption of virus cells (Zhang *et al.* 1995).

The anti-herpes simplex virus (HSV-1) activity of ellagitannins and gallotannin-type compounds (Figure 3) has been studied and ellagitannins showed a significantly stronger activity against virus replication than that of the gallotannins. This activity was produced mainly with epiacutissimin B, epiacutissimin A, acutissimin A and mongolicain (Vilhelmova-Ilieva *et al.* 2019). A current study on the antiviral effect of geraniin from *Spondias mombin* L. (Anacardiaceae) leaf extract against HSV-1

replication using *in vitro* and *in silico* approaches, showed the therapeutic potential of this tannin as an anti-herpes treatment (Siqueira *et al.* 2020).

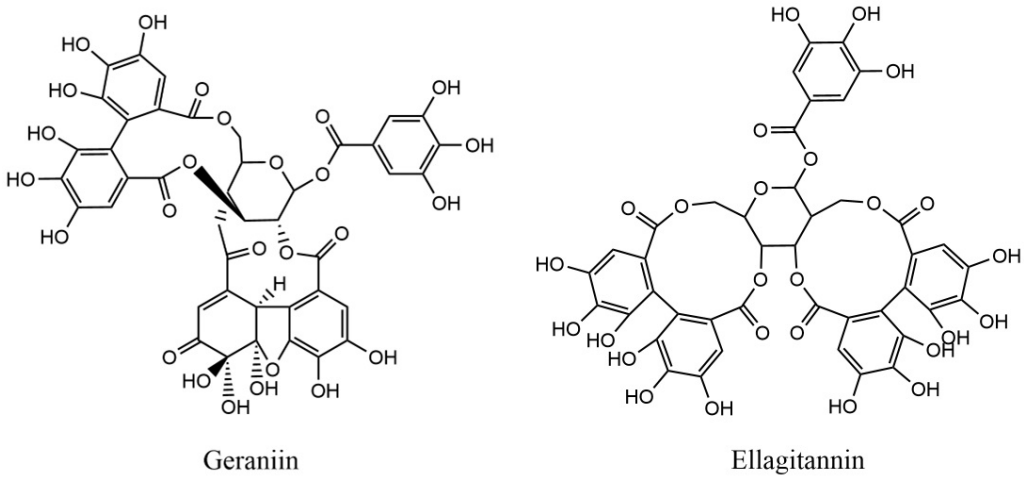

Figure 3. Chemical structure of some tanins, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Phenols

In addition to being a rich source of phenolic compounds, *Plantago major* L. (Plantaginaceae), is a popular traditional Chinese medicine used for treating viral hepatitis. Pure compounds of *P. major* L., especially caffeic acid exhibited the strongest activity against HSV-1 (EC50=15.3µg/ml, SI=671), HSV-2 (EC50=87.3µg/ml, SI=118) and adenovirus 3 (EC50=14.2µg/ml, SI=727) (Chiang *et al.* 2002).

Curcumin from *Punica granatum* L. (Zingiberaceae) root (Figure4), is also an interesting compound with multiple pharmacological properties including antiviral activity (Noureddin *et al.* 2019) although this is not reflected in clinically relevant antiviral activity. However, humans appear to be able to tolerate high doses of curcumin without significant side effects (Chainani-Wu 2003).

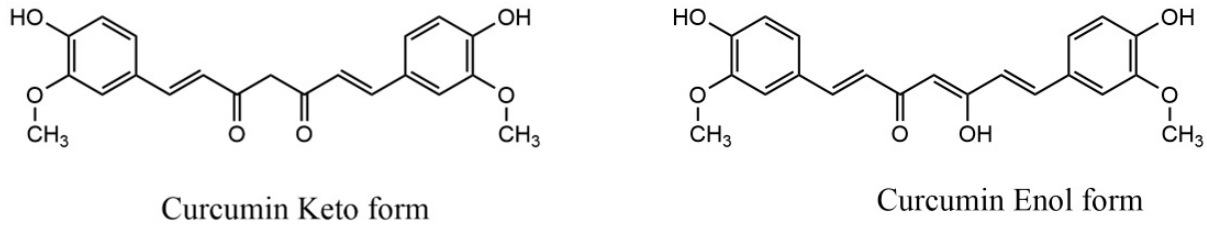

Figure 4. Chemical structure of phenols, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

A large variety of MPs have been reported to have anti-hepatitis C virus activity (Wahyuni *et al.* 2013; Rehman *et al.* 2016). Polyphenols from *Ajuga bracteosa* Wall. (Lamiaceae) which is native to the hilly areas of Pakistan, China, India and Malaysia and *Ajuga parviflora* Benth. Lamiaceae leaves, which are found in Pakistan, Kashmir, and Afghanistan, have significant activity against HCV. They reduce or even stop the growth of this virus and consequently might be useful as an alternative therapy or in combination with existing treatments for HCV (Yousaf *et al.* 2018). This antiviral activity was higher for *Ajuga parviflora* Benth. than *Ajuga bracteosa* Wall.

Gallic acid has shown a strong anti-herpes and anti-influenza activity at the therapeutic range of 0.8-0.05 µg/ml (Berrin *et al.* 2011).

Polysaccharides

The identification of compounds from MPs as an opportunity to discover a new natural antiviral treatment are well illustrated by polysaccharides (Figure5) from many MPs that have been shown to possess interesting biological effects including antiviral activity (Zhao *et al.* 2020). A polysaccharide from a Chinese plant, namely *Astragalus membranaceus* (Fisch.) Bunge (Leguminosae) at a non-cytotoxic concentration (30 µg/mL), significantly suppresses the expressions of two early viral

proteins in the Epstein-Barr virus lytic cycle to exert an antiviral effect (Guo *et al.* 2014). *Astragalus membranaceus* (Fisch.) Bunge has been used for a very long time in China and is believed to have an antiviral effect (Dang *et al.* 2004, Yuan *et al.* 2008).

Houttuynia cordata Thunb. (Saururaceae) is a traditional Chinese medicinal plant. During severe acute respiratory syndrome between 2002 to mid-2003, *Houttuynia cordata* Thunb. was widely usedto prevent SARS. In the mouse*, Houttuynia cordata* Thunb. has shown anti-SARS activity through a significant inhibitory effect on SARS-CoV 3C-like protease (3CL(pro)) and RNA-dependent RNA polymerase (RdRp) (Lau *et al.* 2008). In addition, *Houttuynia cordata* Thunb. has anti-inflammatory activity related to its carrageenins, which are a family of linear sulfated polysaccharides (Lu *et al.* 2006).

Pectin isolated from the fruit pulp of *Inga ssp*. (Leguminosae), a fruit tree found in Central and South America and using HEp-2 cells, inhibited the initial viral replication stages of herpes simplex virus type 1 with an IC50 of 179µg.mL^{-1} and for poliovirus with 58 µg/ml, revealing antiviral potential against these two viruses (De Godoi *et al.* 2019).

Azadirachta indica A. Juss. (Meliaceae) has been used in Ayurvedic medicine in India for over 2000 years for many therapeutic indications (Subapriya & Nagini 2005). The antiherpetic (HSV-1) activity of two polysaccharides isolated from the leaf of *Azadirachta indica* A. Juss. was studied and an antiviral effect was attributed to the interference of polysaccharides in the early stages of HSV-1 replication (Faccin-Galhardi *et al.* 2019).

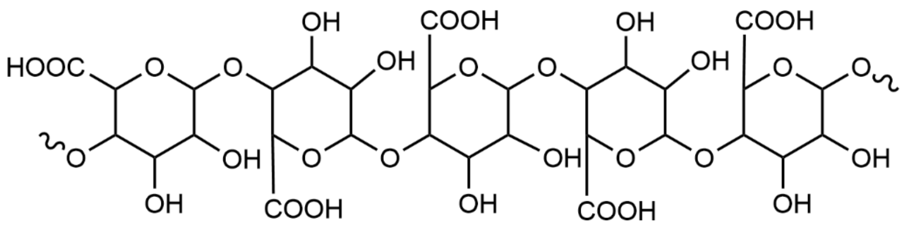

Figure 5. Chemical structure of polysaccharides, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Terpenes and saponins

Saikosaponins (Figure 6), triterpene glycosides contained in many medicinal plants such as Bupleurum spp. (Apiaceae), Heteromorpha spp. (Apiaceae), and *Scrophularia scorodonia* L. (Scrophulariaceae), have shown an antiviral activity towards HCoV-22E9 at concentrations of 0.25-25 mmol/L (Cheng *et al.* 2006). Furthermore, saikosaponin type B2 has potent anticoronaviral activity. Its mode of action possibly involves interference in the early stage of viral replication: absorption and penetration of the virus (Cheng *et al.* 2006).

Radix Bupleuri (Bupleurum Chinese DC., Apiaceae) has been used in traditional Chinese medicine for a very long time. However, saikosaponin from this plant damages the liver (Bochuan *et al.* 2017) when the dosage is high and, for this reason, those who advise clinical use of this herbal extract should be aware of the safe dose range.

A study measuring SARS-CoV-induced cytopathogenic effect on Vero E6 cells has revealed that diterpenoids, mainly of the abietane-type, have shown important anti-SARS-CoV effects (Wen *et al.* 2007).

Dittrichia viscosa (L.) Greuter (Asteraceae) from Morocco, has also revealed antiviral activity against HSV, SINV, and poliovirus (Mouhajir *et al.* 2001). A current Moroccan study has proposed that the bioactive molecule, namely crocin, the chemical primarily responsible for the color of saffron (*Crocus sativus* L., Iridaceae) and β-Eudesmol (Figure 6) present in *Laurus nobilis* L. (Lauraceae) may be inhibitors against the coronavirus (Aanouz *et al.* 2020).

Lectins are natural proteins with binding specificity for different glycan structures from plants (Figure 7). Lectins have antiviral activity against the severe acute respiratory syndrome coronavirus. This activity was described mainly for mannose-binding lectins. A possible target for antiviral intervention for these lectins was identified in the replication cycle of SARS-CoV (Keyaerts *et al.* 2007). Indeed, lectin (glyco)proteins that are found predominantly in the Leguminosae family, have the capacity of reversibly binding to specific carbohydrates by "reading" biological information encoded in the three-dimensional structure of sugars, the glycocode (Wiederschain, 2013). The effect of two Machaerium genus (Leguminosae) lectins, named Machaerium biovulatum agglutinin (MBA) and M. lunatus agglutinin (MLA), on the inhibition of HIV infection has been

evaluated (Animashaun *et al.* 1993, Nascimento *et al.* 2020). The preincubation of these two lectins with the virus prior to infection completely protected against the infection, even at a very low concentration such as 1 µg/mL. These lectins bind to the essential protein for ensuring HIV infectivity.

Furthermore, an inhibition of human parainfluenza virus Type 2 infection elicited by a partial inhibitory effect on virus ribonucleic acid synthesis, inhibition of protein synthesis and prevention of the virus entry on the cells, was reported (Uematsu *et al.* 2012).

Another study showed the capacity of **peanut** agglutinin lectin to interact against herpes simplex virus (Lundström *et al.* 1987).

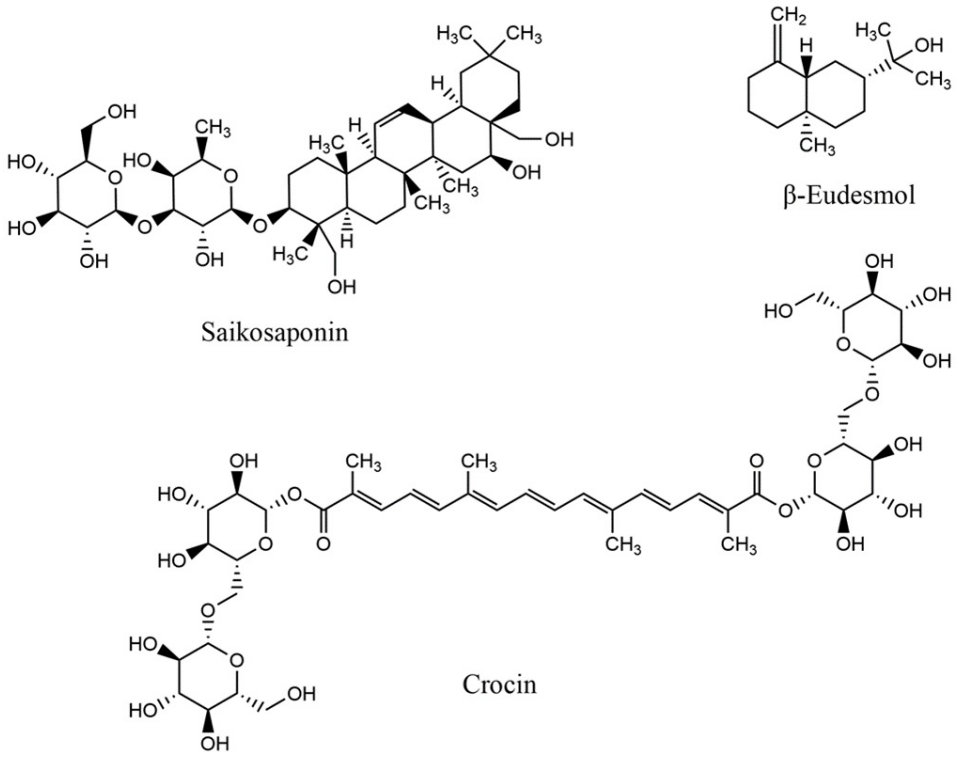

Figure 6. Chemical structure of terpenes and saponins, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Lectins

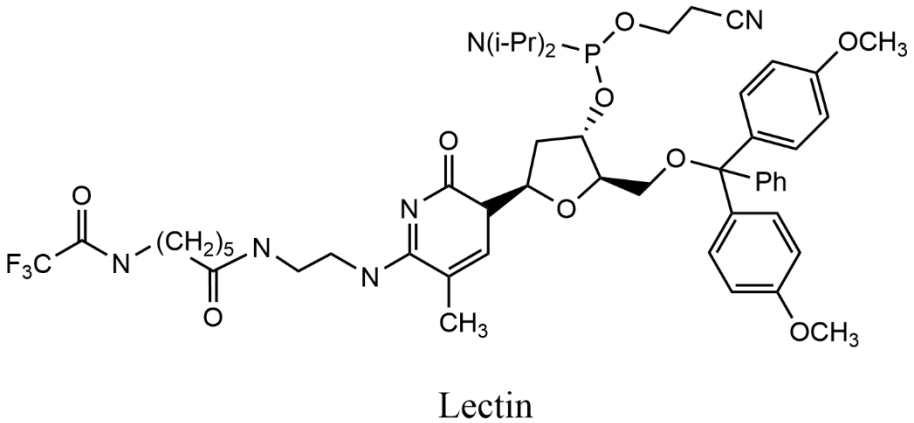

Figure 7. Chemical structure of a lectin, drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Alkaloids

Plant species from the Amaryllidaceae family have shown many promising antiviral alkaloids (Szlávik *et al.* 2004). The DNA and RNA binding activities of these alkaloids have also been demonstrated (Hohmann *et al.* 2002).

Alkaloids from the bulbs of *Leucojum vernum* L. (Amaryllidacea), namely lycorine (Figure 8) and homolycorine, have a high antiretroviral activity with an IC_{50} between 0.4-7.3 µg/ml (Szlávik *et al.* 2004). Lycorine displayed strong antiviral effects against poliovirus, Coxsackie, Semliki forest, measles and HSV-1 viruses (Leven *et al.* 1983, Leven *et al.* 1982). Lycorine also exerts a pronounced inhibitory effect against flaviviruses and Bunyaviruses (Gabrielsen *et al.* 1992). In addition, lycorine obtained from *Lycoris radiata* (L'Hér.) Herb. after fractionation, purification and CPF/MTS essays of the extract of this plant, could be considered as an anti-SARS-CoV component in a cell culture study with an EC50 value of 15.7 ± 1.2 nM (Li *et al.* 2005).

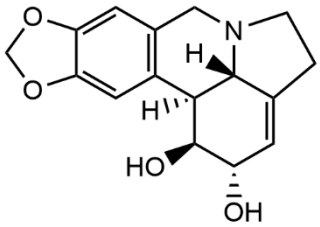

Figure 8. Chemical structure of lycorine (alkaloid), drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Sophora alopecuroides L. (Leguminosae) is found in Japan (Iinuma & Ohyama 1995), Pakistan (AttaurRahman *et al.* 2000), Iran (Pourahmad & Mohammadi 2017), and Mongolia (Kwon *et al.* 2015a). It has been reported that both matrine and oxymatrine alkaloids from *Sophora alopecuroides* L. seeds have antiviral activity (Wang *et al.* 2020a). Another interesting alkaloid with antiviral effect is atropine which has significant anti-herpes and anti-influenza activities at the therapeutic range of 0.8-0.05 µg ml^{-1} (Berrin *et al.* 2011).

We must of course keep in mind the toxicity of alkaloids if studies were designed to examine antiviral potential.

Steroids

Steroids are hormones with an important role in cellular growth modulation and signal transduction. In animal experimentation, brassinosteroids, a natural collection of phytosterols, inhibit replication of many viruses (Kaur Kohli *et al.* 2020).

The bioactive steroid molecule digitoxigenin (Figure 9) from the Moroccan plant *Nerium oleander* L. (Apocynaceae) has been proposed as an inhibitor against the coronavirus (Aanouz *et al.* 2020). In this study authors have found that the sample analyzed from this plant contained 11.25% of digitoxigenin (Aanouz *et al.* 2020). However, it is known that all parts of *Nerium oleander* L. contain digitoxigenin, which is a very toxic cardiotonic steroid that has a digitoxin-like effect (Rajapakse 2009).

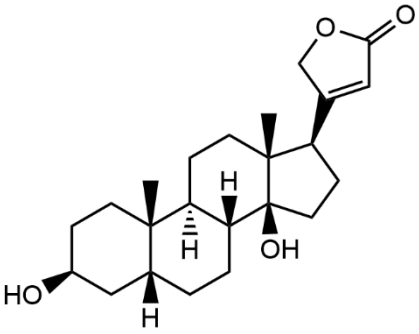

Figure 9. Chemical structure of the digitoxigenin (steroid), drawn with ChemDraw 20.1 (PerkinElmer Inc., Massachusetts, USA).

Conclusion

COVID-19 has significant morbidity and mortality and so the discovery and identification of novel effective anti- COVID-19 drugs from medicinal plants without significant adverse effects is of great importance. MPs already available and identified in this review as interesting from a therapeutic perspective, should be examined as they are already part of some existing healthcare systems and may be useful prophylactic or therapeutic agents for COVID-19. Several plants and phytochemicals discussed in this article could constitute a starting point for future research ranging from experimental studies to clinical trials.

Indeed, this review highlights the interest of medicinal plants in biomedical and clinical applications in interfering in a virus's mode of action and resulting pathology. These include *Artemisia annua* L., *Glycyrrhiza glabra* L. and *Echinacea purpurea* (L.) Moench which were investigated for antiviral and anti-inflammatory properties primarily against the Corona viruses. Plant-specific compounds, such as Glycyrrhizic acid, Alklamides, Cichoric acid, Artemisinin, artesunate, flavones, Triterpene, Saponins, and phenolic compounds like liqcoumarine, glabrocoumarone, coumarin, inhibit viral entry and adsorption, destroy the nucleocapsid and genetic material, and prevent virus replication. Which attest and affirm our ancestors' traditional use of these MPs. Not surprisingly, many researchers are now interested in evaluating the efficacy of compounds from MPs for antiviral properties. Such research should be encouraged mainly with regard to those MPs with antiviral activity because many plant extracts could well be potential candidates to usefully treat COVID-19. This article only aims to indicate potential further research tracks of interest using plants as a possible means of treatment of COVID-19. However, data from this article form a useful starting point for further studies to validate antiviral activities both *in vivo*, as well as meaningful efficacy in humans.

Declarations

List of abbreviations: $3CL^{pro}$ - Viral Main Proteinase; CPE - cytopathic effect; DNA - deoxyribonucleic acid; EC50 - Half maximal effective concentration; HCV - Hepatitis C Virus; HIV - Human Immunodeficiency Virus; HMs - Herbal Medicines; HSV - Herpes Simplex Virus; IC50 - The half maximal inhibitory concentration; *NLRP3* - NOD-- LRR- and pyrin domain-containing protein 3; RNA - ribonucleic acid; SARS- SI - Selectivity index; Severe Acute Respiratory Syndrome; SINV - SINdbis Virus; TM - Traditional Medicine; WHO - World Health Organization

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Consent for publication: Not applicable

Availability of data and materials: The data set generated for the current study are included in this published article.

Competing interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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