Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Therapeutic potential of medicinal plants against COVID-19: The role of antiviral medicinal metabolites

Tariq Khan, PhD [a], Mubarak Ali Khan [b,*], Zia-ur-Rehman Mashwani [c], Nazif Ullah [b], Akhtar Nadhman [d]

[a] Department of Biotechnology, University of Malakand, Chakdara, KP, Pakistan
[b] Department of Biotechnology, Faculty of Chemical and Life Sciences, Abdul Wali Khan University Mardan (AWKUM), Mardan, 23390, Pakistan
[c] Department of Botany, PMAS Arid Agriculture University, Rawalpindi, Pakistan
[d] Department of Integrative Biosciences, CECOS University, Peshawar, Pakistan

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ABSTRACT

There are numerous trials underway to find treatment for the COVID-19 through testing vaccines as well as existing drugs. Apart from the many synthetic chemical compounds, plant-based compounds could provide an array of \suitable candidates for testing against the virus. Studies have confirmed the role of many plants against respiratory viruses when employed either as crude extracts or their active ingredients in pure form. The purpose of this review article is to highlight the importance of phytomedicine against COVID-19. The main aim is to review the mechanistic aspects of most important phytochemical compounds that have showed potential against coronaviruses. Glycyrrhizin from the roots of *Glycyrrhiza glabra* has shown promising potential against the previously epidemic coronavirus, SARS-CoV. Other important plants such as *Artemisia annua*, *Isatis indigotica, Lindera aggregate*, *Pelargonium sidoides*, and *Glychirrhiza* spp. have been employed against SARS-CoV. Active ingredients (e.g. emodin, reserpine, aescin, myricetin, scutellarin, apigenin, luteolin, and betulonic acid) have shown promising results against the coronaviruses. Phytochemicals have demonstrated activity against the coronaviruses through mechanisms such as viral entry inhibition, inhibition of replication enzymes and virus release blockage. However, compared to synthetic drugs, phytomedicine are mechanistically less understood and should be properly evaluated before application. Nonetheless, phytochemicals reduce the tedious job of drug discovery and provide a less time-consuming alternative for drug testing. Therefore, along with other drugs currently tested against COVID-19, plant-based drugs should be included for speedy development of COVID-19 treatment.

1. Introduction

The current pandemic that struck the world in December 2019 and is ongoing till this day, has turned into the deadliest pandemic after influenza pandemic that took place in 1918. This is the third time that a coronavirus has caused an outbreak during the 21st century. The recent one is caused by the novel coronavirus termed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) and is responsible for a respiratory disease named as the coronavirus disease 2019 (COVID-19). However, COVID-19 has turned out to be more deadly than the previously spread SARS and MERS (Middle east respiratory syndrome) coronaviruses. Owing to this, 1.30 million people have died because of COVID-19 and 53.76 million have tested positive for the virus as of November 13, 2020 (Worldometer 2020). The reason that it took only over two months to be declared as "pandemic" is the interconnectedness and ever increased worldwide travel.

The pandemic has led scientists from a diverse area of subjects to work on understanding the origin of the virus, its structure, the disease caused, diagnostic tools and treatment options. Along with the other equally important aspects of the disease, treatment has been the most sought-after aspect. As the virus and the disease it causes are very new, there is currently no vaccine available to get rid of the infection. The current options to treat COVID-19 patients are to focus on symptoms alleviation and provide medication to prevent co-infection with bacteria.

Researchers and scientists across the world are focusing on

* Corresponding author.
E-mail addresses: tariqkhan@uom.edu.pk (T. Khan), makhan@awkum.edu.pk, write2mubarak@gmail.com (M.A. Khan).

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List of abbreviations:

3CLpro	3C-like proteases
ACE2	Angiotensin-converting enzyme 2
CC_{50}	50% cytotoxic concentration
COVID-19	Coronavirus disease 2019
EC_{50}	Half maximal effective concentration
H5N1	Highly pathogenic avian influenza virus
hRSV	Human respiratory syncytial viruses
IC_{50}	Half maximal inhibitory concentration
IFN-β	Interferon beta
MERS	Middle east respiratory syndrome
PLpro	Papain like protease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TNF-α	Tumor necrosis factor alpha
VRI	Viral respiratory infections
WHO	World Health Organization

repurposing the existing drugs, passive immunity and looking for vaccines against the virus (Harrison 2020). Among the available drugs, for instance, the antimalarials Chloroquine and hydroxychloroquine received attention after studies on its efficacy were conducted recently (Gautret et al., 2020; Keyaerts et al., 2004; Wang et al., 2020). However, the medication soon became controversial regarding its efficacy and manifestations of side effects such as fulminant hepatic failure, serious cutaneous adverse reactions, and ventricular arrhythmias (Ferner and Aronson 2020).

Owing to the experimentally proved efficacy of its analogues and their potential side effects, natural quinines could prove potent in alleviating the symptoms of coronaviruses without showing side effects based on its biocompatibility (Devaux et al., 2020).

Apart from a primary food source, plants serve as a very important source of medicine. A thorough understanding of the pathways of plant's secondary metabolism along with their conservation status, ecology and ethnobotany is important for drug development (Nature 2020). To focus on this aspect, medicinal plants produce many important chemical compounds through their secondary metabolism, operating as a self-defense against stress induced by environmental triggers and pathogens. From using the raw plant to extraction of important compounds, medicinal plants are centuries old source in the various traditional herbal medicine systems. For instance, their importance lies in the fact that the WHO concludes that 80% of the world population relies on them for treatment (Bannerman et al., 1983). It has been seen that there is a plethora of medicinal plants already employed against respiratory viruses. For instance, the trials on Traditional Chinese Medicine including that of extracts from the dried fruit of *Forsythiae fructus* are ongoing as a part of the world's race to develop effective treatment for COVID-19 (Maxmen 2020). Therefore, it is no wonder that medicinal plants could be employed as a potent weapon against COVID-19. Traditional herbal medicine coming from these medicinal plants could serve at different fronts including alleviation of symptoms of COVID-19 patients as well as providing raw material for potent antiviral drugs. The current research for treatment of COVID-19 should, therefore, include on a largescale, medicinal plants as an important area of search. This review paper highlights the usefulness of medicinal plants in the fight against COVID-19 in many ways. The paper reviews the important plant derived compounds for immediate application in alleviation of symptoms, and important secondary metabolites as candidates for anti- COVID-19 drug discovery.

2. Traditional plant-based therapies for respiratory problems

Many different plants have been utilized since centuries for improving symptoms such as coughing, weakness and digestive system disorders as well as alleviating anxiety. Plant products such as crude extracts, extract of a specific part i.e. roots, stem, flowers, fruits and seeds, plant-derived chemicals, and nutraceuticals are widely applied in dealing with general ailments including minor cough, flu to complex chest infections. In fact, the one-fourth of the most commonly employed medicinal compounds contain plant-based component.

Some of the most notable plants employed against respiratory problems include *Artemisia vulgaris* (Khan and Gilani 2009), *Boerhavia procumbens* (Bokhari and Khan 2015), *Capparis spinosa* L. (Trombetta et al., 2005), *Carum copticum* (Gilani et al., 2005), *Cistanche tubulosa* (Yamada et al., 2010), *Euphorbia hirta* (Youssouf et al., 2007), *Hyoscyamus niger* (Gilani et al., 2008), and *Zingiber officinalis* (Naik et al., 2013). Apart from these, there are hundreds of plants used for their activity in treating or reducing the symptoms of respiratory problems such as cough, asthma, cold, bronchitis, flu, respiratory tract infections, whopping cough and breathing problems (Table 1). Among the medicinal plants, herbs are mostly used in respiratory problems in the form of decoction, powder, juice, tea or oil (Alamgeer et al., 2018).

Furthermore, leaves of *Alstonia scholaris* were used by Channa et al. (2005) for their effect on asthma in rats and guinea pigs. The study recorded prostaglandin mediated broncho-vasodilatory activity of leaf extracts of *A. scholaris*. It was observed from the findings that the root extract of *A. scholaris* relaxes the calcium chloride induced contraction in guinea-pigs ileum and thus it was inferred that the extract interferes the influx of calcium ions into cells. Similarly, Shah et al. (2011) reported that aerial parts of the *Artemisia maritima* showed potent anti-asthmatic activities through bronchodilation. They suggested that the bronchodilation might have been mediated through blockade of calcium channels and phosphodiesterase. Furthermore, different medicinal plants are traditionally employed for treating breathing problems. For instance, Kapoor et al. (2011) used leaves extracts of *Ficus religiosa* to demonstrate the reduction of histamine & acetylcholine induced pre-convulsive dyspnea (shortness of breath) in guinea pigs. This implies that careful evaluation of important herbs backed by scientific experiments could prove helpful in finding naturally existing, biocompatible solution for alleviation of respiratory problems in COVID-19 patients.

3. Anti-viral plants; a general overview

The use of medicinal plants against human viruses has been in practice since long. Many herbal plants as leaf powder, decoctions, infusions, pastes and pills have been documented against viral infections (Akram et al., 2018). There are hundreds of plants having medicinal properties against human viruses (Mukhtar et al., 2008).

Important anti-viral plants such as *Sambucus nigra*, *Withania somnifera*, *Sylibum marianum* and *Moringa oleifera* have been employed against human viruses such as influenza virus (Ataee et al., 2016), human immunodeficiency virus (HIV) (Salehi et al., 2018), Hepatitis C virus (Ferenci et al., 2008) and Herpes simplex virus type 1 (HSV-1) (Lipipun et al., 2003). Different studies have reported a variety of plants for their potent antiviral activities including that of Ogbole et al. (2018) who studied twenty-seven medicinal plants from Southern Nigeria for their activity against positive stranded RNA viruses such as enteroviruses. Their study concluded that extracts of *Macaranga barteri* showed very strong activity against echoviruses. Similarly, studies are available that reviewed hundreds of medicinal plants have strong antiviral potential (Akram et al., 2018). Such studies indicate that these antiviral plants after careful testing could be employed for alleviating the COVID-19 symptoms.

Furthermore, many studies have been conducted on pure compounds isolated from many different plants for their potent activities against different viruses (Hussain et al., 2017). Notable plants from which anti-viral metabolites have been isolated include *Aloe barbadensis* (Aloe gel), *Artemisia annua* (artemisinin) (Efferth et al., 2008), *Glycyrrhiza*

Table 1
Plant species and bioactive metabolites used for the treatment of viral infections.

Plant name	Common name	Family	Part used	Extraction solvent	Active compound	Effective against virus	Reference
Sambucus nigra L	Elder; elderberry	Adoxaceae (previously Caprifoliaceae)	Flowers, fruits	Methanol, Ethanol	Flavonol (Isoquercetin, rutin, Quercetin-3-O-6″-acetylglucoside), Flavanones (Naringenin), Flavones (Luteolin)	Influenza virus types A and B, herpes simplex virus type-1 (HSV-1)	(Porter and Bode 2017; Serkedjieva et al., 1990)
Origanum vulgare	Oregano	Lamiaceae	Essential oil	Methanol	carvacrol	murine norovirus (MNV) herpes simplex virus type-1 (HSV-1) respiratory syncytial virus (RSV)	(Gilling et al., 2014) (Pilau et al., 2011)
Pulicaria vulgaris Gaertn	Pulicaria	Asteraceae	essential oil	Aqueous	thymol	herpes simplex virus type-1 (HSV-1)	Sharifi-Rad et al. (2017)
Ficus benjamina	Banyan	Moraceae	Leaves	Ethanol extracts	phenolic and flavonoid compounds	Pseudomonas aerugonisa, *Escherichia coli* and Bacillus cerus	Ashraf et al. (2020)
Salvia officinalis	Sage	Lamiaceae	Leaves	hexane and ethyl acetate	caffeic, vanillic, ferulic, rosmarinic acid, luteolin, apigenin, and quercetin	virus type 1 (HIV-1)	Geuenich et al. (2008)
Iresine herbstii Hook. ex Lindl.	Blood leaf or beefsteak plant	Amaranthaceae	Shoot	Ethanol, petroleum ether, Acetonic, dichloromethane	Phytochemicals and other compounds	Newcastle disease virus infection (NDV)	Andleeb et al. (2020)
Ocimum sanctum Linn	Basil	Lamiaceae	leaf extract	methanol	3,4-dimethoxycinnamic acid, caffeic acid, diosmetin, luteolin, kaempferol, rosmarinic acid, apigenin, and genistein	virions carrying diverse envelopes	Mondal et al. (2011)
Hyphaene thebaica L.	Doum palm	Arecaceae	Fruit	Aqueous	Fe2O3 Nanoparticles used for treatment	polio virus-1 and polio virus-2	Mohamed et al. (2020b)
Abutilon figarianum	Webb Gargadan, texas Indian-mallow	Malvaceae	Whole plant	Methanol and dichloromethane (DCM) extracts	flavonoids, alkaloids, fatty acid and phenolic compounds	HBV	Saleem et al. (2020)
Rosmarinus officinalis	Rosemary	Lamiaceae		Aqueous extracts	oleanolic acid	herpes viruses, HIV, influenza	Nolkemper et al. (2006)
Phyllanthus urinaria L.	Leaf-flower, shatterstone, stone-breaker herb	Phyllanthaceae	Root, leaves	Acetone extract	1,3,4,6-Tetra-*O*-galloyl-*d*-glucose (1346TOGDG), Excoecarianin	herpes simplex virus type 1 and 2 (HSV-1; 2)	(Porter and Bode 2017; Serkedjieva et al., 1990)
Allium sativum L	Garlic	Amaryllidaceae	Root, leaves	Aqueous and ethanolic extract	allicin, alliin, diallyl sulfide, diallyl disulfide	influenza A and B, HIV, HSV-1, viral pneumonia, and rhinovirus	Bayan et al. (2014)
Phyllanthus amarus Schum. & Thonn.	Black catnip, gulf leaf flower, stone breaker	Phyllanthaceae	Leaves	Aqueous and ethanolic extract	Gallotannin corilagin	HIV, HSV-1 and HSV-II	Ashraf et al. (2020)
Melissa officinalis	Lemon balm	Lamiaceae	whole plant	Aqueous	monoterpenaldehydes citral	avian influenza virus (AIV) subtype H9N2	Pourghanbari et al. (2016)
Phyllanthus emblica L.	Amla, Indian gooseberry	Leiothrichidae	Fruits	*n*-hexane, ethyl acetate, and nbutanol	tannins, flavonoids, saponins, terpenoids, ascorbic acids	HIV	Andleeb et al. (2020)
Mentha piperita L	Peppermint	Lamiaceae	leaf	Ethanolic	Menthol, limonene, pulegone, caryophyllene and pinene	syncytial virus (RSV)	Li et al. (2017)
Azadirachta indica A. Juss	Neem, nimtree or Indian lilac	Meliaceae	Leaves	Bark extract	Deacetyl-3-cinnamoyl-azadirachtin	Newcastle disease virus (NDV), Hepatitis C virus (HCV)	Mohamed et al. (2020a)
Moringa oleifera Lam.	Moringa horseradish tree	Moringaceae	Leaves, seeds, fruits	Phenolics	(1) O-ethyl-4- (α-L-rhamnosyloxy) benzyl carbamate; (2) 4 (α Lrhamnosyloxy)-benzyl isothiocyanate (3) niazimicin; (4) niazirin (5) p-sitosterol; (6) glycerol-1-(9- octadecanoate); (7) 3 -0- 6 -*O*-oleoyl-β-Dglucopyranosyl b-sitosterol; (8) β-sitosterol- 3-X-O -β -D-glucopyranoside	EBV-EA (Epstein- Barr virusearly antigen)	(Arbab et al., 2017; Saleem et al., 2020)
Morus alba L.	White mulberry, Toot	Moraceae	Root and leaves	Ethanol	Kuwanon S, mulberroside C, cyclomorusin, eudraflavone B hydroperoxide, oxydihydromorusin, leachianone G and α-acetyl-amyrin	Herpes simplex type 1 virus (HSV-1) FMD virus, Foot-and-mouth disease virus	(Akram et al., 2018; Du et al., 2003)
Artemisia annua L.	Annual wormwood	Asteraceae	Whole plant	Ethanol	Artemisinin, deoxyartemisinin, artemisinic acid, arteannuin-B, stigmasterol, friedelin,	SARS-CoV	Lin et al. (2014)

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Table 1 (*continued*)

Plant name	Common name	Family	Part used	Extraction solvent	Active compound	Effective against virus	Reference
					friedelan-3-β-ol, artemetin, and quercetagetin 6,7,3′,4′-tetramethyl ether		
Echinacea purpurea	Purple coneflower	Asteraceae	Root and leaves	Aqueous, Methanol	echinacoside	herpes simplex virus, syncytial virus (RSV)	Hudson and Vimalanathan (2011)
Nigella sativa L.	Black seed, black caraway, roman coriander, kalonji, or fennel flower	Ranunculaceae	Seed	(Aqueous, Methanol, Ethanol, Cloroform, Butanol, Diethyl ether, *n*-Hexane and Acetone	Steroids, tannins, flavanoids, coumarins, cardiac glycosides, saponins and diterpenes	Murine cytomegalovirus (MCMV)	Salem and Hossain (2000) Kazmi et al. (2019)
Melissa officinalis L.	Lemon balm, balm, or balm mint	Lamiaceae	Whole plant	Hot-water extracts	Terpinene, phenol carbon acid (rosmarinic acid), and flavonglychoside acid	Herpes simplex virus, Semliki Forest virus, Newcastle, vaccinia	(Cohen et al., 1964; Schnitzler et al., 2008)
Glycyrrhiza glabra	Licorice	Fabaceae	root extract	Aqueous, Methanol	Glycyrrhizin, liquiritigenin, and glabridi	HIV, RSV, herpes viruses,	Cinatl et al. (2003a)
Withania somnifera (L.)	Dunal Ashwagandha, Indian ginseng	Solanaceae	Root	hydroalcoholic extract, aqueous	flavonoids, alkaloids, fatty acid and phenolic compounds	Infectious bursal disease virus (IBDV), simplex virus type 1 (HSV-1), Herpes simplex virus type 2 (HSV-2)	Serkedjieva et al. (1990)
Sambucus nigra L.	Elderberry -European elder	Adoxaceae	Flowers	Aqueous extra	Flavonoids acids, tannins and polysaccharides, triterpene saponins, phenolic	Influenza herpes simplex virus type 1, virus types A and B, HIV, HSV, hepatitis	(Akram et al., 2018; Du et al., 2003)
Caesalpinia pulcherrima L.	pride-ofbarbados, peacock flower, guletura	Fabaceae	Fruits, seeds, stem, and leaves	Aqueous extract	Glycosides, pulcherrimain, homoisoflavonoids, and brazilide	Herpesvirus −1 and 2 and adenovirus (ADV)-3, ADV-8, and ADV-11	Akram et al. (2018)
Zingiber officinale Rosc.	Adrak, Ginger Rhizome	Zingiberaceae	Rhizome	Aquous extract	Arcurcumene, β-sesquiphellandrene, α zingiberene and β-bisabolene, flavan and 4, 6-dichloroflavan	*Rhinovirus* IB	Saleem et al. (2020)
Hyoscyamus niger L.	Black henbane stinking nightshade; ajwain Kharasani	Solanaceae	Flower	Methanol	Acyclovir	Influenza A	Alizadeh et al. (2014)
Justicia adhatoda L.	Bansa, malabar nut, adhatoda	Acanthaceae	Leaves	aqueous and methanolic extracts	Phenols, tannins, alkaloids, anthraquinone, saponins, flavonoids, and reducing sugars	Influenza virus, Herpes Simplex Virus-2 (HSV-2), HSV-1; Antimicrobial efficacy of drug blended biosynthesized colloidal gold nanoparticles	(Chavan and Chowdhary 2014; Emmanuel et al., 2017)
Ocimum basilicum L.	Mushk, jangli tulsi, kam Kashturi, niazbo, basel	Lamiaceae	Whole plant	aqueous and ethanolic extracts	Apigenin, linalool and ursolic acid	HSV-1, ADV-8, CVB1, EV71, HSV-2, ADV-3	(Chiang et al., 2005b)
Plantago major L.	Bartang, broadleaved plantain	Plantaginaceae	Whole plant	aqueous	Caffeic acid, chlorogenic acid	HSV-1, HSV-2, ADV-3, ADV-11	Akram et al. (2018)
Astilbe rivularis Buch. Ham.	River astilbe Hindi: gosy, pothee	Saxifragaceae	Rhizome	Methanolic extracts	Alkaloids, flavonoids, coumarins and glycosides	HSV-1/Vero cells and influenza virus	Amber et al. (2017b)
Bergenia ciliate (Haw.) Sternb.	Zakham-e-Hayat, bud mawa	Saxifragaceae	Rhizome	Methanolic extracts	Bergenin, tannic acid, gallic acid, catechin	HSV1, influenza virus A	
Polygonum cuspidatum Siebold & Zucc.	knotweed and knotgrass	Polygonaceae	Root	Ethanol extract, water extract	Stilbenoids, anthraquinones, catechins	HBV, HIV-1	Chavan and Chowdhary (2014)
Guazuma ulmifolia Lam	West Indian elm or bay cedar	Malvaceae	Bark	aqueous (AqF) and ethyl acetate (EtOAcF) fraction	Epicatechin, procyanidins B2 and B5, procyanidin C1; epicatechin-(4β → 6)- epicatechin-(4β → 8)-	poliovirus 1 (P-1) and bovine herpesvirus 1 (BHV-1)	Chang et al. (2005)

(*continued on next page*)

Table 1 (*continued*)

Plant name	Common name	Family	Part used	Extraction solvent	Active compound	Effective against virus	Reference
					epicatechin; epicatechin-(4β → 8)-epicatechin-(4β → 6)- epicatechin		
Lycoris radiate (L'Heritier) Herbert.	Red spider lily.	Amaryllidaceae	Stem	Ethanol Chloroform	Lycorine, glycyrrhizin	Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)	Li et al. (2005b)
Glycyrrhiza uralensis Fisch.	Licorice	Fabaceae	Root	Methanol	Echinatin	Root extract is effective against HIV, RSV, herpes viruses, and severe acute respiratory syndrome-related coronavirus (SARS-CoV), which causes a serious type of pneumonia	Yeh et al. (2013)
Glycyrrhiza glabra L.	Licorice, Liquorice, Sweetwood	Fabaceae	Root & Leaves	Aqueous, Methanol	glycyrrhizin, glycyrrhetic acid, glabridin, liquiritin	Corona virus, type A influenza virus, Japanese encephalitis, herpes simplex, vesicular stomatitis virus, Newcastle disease virus (NDV)	(Ashraf et al., 2017; Damle 2014; Hussain et al., 2017)
Isatis tinctoria L.	Dyer's woad, or glastum	Brassicaceae	Leaves	Aqueous, Methanol	Indole type glucosinolates	Antibacterial and Antifungal activity; an ancient dye plant	Ullah et al. (2017b)
Fagonia indica L.	Dhamasa	Zygophyllaceae	Leaves	ethanol extract	flavonoids, sterols and triterpenoids	Antileishmanial effects	Ullah et al. (2017a)
Alysicarpus monilifer (L.) DC.	Necklace-pod alyce clover	Fabaceae	Stem and leaves	Aqueous, Methanol	vitexin and isivitexin	Antibacterial activity against MRSA	Kasithevar et al. (2017)
Ajuga bracteosa Wall. ex Benth	Bugleweed	Lamiaceae	Whole Plant	Methanol	20-Hydroxyecdysone	Antiglycation, cytotoxic, phytotoxic, antioxidant, antiplatelet and antimicrobial activities against various pathogens.	Rehman et al. (2015)
Silybum marianum (L.)	Milk thistle Ount Katara	Asteraceae	Fruit	Ethanol	Silymarin, a mixture of flavanoid complexes	Hepatitis virus; cirrhosis, prostate, skin and breast cancer, cervical cells and kidney ailment	Khan et al. (2014)
Withania coagulans (Stocks) Dunal	Paneer dodi	Solanaceae	Fruit	Aqueous, Methanol	withanolides	Leishmanicidal withanolides active	Kuroyanagi et al. (2012)
Allium sativum L.	Garlic	Alliaceae	Bulb	Methanol	allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide and ajoene	Antiviral activity against influenza A and B, HIV, HSV-1, viral pneumonia, and rhinovirus, which causes the common cold	Bayan et al. (2014)
Hypericum connatum Lam	St John's wort	Hypericaceae	Flowers	Ethanol	amentoflavone, hyperoside, guaijaverine and luteoforol	HSV, HIV, influenza, hepatitis, and coxsackievirus	Akram et al. (2018)
Coronopus didymus, (L.) Sm	Jangli halon; bitter cress	Brassicaceae	Vegetable	Aqueous	Terpene essential oils	Malaria, cancer, digestive, antipyretic, expecto	De Ruiz et al. (1994)
Panax ginseng	Ginseng	Panax	Root extract	Aqueous, Methanol	ginseng called ginsenosides	RSV, herpes viruses, and hepatitis A	Yoo et al. (2012)

glabra (Glycyrrhizinic acid) (Pompei et al., 2009), *Sylibum marianum* (Sylimarin) (Polyak et al., 2013), and *Phyllanthus urinaria* (Ellagic acid) (Kang et al., 2006). Experiments have revealed that there are many important plant-based compounds i.e. secondary metabolites with marked antiviral activities These include alkaloids, flavonoids (such as quercetin), lignans (phyllanthine), polyphenolcs (tannins), and terpenoids (Glycyrrhizinic acid), which have shown strong *anti*-HSV, influenza, HIV, HCV, and anti-dengue activities (Hussain et al., 2017).

4. Medicinal plants for viral respiratory infections (VRI)

Viral respiratory infections (VRI) continue to be among the most

common human illnesses. Antiviral plants have much to offer for patients with the acute bronchitis, acute respiratory syndrome, common cold, influenza, viral pharyngitis. Among these antiviral plants, there are many plants studied for their activity against respiratory viruses. These herbal medicines have been used to treat viral flu caused by influenza virus (Choi et al., 2019), human respiratory syncytial viruses (hRSV) (Shin et al., 2013), and notably during the previous epidemics of this century such as two coronavirus outbreaks (SARS-CoV in 2002 and MERS-CoV in 2012).

Convincingly, there are innumerable herbs that have been shown to have a strong *anti*-VRI activity. These plants show direct antiviral activity (Glycyrrhiza spp), acts as analgesic (*Calendula officinalis*), anti-inflammatory (*Hedera helix*), immune stimulator (*Andrographis paniculate*). Notably important antiviral herbs from important families include *Lomatium dissectum* (desert parsley), and *Osmorhiza occidentalis* (western sweet Cicely) from family Apiaceae, *Rosmarinus officinalis* (rosemary), and *Prunella vulgaris* (heal-all) from family Lamiaceae (Yarnell 2017).

For instance, Tian et al. (2011) showed considerable anti-influenza A effects of aqueous extracts of five traditionally employed herbal medicine (*Duchesnea indica, Fragaria indica*, *Liquidambar formosana*, *Lithospermum erythrorhizon*, *Melia toosendan* and *P. vulgaris*). The study conducted by the Tian et al. (2011) revealed that these the extracts from these plants including *P. vulgaris* can act strongly against influenza virus through anti-neuraminidase activity.

For instance, Sornpet et al. (2017) demonstrated the biological activity of crude extracts of five medicinal plants found in Asia (*Andrographis paniculata, Curcuma longa, Gynostemma pentaphyllum*, *Kaempferia parviflora*, and *Psidium guajava*) against highly pathogenic avian influenza virus (H5N1). The study concluded that aqueous and methanolic extract of all the plants resulted in a significant antiviral activity. Among the plants *C. longa* and *K. parviflora* boosted the immune response against H5N1 by increasing the messenger RNA expression of tumor necrosis factor alpha (TNF-α), and interferon beta (IFN-β). Similarly, Rajasekaran et al. (2013) showed that fifty medicinal plants, originating from the tropical rainforests possess potent anti-influenza virus activity. The tested plants proved to be minimally cytotoxic and had significant potential for the inhibition of viral neuraminidase and hemagglutination. Similarly, Choi et al. (2019), successfully employed Geranii Herba (*Geranium thunbergii*) for the inhibition of neuraminidase activity in influenza viruses. In fact, there are many studies available on the strong anti-influenza virus activity of different plants.

Furthermore, Chathuranga et al. (2019) assessed the *anti*-RSV activity of herbs *Plantago asiatica* and *Clerodendrum trichotomum*. Through this study, it was reported that lower concentrations of *P. asiatica* and *C. trichotomum* extract significantly reduced replication and transcription in RSV genes and in turn reduced its protein synthesis thus reducing the RSV-induced cell death.

Among these antiviral herbs, those specifically important to mention are the *anti*-coronavirus medicinal plants. Plant extracts can be useful against COVID-19 because it belongs to the β genus of coronavirus and is thus closely related to the previous coronaviruses against which these plants have shown potent activity. There is a whole list of herbs assessed for their activity against SARS-CoV viruses (Table 2). Most notable among them are the *Lycoris radiata* (Li et al., 2005c), *Artemisia annua*, *Lindera aggregate*, *Isatis indigotica* (Lin et al., 2005), *Torreya nucifera* (Ryu et al., 2010), *Houttuynia cordata* (Lau et al., 2008), *Pelargonium sidoides* (Whitehead et al., 2019), and *Glychirrhiza* spp. (Fiore et al., 2008).

For instance, *I. indigotica* root extract showed significant *anti*-SARS-CoV activity via inhibitory effects on 3C-like proteases (3CLpro) in the virus (Lin et al., 2005). Similarly, in another study, aqueous extract of *H. chordata* showed inhibition of RNA-dependent RNA polymerase (RdRp) and 3CLpro activity in SARS-CoV (Lau et al., 2008). It was also revealed through flow cytometry-based analysis that extracts of *H. chordata* boosted immune response against SARS-CoV through increasing the proportion of cluster of differentiation ($CD4^+$ and $CD8^+$) T cells. Similarly, root extract of *P. sidoides* has been shown to interfere with replication of human coronaviruses (Whitehead et al., 2019). Currently, there are numerous studies available on plant-based compounds from limited number of plants against coronaviruses. Plants used in the form of extracts or any other form against different respiratory viruses could be employed to work against COVID-19. One area that bears enormous potential exploring these and many other such plants which are used against viruses having similar structural features as that of COVID-19, exhibiting the same pattern of infection, similar pathophysiology, and similar symptoms. This can be demonstrated by a detailed analysis of replication cycle of the COVID-19 (Fig. 1). For example, those plant products used against viruses belonging to the same origin as COVID-19 (Cyprus_Mail, 2020), or those having genome of similar orientation (i.e. positive stranded RNA viruses (Ogbole et al., 2018) could be employed for fighting against COVID-19.

5. Plant-derived antiviral compounds

The diverse medicinal capabilities of plants lie in the complexities of their secondary metabolism. Although it is very easy to apply herbal medicine as a whole plant crude extract, decoction, tea, the efficacy of plant-based chemical compounds can be realized only if they are applied in their pure forms or in a mixture to form a compound drug. There are innumerable chemical compounds isolated from plants which are the potent antiviral drug (Denaro et al., 2020). This study reviewed a diversity of polyphenolic compounds isolated from different plants for their antiviral activity. As indicated in Table 3, studies have shown the efficacy of hundreds of different compounds against human viruses for their direct anti-viral activity or alleviation of symptoms (Amber et al., 2017a; Li and Peng 2013). For instance, important compounds such as natural mixture of polyphenols from almond that include catechin, naringenin-7-*O*-glucoside, kaempferol-3-*O*-glucoside, epicatechin, isorhamnetin-3-*O*-rutinoside, and isorhamnetin-3-*O*-glucoside has been shown to reduce the HSV DNA accumulation and cytopathic effects by the virus (Musarra-Pizzo et al., 2019). Similarly, Pentagalloylglucose isolated from *Phyllanthus emblica* has been shown to inhibit HSV-induced rearrangements of actin cytoskeleton (Pei et al., 2011). It has been observed that generally, phytochemicals acts by interference with viral entry via attachment to viral proteins (Kesharwani et al., 2017), inhibits viral replication (Langland et al., 2018; Li et al., 2005a), stops transcription (Yarmolinsky et al., 2012), and expression of viral proteins (Kuo et al., 2006).

6. Plant-derived compounds against respiratory viruses

Among the many compounds, there are many of them used against respiratory viruses. For instance, theaflavin has been shown to inhibit hemagglutinin and neuraminidase in H1N1 influenza virus, curcumin disrupts the envelop of H1N1 and H9N2 influenza viruses (Bahramsoltani et al., 2016) and glycyuralin F interferes with viral infection (Ji et al., 2016). Similarly, apigenin, linalool and Ursolic acid isolated as pure constituents from *Ocimum basilicum* have showed anti-viral effects in bronchitis caused by human adenoviruses (Chiang et al., 2005). Furthermore, other studies have also found activity of many different compounds against other respiratory viruses such as RSV and coronaviruses. Carnosic acid found in *Rosmarinus officinalis* has been found to be highly *anti*-hRSV-specific compound. The study showed that carnosic acid inhibited both A- and B- type hRSV, while it did not affect the replication of influenza A virus and thus could be used as a more specific treatment for hRSV (Shin et al., 2013). Focusing on the scope of the current review and to have a deep insight into herbal medicine against coronaviruses, we will now highlight the phytochemicals that are previously employed against coronaviruses and thus bears potential against COVID-19.

Table 2
Plant species and bioactive metabolites used for the treatment of SARS-CoV infection.

Plant name	Common name	Family	Part used	Metabolite	References
Anemarrhena asphodeloides	Anemarrhena rhizome, Zhi mu	Asparagaceae	rhizome	Sarsasapogenin, Sarsasapongenin (saponins)	Tang and Eisenbrand (1992)
Areca catechu L.	areca nut, betel nut	Arecaceae	dried ripe seed	Arecoline, Arecaidine, Guvacine, Guvacoline, Arecolidine, Homoarecoline	(Peng et al., 2015; Zhang et al., 2014a)
Armeniaca sibirica L.	Siberian apricot	Rosaceae	Leaves	Sibiriaester A, Sibiriaester B	Wu et al. (2018)
Prunus armeniaca Linne var. ansu Maxim owicz		Rosaceae	dried seed part	Amygdalin	Park et al. (2013)
Prunus armeniaca L. var. ansu Maxim.	Natural Bitter Apricot Seed	Rosaceae	the dried, ripe seeds	Amygdalin, Neoamygdalin and Amygdalin Amide	Xu et al. (2017)
Astragalus membranaceus Bge. Var. mongholicus	Astragali radix	Fabaceae	dried root	Astragaloside, Isoastragloside	He and Findlay (1991)
Dioscorea opposita Thunb	Chinese yam	Dioscoreaceae	root	Diosgenin	Zhang et al. (2014b)
Dryopteris crassirhizoma	thick stemmed wood fern	Dryopteridaceae	Root	hexacosanic acid, pentacosanol, nerolidol, dryocrassin ABBA, flavaspidic acid AB	Gao et al. (2003)
Ephedra sinica		Ephedraceae	stem	ephedrine, pseudoephedrine, N-methylephedrine, and 6-methoxykynurenic acid	Zhao et al. (2009)
Ephedrae herba		Ephedraceae	Aerial parts	(−)-ephedrine, (+)-pseudoephedrine, (−)-methylephedrine, (+)-methylpseudoephedrine, (−)-norephedrine, and (+)-norpseudoephedrine	Liu et al. (1993)
Glycine max L. Merill	Fermented soy, Natto		Fermented bean	Globulins, β-conglycinin, glycinin	Yang et al. (2011)
Lonicera macranthoides Hand.-Mazz., *Lonicera hypoglauca* Miq., *Lonicera confusa* DC and Lonicera fulvotomentosa	Shan Yin Hua	Caprifoliaceae	Dried leaves	200 compounds have been isolated and identified, mostly falavonoids and essential oil, Caffeic acid, Chlorogenic acid, Macranthoin F	Tang et al. (2018)
Arctium lappa L.	Seeds of burdock fruit	Caprifoliaceae	dried fruits	Arctiin, Arctigenin, Matairesinol	Wagner et al. (2016)
Forsythia suspensa (Thunb.) Vahl	weeping forsythia, golden-bell	Oleaceae	dried fruits	Forsythoside A, Forsythoside B, Isoforsythoside	Zhou et al. (2017)
Glycyrrhiza uralensis Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L. (Fam. Fabaceae)	liquorice root	Fabaceae	dried root and rhizome	Glycyrrhizin, Glycyrrhetinic acid, Glycyrretol	Wagner et al. (2015a)
Glycyrrhizae, uralensis	Chinese liquorice	Fabaceae	Rhizome, root	glycyrrhizin	Tanemoto et al. (2015)
Lophatherum gracile Brongn	Herba Lophatheri	Poaceae	Dried stem and leaf	Luteolin, isoorientin, isovitexin, swertisin	Fan et al. (2015)
Mentha haplocalyx Briq.		Lamiaceae	Aerial parts (stem and leaf)	spicatoside A, spicatoside B, menthalactone, maniladiol,	He et al. (2019)
Schizonepeta tenuifolia	Herba Schizonepetae	Saururaceae	Leaves and Spikes	(−)-menthone, (+)-pulegone, (−)-limonene and (+)-menthofuran	(Schwarz et al., 2011; Song et al., 2016)
Isatis tinctorial L.	Woad or dyer's woad	Brassicaceae	dried root	Isatin, Isatan A – B − C, Isoindigo, Isoorientin,	Speranza et al. (2020)
Lonicera japonica	Japanese honeysuckle and golden-and-silver honeysuckle	Caprifoliaceae	Flower bud, roots	Stryspinoside, chlorogenic acid, loganin aglycone, caffeic acid	(Wang et al., 2013; Yu et al., 2016)
Pogostemon cablin. (Blanco) Benth.	Patchouli	Lamiaceae	Leaves	*Pogostone, friedelin, epifriedelinol, pachypodol, α-Copaene,* γ-Patchoulene	(Guan et al., 1994; van Beek and Joulain 2018)
Platycodon grandifl orum (Jacq.) A. DC.	Radix Platycodonis	Campanulaceae	dried root	Platycodin A, C and D, deapioplatycoside E, deapioplatycodin D3, platycodin D3, platycodin D2, platycodin D, polygalacin D, polygalacin D2, polygalacin D3, platycoside B, C, E, J, F, O, M-3, N platyconic acid B lactone, deapio-platyconic acid B lactone, platyconic acid A,	Wagner et al. (2015b)
Rheum palmatum	Chinese rhubarb, ornamental rhubarb, Turkey rhubarb	Polygonaceae	dried root	Gallic acid glucoside, Epicatechin glucoside, Gentisin glucoside, Rhein, Aloe-emodin, Emodin sulphate	El-Saied et al. (2018)
Phragmites communis L.	Common Reed	Poaceae	rhizome	ferulic acid, *p*-coumaric acid, syringic acid, vanillic acid, p-hydroxy benzoic acid, palmitic acid, heptadecanoic acid, β-sitosterol, stigmasterol, α-D-glucose and β-D-glucose	Gao et al. (2009)
Rhodiola rosea	Rosenroot, arctic root or golden root	Crassulaceae	Leaves	rosavin, rosin, rosarin, salidroside (rhodioloside), tyrosol, rodiolin, rodionin, rodiosin, acetylrodalgin, tricin, rosiridol, rosaridin	Brown et al. (2002)
Saposhnikovia divaricata (Turcz.) Schischk.		Apiaceae	root	Hamaduol, Ledebouriellol, Divaricatol, Cimifugin, Anomalin, Scopoletin, Marmesin, Isofraxidin, Fraxidin, Divaricoumarin A-B-C,	Kreiner et al. (2017)
Scutellaria baicalensis		Lamiaceae	Dried root	Baicalein, Wogonin, neobaicalein, and skullcapflavone	

(*continued on next page*)

Table 2 (*continued*)

Plant name	Common name	Family	Part used	Metabolite	References
Lanxangia tsaoko (Syn: Amomum tsao-ko)	Baikal skullcap or Chinese skullcap cao guo	Zingiberaceae	Ripe fruit and leaves	cineole	Bonham et al. (2005) Lee et al. (2019)

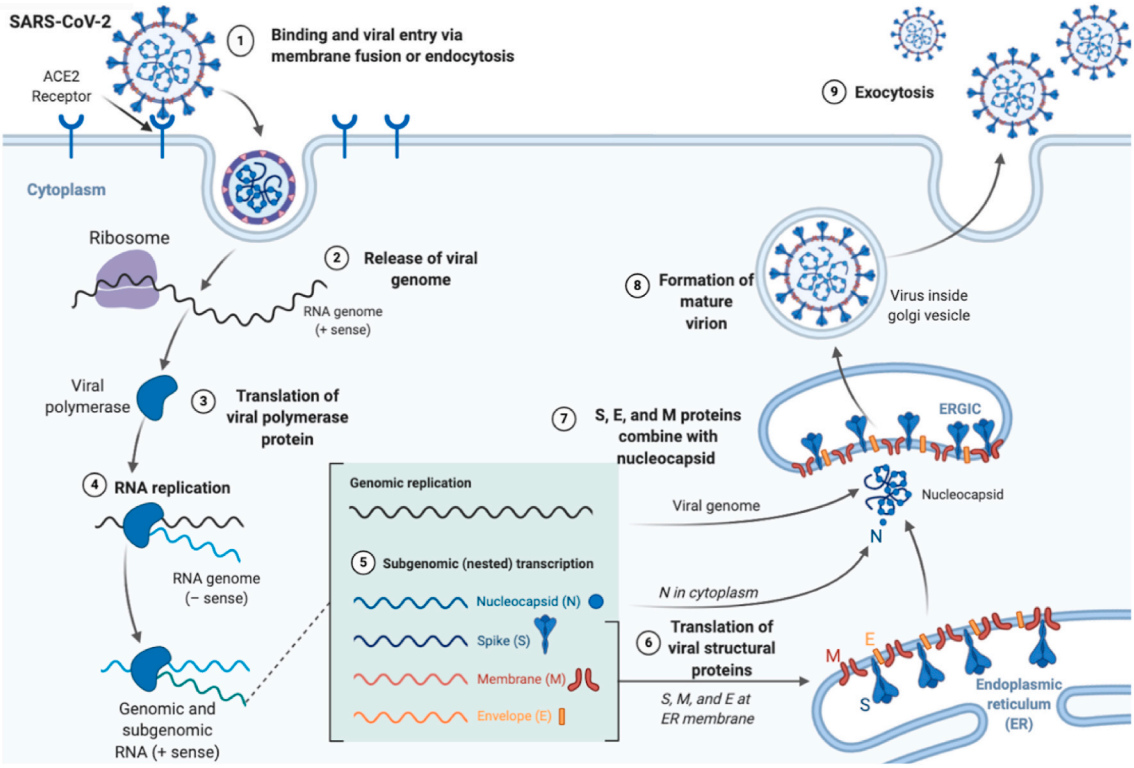

Fig. 1. Replication cycle of COVID-19 in the human body (Created with BioRender.com).

7. Phytochemicals against coronaviruses; a promising avenue

The pandemic caused by COVID-19 warrants search for safe antiviral compounds to treat the disease. At present, no specific treatment has been identified for COVID-19. The novelty of COVID-19 means that its behavior is very uncertain and, therefore, it is difficult to determine the efficacy of herbal products against the virus or as prophylactic agents. However, as the current COVID-19 viruses bears resemblance to the previous outbreak causing SARS-CoV and MERS-CoV, so the herbal compounds employed against the previous coronaviruses may prove as valuable drug candidates if researched properly. There are hundreds of different herbal products tested against the coronaviruses. Most of these products have their selectivity indexes up to 100 which hints towards their safety (De Clercq 2006). Selectivity index (SI) (CC_{50}/EC_{50}) is the measure of effectiveness of drugs. Higher SI values mean that the drug tested is theoretically more effective and safer during *in vivo* experiments.

For instance, after the first outbreak of SARS-CoV, reported that Glycyrrhizin, a saponin from Liquorice roots, can inhibit the replication of SARS-associated coronavirus with EC_{50} value ranging from 300 to 600 mg/L (during and after virus adsorption, respectively). The CC_{50} was recorded to be higher than 20,000 mg/L. This means that at a dose of 20,000 mg/L, there was only 20–30% reduction of cell viability recorded thus indicating the low cytotoxicity of the compound. It was demonstrated that glycyrrhizin given to infected cells at 4000 mg/L, completely blocked replication of the virus (Fig. 2). The study also indicated that Glycyrrhizin is a safer alternative to other antiviral compounds such as Ribavirin which is usually responsible for hemolysis and a drastic reduction of haemoglobin in SARS patients (Cinatl et al., 2003b). Although there are certain side effects to using untested herbal products and every product should be properly tested, phytochemicals are usually intrinsically safe based on their biocompatibility, lesser toxicity than xenobiotics and environment-friendliness. At the time of SARS outbreak in 2002, the mechanism of action of phytochemicals like Glycyrrhizin wasn't exactly clear. Further studies on Glycyrrhizin attempted to decipher the mechanism of action and produce a more potent form of the phytochemical against coronaviruses. Hoever et al. (2005) showed that addition of 2-acetamido-β-D-glucopyranosylamine into the glycoside chain of glycyrrhizin results in a 10-fold increase in its activity against the virus. The spike proteins (S-proteins) of coronaviruses are heavily glycosylated. This study showed that the addition of glycyrrhizin (with the added 2-acetamido-β-D-glucopyranosylamine) blocks the entry of the virus into the cells. Glycyrrhizin has also been shown to disappear from the blood plasma of treated subjects after oral administration of 100 mg glycyrrhizin. This might be because it is metabolized to glycyrrhetinic acid by intestinal bacteria which contain β-D-glucuronidase (Chen et al., 2004).

8. Mechanistic aspects of using phytochemicals against SARS-CoV-2

Coronaviruses acts against the host immune system through its proteases; papain like protease (PLpro) and 3CLpro. The PLpro of SARS-CoV antagonize the innate immune response. The host's immune

Table 3
Medicinal plant metabolites with known mechanism of action against SARS-CoV infection.

S. No.	Metabolites	Mode of action	References
1.	Phenolic compounds	Inhibit the cleavage activity of SARS-3CLpro enzyme	Lin et al. (2005)
2.	2-undecanone, decanoyl acetaldehyde, myrcene	Inhibit the viral SARS-3CLpro activity	Fung et al. (2011)
3.	Quercetin, Isoquercitrin, Hyperin, Rutin	Block viral RNA-dependent RNA polymerase activity (RdRp	(Lau et al., 2008a)
4.	Myricetin and Scutellarein	Inhibit nsP13 by affecting the ATPase activity	Yu et al. (2012)
5.	Glycyrrhizin	Inhibit viral adsorption and penetration	Cheng et al. (2006b)
6.	Herbacetin, quercetin, isobavaschalcone, 3-β-D-glucoside and helichrysetin	Inhibit cleavage activity of MERS-3CLpro enzyme	Jo et al. (2019)
7.	Tetrandrine, Fangchinoline, and Cepharanthine	Inhibit the expression of HCoV– OC43 spike and nucleocapsid protein.	Zou et al. (2019)
8.	Herbacetin, Rhoifolin, Pectolinarin, Quercetin, Epigallocatechin Gallate, and Gallocatechin gallate	Inhibit SARS-3CLpro activity	Nguyen et al. (2012)
9.	Quercetin	Inhibit the cellular entry of SARS-CoV	Chen et al. (2008)
10.	Kaempferol	Inhibit 3a ion channel of coronavirus	Schwarz et al. (2014)
11.	Saikosaponins	Prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration	Cheng et al. (2006b)
12.	luteolin	Avidly binds with surface spike protein of SARS-CoV	(Yi et al., 2004a)

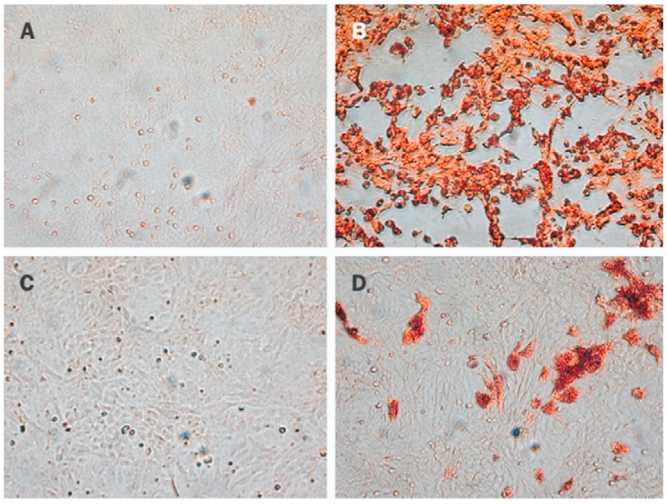

Fig. 2. Vero cells treated with Glycyrrhizin highlight the importance of plant-derived compounds for COVID-19. (A) mock infected cells, (B) infected cells without treatment. (C) infected cells treated with 4000 mg/L glycyrrhizin. (D) infected cells treated with 1000 mg/L glycyrrhizin [Adopted from Cinatl et al. (2003b)].

response first recognizes viral RNA and then recruits adaptor mitochondrial antiviral-signaling proteins to transduce signals to the downstream kinase complex for activation of transcription factor, NF-κB and IRF-3. Next, these transcription factors induce the expression of type I interferons (IFN-α and -β). Type I IFN induces the activation of STAT transcription factors resulting in the expression of IFN-stimulated genes (ISGs), which establishes an antiviral state in surrounding cells. SARS-CoV PLpro acts either via deISGylating or deubiquitinating proteins or both within these pathways. This results in antagonism of the host antiviral response and thus successful evasion of immune response by the SARS-CoV (Báez-Santos et al., 2015). This means that candidate drugs could be helpful if they either inhibit viral entry, replication or provoke immune response to produce Type I IFN against SARS-CoV.

It became clear through many studies after the first outbreak of SARS-CoV, that plant extracts and plant-derived compounds act against viruses in different mechanisms. These range from direct antiviral activity, immune stimulator, analgesic, inflammation modulator, and symptom management. The direct antiviral activity encompasses inhibition of early replication via viral entry inhibition (Cheng et al., 2006a), and late replication inhibition (Kim et al., 2011) (Fig. 3) (Fig. 4).

8.1. *Inhibition of SARS-CoV entry by phytochemicals*

Viral entry inhibition by plant derived compounds is another promising area of finding the suitable drug candidate. Coronaviruses enter the cell after binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2). This entry is made possible through the attachment of SARS-CoV spike (S) protein to ACE2. Many different phytochemicals have shown a strong inhibition of the interaction of SARS-CoV S protein and ACE2. For example, anthraquinone compounds; emodin, and rhein, and a flavonoid; chrysin, derived from genus *Rheum* and *Polygonum* were tested for their activity against SARS-CoV. The study found that emodin showed the strongest effect and significantly blocked the S protein and ACE2 interaction with IC_{50} value of 200 μM (Ho et al., 2007).

Flavonoids and polyphenolic compounds like luteolin, quercetin and etra-*O*-galloyl- β-D-glucose have been shown to significantly block the entry of SARS-CoV into the cells. Yi et al. (2004) studied the effects of these small molecules on the entry of SARS-CoV. All three molecules (luteolin, quercetin and etra-*O*-galloyl- β-D-glucose) showed promising results with EC_{50} of 83.4 μM, 10.6 μM and 4.5 μM, respectively. Assays based on a human immunodeficiency virus (HIV)-luc/SARS pseudo-typed virus were used for experiments on viral entry inhibition. The results confirmed that along with luteolin, and etra-*O*-galloyl-β-D-glucose, quercetin also had activity against HIV-luc/SARS with a lower cytotoxicity of quercetin. Therefore, as an FDA-approved drug ingredient, quercetin can be applied as a potential drug in the clinical treatment of COVID-19.

9. Inhibition of replication in SARS-CoV

Furthermore, fractionation and purification of *L. radiata* extract resulted in isolation of an alkaloid, lycorine which was assessed as an *anti*-SARS-CoV component. The compound with an EC_{50} value of 15.7 ± 1.2 nM and CC_{50} value of 14980.0 ± 912.0 nM in cytotoxicity assay. Lycorine was found to inhibit viral replication at a concentration that is lower than that of glycyrrhizin. The results suggested that the phytochemical compound lycorine is a promising candidate for the development of new *anti*-SARS-CoV drugs in the treatment of SARS (Li et al., 2005c).

The replication of SARS-CoV is usually inhibited by interfering with the functions of the main viral proteinase (Mpro, or 3CLpro). The 3CLpro regulates the activities of the coronavirus replication complex and has thus been one of the main targets in finding a drug against the coronaviruses (Anand et al., 2003). Apart from these, replication of SARS-CoV has also been inhibited by Reserpine, an alkaloid isolated from the dried root of *Rauvolfia serpentina* (Indian snakeroot) and Aescin, a saponin from *Aesculus hippocastanum* (European chestnut tree). The EC_{50} values for Reserpine and were found to be 3.4 μM and 6.0 μM while the and CC_{50} values were 25 μM and 15 μM, respectively. Different assays such as enzyme linked immunosorbent assay (ELISA), Western blot analysis, immunofluorescence and flow cytometry assays confirmed

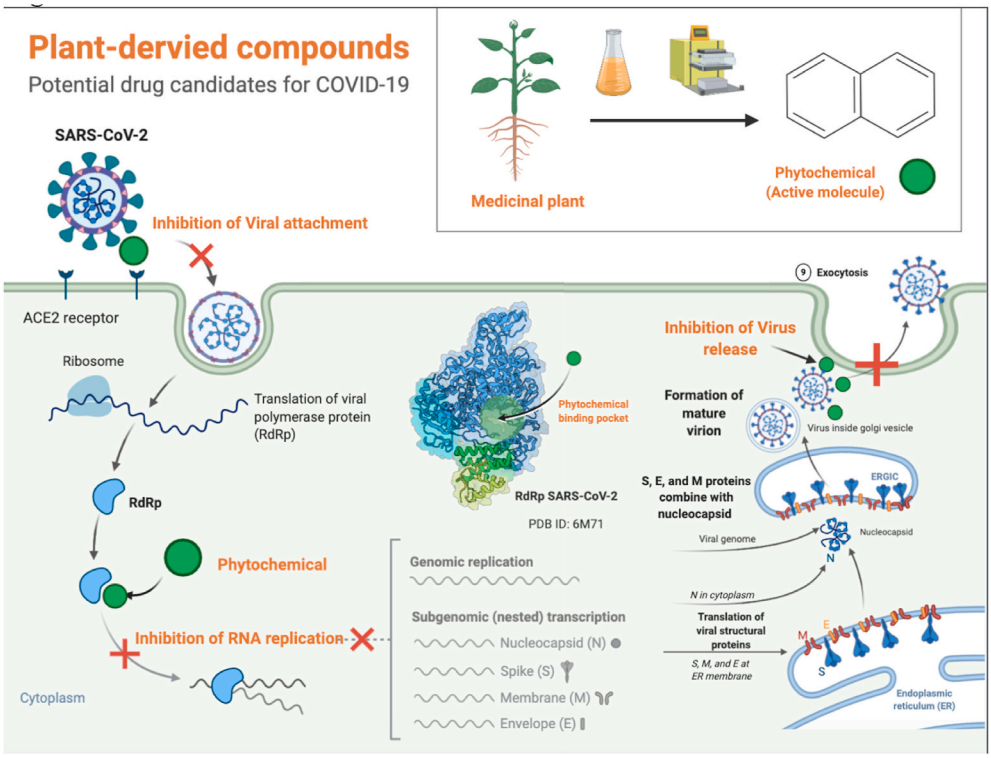

Fig. 3. The intervention points for phytomedicine against SARS Coronaviruses.

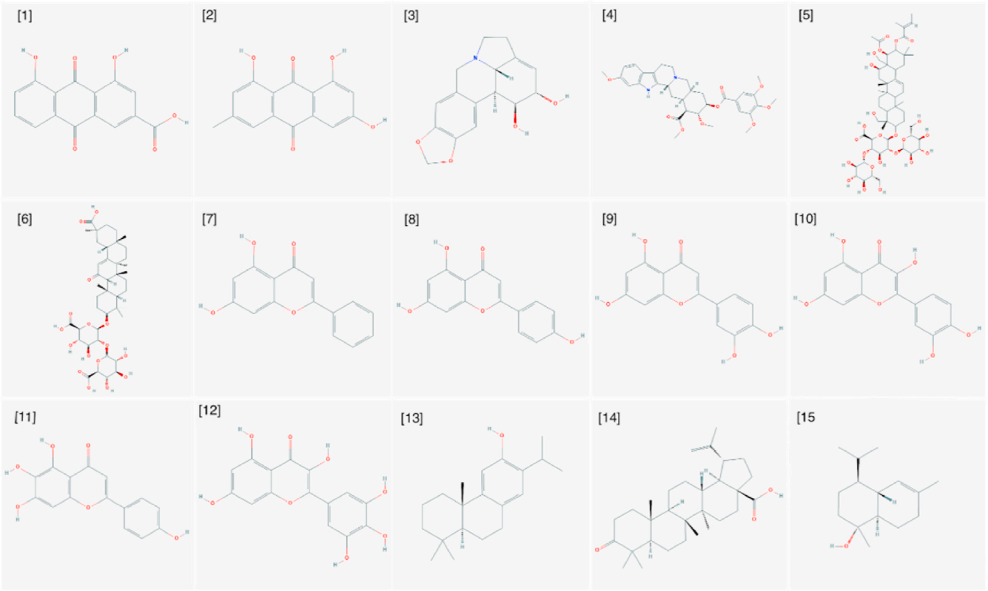

Fig. 4. Structural representation of important phytochemicals. [1] Rhein (CID = 10,168); [2] Emodin (CID = 3220); [3] Lycorine (CID = 72,378); [4] Reserpine (CID = 5770); [5] Aescin (CID = 16211024); [6] Glycyrrhizin (CID = 128,229); [7] Chrysin (CID = 5281607); [8] Apigenin (CID = 5280443); [9] Luteolin (CID = 5280445); [10] Quercetin (CID = 5280343); [11] Scutellarein (CID = 5281697); [12] Myricetin (CID = 5281672); [13] Ferruginol (CID = 442,027); [14] Betulonic acid (CID = 122,844); and [15] α-cadinol (CID = 10398656); (Adopted from NCBI PubChem).

the *anti*-SARS-CoV activity of these compounds. Reserpine and Aescin have been shown to interfere with the viral entry to the cell and also inhibit the activity of 3CLpro enzyme of the virus inside the cell (Wu et al., 2004).

Plant lectins have also been showed to potently block the entry of SARS-CoV into the cells. Keyaerts et al. (2007) showed that lectins isolated from many different plants showed a promising *anti*-SARS-CoV activity with EC_{50} ranging from 0.45 to >100 μg/mL and CC_{50} value ranging from 50 to 100 μg/mL. Among all of them, the highest *anti*--coronavirus activity through cytopathic effects was reported among mannose-binding lectins isolated from *Allium porrum* with a selectivity index of >222. The study revealed that apart from interference with viral replication during the viral life cycle, the lectins seemed to inhibit viral entry to the cell.

Flavonoids have also been shown to possess a considerable activity against the coronaviruses. Ryu et al. (2010) reported that flavonoids such as apigenin, luteolin, and quercetin purified from ethanolic leaf extracts of *Torreya nucifera*, an Asian traditional medicinal plant also showed significant SARS-CoV 3CLpro inhibiting activity. The IC_{50} values of the 3CLpro inhibitors (apigenin, luteolin, and quercetin) were recorded to be 280.8, 20.2, and 23.8 μM, respectively. The results of these of these enzymatic studies were confirmed through binding energy

studies via molecular docking. Furthermore, among these compounds, a carbon moiety of apigenin showed stronger activity compared to other flavonoids.

Similarly, terpenoids were also found to be effective in blocking viral replication. Ferruginol, pinusolidic acid, and α-cadinol were purified from ethyl acetate extracts of *Chamaecyparis obtuse*, along with cedrane-3β,12-diol, and betulonic acid, isolated from *Juniperus formosana* and cryptojaponol isolated from *Cryptomeria japonica.* The study indicated that most of the terpenoids inhibited the replication of SARS-CoV at EC_{50} between 3.8 and 7.5 μM and an CC_{50} value greater than 250 μM. It was confirmed through ELISA that the terpenoids block the S proteins of the virus to induce replication inhibition activity. The study also confirmed a strong *anti*-3CLpro activity through docking studies and concluded that, in their pure form, terpenoids could be beneficial as drug candidates against SARS-CoV (Wen et al., 2007).

Apart from the viral replication inhibition and anti-3CLpro activity, plant-based compounds have proved effective in blocking the activity of important enzymes such as SARS helicase. Yu et al. (2012) studied the inhibitory effects of 64 purified natural compounds against the activity of SARS helicases. Among these flavonoids, myricetin and scutellarein, isolated from *Aglaia perviridis* showed significant *anti*-SARS-CoV activity. Studies on fluorescence resonance energy transfer (FRET)-based double-strand DNA unwinding assay and colorimetry-based ATP hydrolysis assay confirmed that flavonoids such as scutellarein and myricetin potently inhibit the SARS-CoV helicase protein *in vitro* by affecting the ATPase activity. Based on their lower IC_{50} values, 2.71 ± 0.19 μM and 0.86 ± 0.48 μM, respectively, and no cytotoxicity against breast cancer cell lines, myricetin and scutellarein could thus prove as SARS-CoV chemical inhibitors.

9.1. Other mechanisms

Phytochemicals can also play a role in other aspects of the SARS-CoV infection. For instance, Schwarz et al. (2011) showed that, emodin, the anthraquinone from family *Polygonaceae* can inhibit the 3a ion channel of coronavirus and thus inhibit the release of SARS-CoV form infected cells (Fig. 3). Apart from this, phytochemicals can be effective in the immune modulation against coronaviruses (Lau et al., 2008) and can also act analgesics, and symptom management such as reduction of hypoxemia and dyspnea management. These studies suggest that phytochemicals can be employed against SARS-CoV-2, for their diverse roles and potency against other coronaviruses such as SARS-CoV.

10. The role of bioinformatics in the development of sensitive, specific and cost-effective antiviral agents from medicinal plants

The research related to bringing plant-based drugs from bench to boardroom is lagging behind synthetic drugs despite the fact that phytomedicine have an enormous potential in treatment an array of ailments. The lag is especially prominent when it comes to comparing the rapidity of its availability to synthetic drugs. This is one of the most important reasons that put medicinal plants biotechnology research on a priority list. This has created a plethora of information regarding medicinal plants and their utility against different disease-causing agents. The information available are scattered throughout different databases and web sources (Gu and Chen 2014). For this purpose, a counter approach is sought through the use of computational tools. Bioinformatic tools play an important role in analyzing the available data and thus choosing the best drug candidates aided with the wet lab research. Furthermore, Computational approaches offer their value in terms of deciphering genetic pathways that are associated with the production of antiviral secondary metabolites from medicinal plants (Sharma and Sarkar, 2013. Several databases have been developed to provide catalogue information related to scientific publications in general including the National Center for Biotechnology Information (NCBI), and Kyoto Encyclopedia of Genes and Genomes (KEGG). Similarly, databases like the Arabidopsis information resources (TAIR), Medicinal Plant Database for Drug Designing (MPD3), and the International Ethnobotany Database (ebDB) provide more specific and useful information about medicinal plants and their metabolic pathways. The later of these is a noncommercial repository for ethnobotanical research providing complete location information, strong searching and data export features (http://ebdb.org). Similarly, MPD3 is a free database that provides information about phytochemicals including their structure and potential activities through reference to original research papers. These databases have already helped researchers to evaluate the potential of phytochemicals/traditional Chinese medicinal compounds against protiens and enzymes of the novel SARS-CoV-2. For instance (ul Qamar et al., 2020), assessed the activity of phytochemicals from a medicinal plant library containing 32,297 potential anti-viral phytochemicals/traditional Chinese medicinal compounds against the viral 3-chymotrypsin-like cysteine protease (3CLpro). Their analyses concluded at least nine hits for a potential class of drugs among the phytochemicals against the SARS-CoV-2. Similarly, molecular docking studies of stilbenoids against SARS-CoV-2 spike proteins have shown that stilbene based compounds (especially resveratrol) and flavonoids such as quercetin, fisetin, and kaemferol can be promising *anti*-SARS-CoV-2 drug candidates acting through disruption of the spike protein (Wahedi et al., 2020) (Pandey et al., 2020). Apart from stilbenoids and flavanoids studied for their in silico molecular dynamics, amongst the phytochemicals studied, essential oils have also been shown to possess potent acitivity against SARS-CoV-2. For instance, Abdelli et al. (2020) concluded that natural compounds (Isothymol, Limonene, *P*-cymene, Thymol and γ-terpinene) can block the activity of angiotensin converting enzyme 2 (ACE2) as a receptor for SARS-CoV-2 that is hampering the attachment of the virus to the cell surface.

11. Safety and regulatory aspects of using phytomedicine

This paper highlights the importance of phytotherapeutic agents as candidates in search for drugs against COVID-19. Based on the novelty of the virus and the disease caused, safety concerns still loom over the use of phytomedicine. Therefore, safety aspects must be taken into consideration. Insufficient data exist for most of the plants to guarantee their quality, efficacy and safety. Untested use of pure compounds is not recommended, and these compounds should first go through the proper efficacy and safety testing. The Food and Drug Administration (FDA) for example provides guidelines for safe use of natural products as drugs (FDA 2006). Similarly, the European Medicines Agency (EMA), asserts that herbal medicinal products should only be used traditionally if they have been used for at least 30 years, including at least 15 years within the European Union and are not administered by injection. Furthermore, marketing and well established use should only be authorized after scientific literature is available that confirms that the pure constituent/active ingredient of the herbal product has a recognized efficacy (Calapai 2008; EMA 2001). However, there is a wrong perception, that herbal drugs are fully safe and free from any side effects. There are hundreds of toxic constituents in different plants. Compared to synthetic compounds, natural products and plant-based compounds have shown lesser toxicity and thus requires less stringent evaluation. However, to avoid the side effects of the unregulated use of these plant-based compounds, safety regulation on the use of the products is important (Calixto 2000). It is, suggested that while bringing harmony with other agencies, regulatory authorities should work for regulating herbal products and using them as drug candidates for treating COVID-19.

12. Conclusions

Medicinal plants can provide a very plausible platform for the search for drug candidates to be tested against COVID-19. The secondary metabolism of many plants serves as a treasure of phytochemicals, which have shown promising results against human viruses. More

specifically, phytochemicals serve as phytotherapeutic agents against the coronaviruses especially SARS coronaviruses. Phytochemicals are advantageous in their timeliness, the sense that they are biocompatible and less toxic to synthetic drugs. Based on studies of phytomedicine against the previous SARS-CoV, the most potent phytochemicals could be filtered and put to test against COVID-19. Similarly, while trials are underway for testing vaccines, traditional herbal medicine in the form of decoctions, tea or powder could be tested (based on enough evidence of efficacy) for the alleviation of symptoms.

Credit author statement

Khan MA conceived the idea, Khan T and Khan MA wrote the whole manuscript, Mashwani Z curated the tabulated data, Nadhman A made the animated figures and Ullah N reviewed the article and fixed the language mistakes.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

Akram, M., Tahir, I.M., Shah, S.M.A., Mahmood, Z., Altaf, A., Ahmad, K., Munir, N., Daniyal, M., Nasir, S., Mehboob, H., 2018. Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: a systematic review. Phytother Res. 32 (5), 811–822. https://doi.org/10.1002/ptr.6024.

Alamgeer, Younis, W., Asif, H., Sharif, A., Riaz, H., Bukhari, I.A., Assiri, A.M., 2018. Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence. Chin. Med. 13 (1), 48. https://doi.org/10.1186/s13020-018-0204-y.

Alizadeh, A., Moshiri, M., Alizadeh, J., Balali-Mood, M., 2014. Black henbane and its toxicity–a descriptive review. Avicenna journal of phytomedicine 4 (5), 297.

Amber, R., Adnan, M., Tariq, A., Mussarat, S., 2017. A review on antiviral activity of the Himalayan medicinal plants traditionally used to treat bronchitis and related symptoms. J. Pharm. Pharmacol. 69 (2), 109–122.

Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J.R., Hilgenfeld, R., 2003. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science 300 (5626), 1763. https://doi.org/10.1126/science.1085658.

Andleeb, R., Ashraf, A., Muzammil, S., Naz, S., Asad, F., Ali, T., Rafi, R., Al-Ghanim, K., Al-Misned, F., Ahmed, Z., 2020. Analysis of bioactive composites and antiviral activity of Iresine herbstii extracts against Newcastle disease virus in ovo. Saudi J. Biol. Sci. 27 (1), 335–340.

Arbab, A.H., Parvez, M.K., Al-Dosari, M.S., Al-Rehaily, A.J., 2017. In vitro evaluation of novel antiviral activities of 60 medicinal plants extracts against hepatitis B virus. Experimental and therapeutic medicine 14 (1), 626–634.

Ashraf, A., Ashraf, M.M., Rafiqe, A., Aslam, B., Galani, S., Zafar, S., Asad, F., Asghar, R. D., Akram, S., Ahmed, H., 2017. In vivo antiviral potential of Glycyrrhiza glabra extract against Newcastle disease virus. Pak. J. Pharm. Sci. 30.

Ashraf, A., Zafar, S., Ashraf, M.Y., Ijaz, M.U., Muzammal, S., Asad, F., Jabeen, F., Shahid, M., 2020. Phytochemical composition and potent biological activities OF FICUS benjamina var. Comosa leaves extract. Pakistan J. Bot. 52 (2), 531–535.

Ataee, R., Falahati, A., Ebrahimzadeh, M.A., Shokrzadeh, M., 2016. Anticonvulsant activities of Sambucus nigra. Eur. Rev. Med. Pharmacol. Sci. 20 (14), 3123–3126.

Báez-Santos, Y.M., John, S.E.S., Mesecar, A.D., 2015. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antivir. Res. 115, 21–38.

Bahramsoltani, R., Sodagari, H.R., Farzaei, M.H., Abdolghaffari, A.H., Gooshe, M., Rezaei, N., 2016. The preventive and therapeutic potential of natural polyphenols on influenza. Expert Rev. Anti-infect. Ther. 14 (1), 57–80. https://doi.org/10.1586/14787210.2016.1120670.

Bannerman, R.H.O., Burton, J., Bannerman, R.H., Ch'en, W.C., World Health, O., 1983. Traditional Medicine and Health Care Coverage: A Reader for Health Administrators and Practitioners. World Health Organization.

Bayan, L., Koulivand, P.H., Gorji, A., 2014. Garlic: a review of potential therapeutic effects. Avicenna journal of phytomedicine 4 (1), 1.

Bokhari, J., Khan, M.R., 2015. Evaluation of anti-asthmatic and antioxidant potential of Boerhavia procumbens in toluene diisocyanate (TDI) treated rats. J. Ethnopharmacol. 172, 377–385. https://doi.org/10.1016/j.jep.2015.06.049.

Bonham, M., Posakony, J., Coleman, I., Montgomery, B., Simon, J., Nelson, P.S., 2005. Characterization of chemical constituents in Scutellaria baicalensis with antiandrogenic and growth-inhibitory activities toward prostate carcinoma. Clin. Canc. Res. 11 (10), 3905–3914.

Brown, R.P., Gerbarg, P.L., Ramazanov, Z., 2002. Rhodiola rosea. A phytomedicinal overview. HerbalGram 56, 40–52.

Calapai, G., 2008. European legislation on herbal medicines: a look into the future. Drug Saf. 31 (5), 428–431. https://doi.org/10.2165/00002018-200831050-00009.

Calixto, J.B., 2000. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 33 (2), 179–189. https://doi.org/10.1590/s0100-879x2000000200004.

Chang, J.-S., Liu, H.-W., Wang, K.-C., Chen, M.-C., Chiang, L.-C., Hua, Y.-C., Lin, C.-C., 2005. Ethanol extract of Polygonum cuspidatum inhibits hepatitis B virus in a stable HBV-producing cell line. Antivir. Res. 66 (1), 29–34.

Channa, S., Dar, A., Ahmed, S., Atta ur, R., 2005. Evaluation of Alstonia scholaris leaves for broncho-vasodilatory activity. J. Ethnopharmacol. 97 (3), 469–476. https://doi.org/10.1016/j.jep.2004.12.009.

Chathuranga, K., Kim, M.S., Lee, H.-C., Kim, T.-H., Kim, J.-H., Gayan Chathuranga, W.A., Ekanayaka, P., Wijerathne, H., Cho, W.-K., Kim, H.I., 2019. Anti-respiratory syncytial virus activity of Plantago asiatica and Clerodendrum trichotomum extracts in vitro and in vivo. Viruses 11 (7), 604.

Chavan, R., Chowdhary, A., 2014. In vitro inhibitory activity of Justicia adhatoda extracts against influenza virus infection and hemagglutination. Int. J. Pharmaceut. Sci. Rev. Res. 25 (2), 231–236.

Chen, C.-J., Michaelis, M., Hsu, H.-K., Tsai, C.-C., Yang, K.D., Wu, Y.-C., Cinatl Jr., J., Doerr, H.W., 2008. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. J. Ethnopharmacol. 120 (1), 108–111.

Chen, F., Chan, K.H., Jiang, Y., Kao, R.Y.T., Lu, H.T., Fan, K.W., Cheng, V.C.C., Tsui, W.H.W., Hung, I.F.N., Lee, T.S.W., 2004. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J. Clin. Virol. 31 (1), 69–75.

Cheng, P.W., Ng, L.T., Chiang, L.C., Lin, C.C., 2006. Antiviral effects of saikosaponins on human coronavirus 229E in vitro. Clin. Exp. Pharmacol. Physiol. 33 (7), 612–616.

Chiang, L.C., Ng, L.T., Cheng, P.W., Chiang, W., Lin, C.C., 2005. Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. Clin. Exp. Pharmacol. Physiol. 32 (10), 811–816. https://doi.org/10.1111/j.1440-1681.2005.04270.x.

Choi, J.-G., Kim, Y.S., Kim, J.H., Chung, H.-S., 2019. Antiviral activity of ethanol extract of Geranii Herba and its components against influenza viruses via neuraminidase inhibition. Sci. Rep. 9 (1), 12132. https://doi.org/10.1038/s41598-019-48430-8.

Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., Doerr, H., 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361 (9374), 2045–2046.

Cohen, R.A., Kucera, L.S., Herrmann Jr., E.C., 1964. Antiviral activity of melissa officinalis (lemon balm) extract. PSEBM (Proc. Soc. Exp. Biol. Med.) 117 (2), 431–434.

Cyprus_Mail, 2020. Herbal medicines and coronavirus strains: what does previous experience teach us? Cyprus Mail 2 (3), 26–28.

Damle, M., 2014. Glycyrrhiza glabra (Liquorice)-a potent medicinal herb. International Journal of Herbal Medicine 2 (2), 132–136.

De Clercq, E., 2006. Potential antivirals and antiviral strategies against SARS coronavirus infections. Expert Rev. Anti-infect. Ther. 4 (2), 291–302. https://doi.org/10.1586/14787210.4.2.291.

De Ruiz, R., Fusco, M., Sosa, A., Ruiz, S., 1994. Constituents of coronopus didymus. FITOTERAPIA-MILANO 65, 181-181.

Denaro, M., Smeriglio, A., Barreca, D., De Francesco, C., Occhiuto, C., Milano, G., Trombetta, D., 2020. Antiviral activity of plants and their isolated bioactive compounds: an update. Phytother Res. 34 (4), 742–768. https://doi.org/10.1002/ptr.6575.

Devaux, C.A., Rolain, J.-M., Colson, P., Raoult, D., 2020. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int. J. Antimicrob. Agents 105938. https://doi.org/10.1016/j.ijantimicag.2020.105938.

Du, J., He, Z.-D., Jiang, R.-W., Ye, W.-C., Xu, H.-X., But, P.P.-H., 2003. Antiviral flavonoids from the root bark of Morus alba L. Phytochemistry 62 (8), 1235–1238.

Efferth, T., Romero, M.R., Wolf, D.G., Stamminger, T., Marin, J.J., Marschall, M., 2008. The antiviral activities of artemisinin and artesunate. Clin. Infect. Dis. : an official publication of the Infectious Diseases Society of America 47 (6), 804–811. https://doi.org/10.1086/591195.

El-Saied, M.A., Sobeh, M., Abdo, W., Badr, O.M., Youssif, L.T., Elsayed, I.H., Osman, S. M., Wink, M., 2018. Rheum palmatum root extract inhibits hepatocellular carcinoma in rats treated with diethylnitrosamine. J. Pharm. Pharmacol. 70 (6), 821–829.

EMA, 2001. In: Human Regulatory; Herbal Medicinal Products. https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products. (Accessed 14 April 2020).

Emmanuel, R., Saravanan, M., Ovais, M., Padmavathy, S., Shinwari, Z.K., Prakash, P., 2017. Antimicrobial efficacy of drug blended biosynthesized colloidal gold nanoparticles from Justicia glauca against oral pathogens: a nanoantibiotic approach. Microb. Pathog. 113, 295–302.

Fan, J.-S., Lee, I.J., Lin, Y.-L., 2015. Flavone glycosides from commercially available Lophatheri Herba and their chromatographic fingerprinting and quantitation. J. Food Drug Anal. 23 (4), 821–827. https://doi.org/10.1016/j.jfda.2015.05.003.

FDA, 2006. Complementary and alternative medicine products and their regulation by the food and drug administration draft guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/complementary-and-alternative-medicine-products-and-their-regulation-food-and-drug-administration#i. (Accessed 14 April 2020).

Ferenci, P., Scherzer, T.M., Kerschner, H., Rutter, K., Beinhardt, S., Hofer, H., Schöniger–Hekele, M., Holzmann, H., Steindl–Munda, P., 2008. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. Gastroenterology 135 (5), 1561–1567. https://doi.org/10.1053/j.gastro.2008.07.072.

Ferner, R.E., Aronson, J.K., 2020. Chloroquine and hydroxychloroquine in covid-19. BMJ 369, m1432. https://doi.org/10.1136/bmj.m1432.

Fiore, C., Eisenhut, M., Krausse, R., Ragazzi, E., Pellati, D., Armanini, D., Bielenberg, J., 2008. Antiviral effects of Glycyrrhiza species. Phytother Res. : PT 22 (2), 141–148. https://doi.org/10.1002/ptr.2295.

Fung, K., Leung, P., Tsui, K., Wan, C., Wong, K., Waye, M., Au, W., Wong, C., Lam, W., Lau, B., 2011. Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study. Hong Kong medical journal= Xianggang yi xue za zhi 17, 41.

Gao, H.-X., Ding, A.-W., Tang, Y.-P., Zhang, X., Duan, J.-A., 2009. Chemical constituents from the rhizomas of Phragmites communis. 中國天然藥物 7 (3), 196–198.

Gao, Z-p, Li, S-w, Lu, Y-r, Lei, H-m, 2003. Studies on the chemical constituents of Dryopteris crassirhizoma. CHINESE PHARMACEUTICAL JOURNAL-BEIJING- 38 (4), 260–262.

Gautret, P., Lagier, J.-C., Parola, P., Hoang, V.T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V.E., Dupont, H.T., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J.-M., Brouqui, P., Raoult, D., 2020. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.

Geuenich, S., Goffinet, C., Venzke, S., Nolkemper, S., Baumann, I., Plinkert, P., Reichling, J., Keppler, O.T., 2008. Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density. Retrovirology 5 (1), 27.

Gilani, A.H., Jabeen, Q., Ghayur, M.N., Janbaz, K.H., Akhtar, M.S., 2005. Studies on the antihypertensive, antispasmodic, bronchodilator and hepatoprotective activities of the Carum copticum seed extract. J. Ethnopharmacol. 98 (1), 127–135. https://doi.org/10.1016/j.jep.2005.01.017.

Gilani, A.H., Khan, A-u, Raoof, M., Ghayur, M.N., Siddiqui, B.S., Vohra, W., Begum, S., 2008. Gastrointestinal, selective airways and urinary bladder relaxant effects of Hyoscyamus Niger are mediated through dual blockade of muscarinic receptors and Ca2+ channels. Fund. Clin. Pharmacol. 22 (1), 87–99. https://doi.org/10.1111/j.1472-8206.2007.00561.x.

Gilling, D.H., Kitajima, M., Torrey, J., Bright, K.R., 2014. Antiviral efficacy and mechanisms of action of oregano essential oil and its primary component carvacrol against murine norovirus. J. Appl. Microbiol. 116 (5), 1149–1163.

Gu, P., Chen, H., 2014. Modern bioinformatics meets traditional Chinese medicine. Briefings Bioinf. 15 (6), 984–1003.

Guan, L., Quan, L.H., Xu, L.Z., Cong, P.Z., 1994. [Chemical constituents of Pogostemon cablin (Blanco) Benth]. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica, 19 (6), 355–356, 383.

Harrison, C., 2020. Coronavirus puts drug repurposing on the fast track. Nat. Biotechnol. 38 (4), 379–381. https://doi.org/10.1038/d41587-020-00003-1.

He, X.-F., Geng, C.-A., Huang, X.-Y., Ma, Y.-B., Zhang, X.-M., Chen, J.-J., 2019. Chemical constituents from mentha haplocalyx briq.(mentha canadensis L.) and their α-glucosidase inhibitory activities. Natural products and bioprospecting 9 (3), 223–229.

He, Z.-Q., Findlay, J.A., 1991. Constituents of Astragalus membranaceus. J. Nat. Prod. 54 (3), 810–815. https://doi.org/10.1021/np50075a009.

Ho, T.Y., Wu, S.L., Chen, J.C., Li, C.C., Hsiang, C.Y., 2007. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antivir. Res. 74 (2), 92–101. https://doi.org/10.1016/j.antiviral.2006.04.014.

Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., Cinatl, J., 2005. Antiviral activity of glycyrrhizic acid derivatives against SARS−Coronavirus. J. Med. Chem. 48 (4), 1256–1259. https://doi.org/10.1021/jm0493008.

Hudson, J., Vimalanathan, S., 2011. Echinacea—a source of potent antivirals for respiratory virus infections. Pharmaceuticals 4 (7), 1019–1031.

Hussain, W., Haleem, K.S., Khan, I., Tauseef, I., Qayyum, S., Ahmed, B., Riaz, M.N., 2017. Medicinal plants: a repository of antiviral metabolites. Future Virol. 12 (6), 299–308. https://doi.org/10.2217/fvl-2016-0110.

Ji, S., Li, Z., Song, W., Wang, Y., Liang, W., Li, K., Tang, S., Wang, Q., Qiao, X., Zhou, D., Yu, S., Ye, M., 2016. Bioactive constituents of Glycyrrhiza uralensis (licorice): discovery of the effective components of a traditional herbal medicine. J. Nat. Prod. 79 (2), 281–292. https://doi.org/10.1021/acs.jnatprod.5b00877.

Jo, S., Kim, H., Kim, S., Shin, D.H., Kim, M.S., 2019. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chem. Biol. Drug Des. 94 (6), 2023–2030.

Kang, E.H., Kown, T.Y., Oh, G.T., Park, W.F., Park, S.I., Park, S.K., Lee, Y.I., 2006. The flavonoid ellagic acid from a medicinal herb inhibits host immune tolerance induced by the hepatitis B virus-e antigen. Antivir. Res. 72 (2), 100–106. https://doi.org/10.1016/j.antiviral.2006.04.006.

Kapoor, M., Jasani, N., Acharya, N., Acharya, S., Kumar, V., 2011. Phytopharmacological evaluation and anti–asthmatic activity of Ficus religiosa leaves. Asian Pacific Journal of Tropical Medicine 4 (8), 642–644. https://doi.org/10.1016/S1995-7645(11)60163-6.

Kasithevar, M., Saravanan, M., Prakash, P., Kumar, H., Ovais, M., Barabadi, H., Shinwari, Z.K., 2017. Green synthesis of silver nanoparticles using Alysicarpus monilifer leaf extract and its antibacterial activity against MRSA and CoNS isolates in HIV patients. Journal of Interdisciplinary Nanomedicine 2 (2), 131–141.

Kazmi, A., Khan, M.A., Ali, H., 2019. Biotechnological approaches for production of bioactive secondary metabolites in Nigella sativa: an up-to-date review. International Journal of Secondary Metabolite 6 (2), 172–195.

Kesharwani, A., Polachira, S.K., Nair, R., Agarwal, A., Mishra, N.N., Gupta, S.K., 2017. Anti-HSV-2 activity of Terminalia chebula Retz extract and its constituents, chebulagic and chebulinic acids. BMC Compl. Alternative Med. 17 (1), 110. https://doi.org/10.1186/s12906-017-1620-8.

Keyaerts, E., Vijgen, L., Maes, P., Neyts, J., Ranst, M.V., 2004. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem. Biophys. Res. Commun. 323 (1), 264–268. https://doi.org/10.1016/j.bbrc.2004.08.085.

Khan, A-u, Gilani, A.H., 2009. Antispasmodic and bronchodilator activities of Artemisia vulgaris are mediated through dual blockade of muscarinic receptors and calcium influx. J. Ethnopharmacol. 126 (3), 480–486. https://doi.org/10.1016/j.jep.2009.09.010.

Keyaerts, E., Vijgen, L., Pannecouque, C., Damme, E.V., Peumans, W., Egberink, H., Balzarini, J., Ranst, M.V., 2007. Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Res 753, 179–187. https://doi.org/10.1016/j.antiviral.2007.03.003.

Khan, M.A., Abbasi, B.H., Shinwari, Z.K., 2014. Thidiazuron enhanced regeneration and silymarin content in Silybum marianum L. Pakistan J. Bot. 46 (1), 185–190.

Kim, M.K., Yu, M.-S., Park, H.R., Kim, K.B., Lee, C., Cho, S.Y., Kang, J., Yoon, H., Kim, D.-E., Choo, H., Jeong, Y.-J., Chong, Y., 2011. 2,6-Bis-arylmethyloxy-5-hydroxychromones with antiviral activity against both hepatitis C virus (HCV) and SARS-associated coronavirus (SCV). Eur. J. Med. Chem. 46 (11), 5698–5704. https://doi.org/10.1016/j.ejmech.2011.09.005.

Kreiner, J., Pang, E., Lenon, G.B., Yang, A.W.H., 2017. Saposhnikoviae divaricata: a phytochemical, pharmacological, and pharmacokinetic review. Chin. J. Nat. Med. 15 (4), 255–264. https://doi.org/10.1016/S1875-5364(17)30042-0.

Kuo, Y.-C., Kuo, Y.-H., Lin, Y.-L., Tsai, W.-J., 2006. Yatein from Chamaecyparis obtusa suppresses herpes simplex virus type 1 replication in HeLa cells by interruption the immediate-early gene expression. Antivir. Res. 70 (3), 112–120. https://doi.org/10.1016/j.antiviral.2006.01.011.

Kuroyanagi, M., Murata, M., Nakane, T., Shirota, O., Sekita, S., Fuchino, H., Shinwari, Z. K., 2012. Leishmanicidal active withanolides from a Pakistani medicinal plant, Withania coagulans. Chem. Pharm. Bull. 60 (7), 892–897.

Langland, J., Jacobs, B., Wagner, C.E., Ruiz, G., Cahill, T.M., 2018. Antiviral activity of metal chelates of caffeic acid and similar compounds towards herpes simplex, VSV-Ebola pseudotyped and vaccinia viruses. Antivir. Res. 160, 143–150. https://doi.org/10.1016/j.antiviral.2018.10.021.

Lau, K.-M., Lee, K.-M., Koon, C.-M., Cheung, C.S.-F., Lau, C.-P., Ho, H.-M., Lee, M.Y.-H., Au, S.W.-N., Cheng, C.H.-K., Lau, C.B.-S., Tsui, S.K.-W., Wan, D.C.-C., Waye, M.M.-Y., Wong, K.-B., Wong, C.-K., Lam, C.W.-K., Leung, P.-C., Fung, K.-P., 2008. Immunomodulatory and anti-SARS activities of Houttuynia cordata. J. Ethnopharmacol. 118 (1), 79–85. https://doi.org/10.1016/j.jep.2008.03.018.

Lee, S., Lee, J.C., Subedi, L., Cho, K.H., Kim, S.Y., Park, H.-J., Kim, K.H., 2019. Bioactive compounds from the seeds of Amomum tsaoko Crevost et Lemaire, a Chinese spice as inhibitors of sphingosine kinases, SPHK1/2. RSC Adv. 9 (58), 33957–33968. https://doi.org/10.1039/C9RA07988B.

Li, H., Zhou, C.X., Pan, Y., Gao, X., Wu, X., Bai, H., Zhou, L., Chen, Z., Zhang, S., Shi, S., Luo, J., Xu, J., Chen, L., Zheng, X., Zhao, Y., 2005a. Evaluation of antiviral activity of compounds isolated from ranunculus sieboldii and ranunculus sceleratus. Planta Med. 71 (12), 1128–1133. https://doi.org/10.1055/s-2005-873169.

Li, S-y, Chen, C., Zhang, H-q, Guo, H-y, Wang, H., Wang, L., Zhang, X., Hua, S-n, Yu, J., Xiao, P-g, 2005b. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antivir. Res. 67 (1), 18–23.

Li, T., Peng, T., 2013. Traditional Chinese herbal medicine as a source of molecules with antiviral activity. Antivir. Res. 97 (1), 1–9. https://doi.org/10.1016/j.antiviral.2012.10.006.

Li, Y., Liu, Y., Ma, A., Bao, Y., Wang, M., Sun, Z., 2017. In vitro antiviral, anti-inflammatory, and antioxidant activities of the ethanol extract of Mentha piperita L. Food science and biotechnology 26 (6), 1675–1683.

Lin, C.-W., Tsai, F.-J., Tsai, C.-H., Lai, C.-C., Wan, L., Ho, T.-Y., Hsieh, C.-C., Chao, P.-D. L., 2005. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antivir. Res. 68 (1), 36–42.

Lin, L.-T., Hsu, W.-C., Lin, C.-C., 2014. Antiviral natural products and herbal medicines. Journal of traditional and complementary medicine 4 (1), 24–35.

Lipipun, V., Kurokawa, M., Suttisri, R., Taweechotipatr, P., Pramyothin, P., Hattori, M., Shiraki, K., 2003. Efficacy of Thai medicinal plant extracts against herpes simplex virus type 1 infection in vitro and in vivo. Antivir. Res. 60 (3), 175–180. https://doi.org/10.1016/S0166-3542(03)00152-9.

Liu, Y.M., Sheu, S.J., Chiou, S.H., Chang, H.C., Chen, Y.P., 1993. A comparative study of commercial samples of ephedrae herba. Planta Med. 59 (4), 376–378. https://doi.org/10.1055/s-2006-959706.

Maxmen, A., 2020. More than 80 clinical trials launch to test coronavirus treatments. Nature 578 (7795), 347–348. https://doi.org/10.1038/d41586-020-00444-3.

Mohamed, H.E.A., Afridi, S., Khalil, A.T., Ali, M., Zohra, T., Akhtar, R., Ikram, A., Shinwari, Z.K., Maaza, M., 2020a. Promising antiviral, antimicrobial and therapeutic properties of green nanoceria. Nanomedicine 15 (5), 467–488.

Mohamed, H.E.A., Afridi, S., Khalil, A.T., Ali, M., Zohra, T., Salman, M., Ikram, A., Shinwari, Z.K., Maaza, M., 2020b. Bio-redox potential of Hyphaene thebaica in bio-fabrication of ultrafine maghemite phase iron oxide nanoparticles (Fe2O3 NPs) for therapeutic applications. Mater. Sci. Eng. C 110890.

Mondal, S., Varma, S., Bamola, V.D., Naik, S.N., Mirdha, B.R., Padhi, M.M., Mehta, N., Mahapatra, S.C., 2011. Double-blinded randomized controlled trial for immunomodulatory effects of Tulsi (Ocimum sanctum Linn.) leaf extract on healthy volunteers. J. Ethnopharmacol. 136 (3), 452–456.

Mukhtar, M., Arshad, M., Ahmad, M., Pomerantz, R.J., Wigdahl, B., Parveen, Z., 2008. Antiviral potentials of medicinal plants. Virus Res. 131 (2), 111–120. https://doi.org/10.1016/j.virusres.2007.09.008.

Musarra-Pizzo, M., Ginestra, G., Smeriglio, A., Pennisi, R., Sciortino, M.T., Mandalari, G., 2019. The antimicrobial and antiviral activity of polyphenols from almond (prunus dulcis L.) skin. Nutrients 11 (10), 2355.

Naik, S.R., Bhagat, S., Shah, P.D., Tare, A.A., Ingawale, D., Wadekar, R.R., 2013. Evaluation of anti-allergic and anti-anaphylactic activity of ethanolic extract of Zizyphus jujuba fruits in rodents. Revista Brasileira de Farmacognosia 23, 811–818.
Nature, 2020. Redeploying plant defences. Nature Plants 6 (3). https://doi.org/10.1038/s41477-020-0628-0, 177-177.
Nguyen, T.T.H., Woo, H.-J., Kang, H.-K., Kim, Y.-M., Kim, D.-W., Ahn, S.-A., Xia, Y., Kim, D., 2012. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotechnol. Lett. 34 (5), 831–838.
Nolkemper, S., Reichling, J., Stintzing, F.C., Carle, R., Schnitzler, P., 2006. Antiviral effect of aqueous extracts from species of the Lamiaceae family against Herpes simplex virus type 1 and type 2 in vitro. Planta Med. 72 (15), 1378–1382.
Ogbole, O.O., Akinleye, T.E., Segun, P.A., Faleye, T.C., Adeniji, A.J., 2018. In vitro antiviral activity of twenty-seven medicinal plant extracts from Southwest Nigeria against three serotypes of echoviruses. Virol. J. 15 (1), 110. https://doi.org/10.1186/s12985-018-1022-7.
Park, J.-H., Seo, B-l, Cho, S.-Y., Park, K.-R., Choi, S.-H., Han, C.-K., Song, C.-H., Park, S.-J., Ku, S.-K., 2013. Single oral dose toxicity study of prebrewed armeniacae semen in rats. Toxicological research 29 (2), 91–98.
Pei, Y., Xiang, Y.-F., Chen, J.-N., Lu, C.-H., Hao, J., Du, Q., lai, C-c, Qu, C., Li, S., Ju, H.-Q., Ren, Z., Liu, Q.-Y., Xiong, S., Qian, C.-W., Zeng, F.-L., Zhang, P.-Z., Yang, C.-R., Zhang, Y.-J., Xu, J., Kitazato, K., Wang, Y.-F., 2011. Pentagalloylglucose downregulates cofilin 1 and inhibits HSV-1 infection. Antivir. Res. 89 (1), 98–108. https://doi.org/10.1016/j.antiviral.2010.11.012.
Peng, W., Liu, Y.-J., Zhao, C.-B., Huang, X.-S., Wu, N., Hu, M.-B., Xie, D.-S., Wu, C.-J., 2015. In silico assessment of drug-like properties of alkaloids from Areca catechu L nut. Trop. J. Pharmaceut. Res. 14 (4), 635–639.
Pilau, M.R., Alves, S.H., Weiblen, R., Arenhart, S., Cueto, A.P., Lovato, L.T., 2011. Antiviral activity of the Lippia graveolens (Mexican oregano) essential oil and its main compound carvacrol against human and animal viruses. Braz. J. Microbiol. 42 (4), 1616–1624.
Polyak, S.J., Oberlies, N.H., Pécheur, E.-I., Dahari, H., Ferenci, P., Pawlotsky, J.-M., 2013. Silymarin for hepatitis C virus infection. Antivir. Ther. 18 (2), 141.
Pompei, R., Laconi, S., Ingianni, A., 2009. Antiviral properties of glycyrrhizic acid and its semisynthetic derivatives. Mini Rev. Med. Chem. 9 (8), 996–1001. https://doi.org/10.2174/138955709788681636.
Porter, R.S., Bode, R.F., 2017. A review of the antiviral properties of black elder (Sambucus nigra L.) products. Phytother Res. 31 (4), 533–554.
Pourghanbari, G., Nili, H., Moattari, A., Mohammadi, A., Iraji, A., 2016. Antiviral activity of the oseltamivir and Melissa officinalis L. essential oil against avian influenza A virus (H9N2). VirusDisease 27 (2), 170–178.
Rajasekaran, D., Palombo, E.A., Yeo, T.C., Ley, D.L.S., Tu, C.L., Malherbe, F., Grollo, L., 2013. Identification of traditional medicinal plant extracts with novel anti-influenza activity. PloS One 8 (11).
Rehman, N.U., Begum, N., Ali, L., Al-Harrasi, A., Abbas, G., Ahmad, S., Khan, A.L., Shinwari, Z.K., Hussain, J., 2015. Lipid peroxidation, antiglycation, cytotoxic, phytotoxic, antioxidant, antiplatelet and antimicrobial activities of ajuga bracteosa against various pathogens. Pakistan J. Bot. 47, 1195–1197.
Ryu, Y.B., Jeong, H.J., Kim, J.H., Kim, Y.M., Park, J.-Y., Kim, D., Naguyen, T.T.H., Park, S.-J., Chang, J.S., Park, K.H., Rho, M.-C., Lee, W.S., 2010. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. Bioorg. Med. Chem. 18 (22), 7940–7947. https://doi.org/10.1016/j.bmc.2010.09.035.
Saleem, H., Sarfraz, M., Ahsan, H.M., Khurshid, U., Kazmi, S.A.J., Zengin, G., Locatelli, M., Ahmad, I., Abdallah, H.H., Mahomoodally, M.F., 2020. Secondary metabolites profiling, biological activities and computational studies of abutilon figarianum webb (malvaceae). Processes 8 (3), 336.
Salehi, B., Kumar, N.V.A., Sener, B., Sharifi-Rad, M., Kilic, M., Mahady, G.B., Vlaisavljevic, S., Iriti, M., Kobarfard, F., Setzer, W.N., Ayatollahi, S.A., Ata, A., Sharifi-Rad, J., 2018. Medicinal plants used in the treatment of human immunodeficiency virus. Int. J. Mol. Sci. 19 (5) https://doi.org/10.3390/ijms19051459.
Salem, M.L., Hossain, M.S., 2000. Protective effect of black seed oil from Nigella sativa against murine cytomegalovirus infection. Int. J. Immunopharm. 22 (9), 729–740.
Schnitzler, P., Schuhmacher, A., Astani, A., Reichling, J., 2008. Melissa officinalis oil affects infectivity of enveloped herpesviruses. Phytomedicine 15 (9), 734–740.
Schwarz, S., Sauter, D., Wang, K., Zhang, R., Sun, B., Karioti, A., Bilia, A.R., Efferth, T., Schwarz, W., 2014. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta Med. 80, 177–182, 02/03.
Schwarz, S., Wang, K., Yu, W., Sun, B., Schwarz, W., 2011. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antivir. Res. 90 (1), 64–69. https://doi.org/10.1016/j.antiviral.2011.02.008.
Serkedjieva, J., Manolova, N., Zgórniak-Nowosielska, I., Zawilińska, B., Grzybek, J., 1990. Antiviral activity of the infusion (SHS-174) from flowers of Sambucus nigra L., aerial parts of Hypericum perforatum L., and roots of Saponaria officinalis L. against influenza and herpes simplex viruses. Phytother Res. 4 (3), 97–100.
Shah, A.J., Gilani, A.-H., Abbas, K., Rasheed, M., Ahmed, A., Ahmad, V.U., 2011. Studies on the chemical composition and possible mechanisms underlying the antispasmodic and bronchodilatory activities of the essential oil of Artemisia maritima L. Arch Pharm. Res. (Seoul) 34 (8), 1227. https://doi.org/10.1007/s12272-011-0801-0.
Sharifi-Rad, J., Salehi, B., Schnitzler, P., Ayatollahi, S., Kobarfard, F., Fathi, M., Eisazadeh, M., Sharifi-Rad, M., 2017. Susceptibility ofherpes simplex virus type 1 to monoterpenes thymol, carvacrol, p-cymene and essential oilsofSinapis arvensisL., Lallemantia royleanaBenth. and Pulicaria vulgaris Gaertn. Cell. Mol. Biol. 63 (8).
Shin, H.-B., Choi, M.-S., Ryu, B., Lee, N.-R., Kim, H.-I., Choi, H.-E., Chang, J., Lee, K.-T., Jang, D.S., Inn, K.-S., 2013. Antiviral activity of carnosic acid against respiratory syncytial virus. Virol. J. 10 (1), 303. https://doi.org/10.1186/1743-422X-10-303.
Song, X.W., Li, G.Y., Wang, D.Q., Han, B.X., 2016. Evolution of the Origin of Herba Schizonepetae. Zhonghua yi shi za zhi, Beijing, China, pp. 140–143. https://doi.org/10.3760/cma.j.issn.0255-7053.2016.03.002, 1980) vol. 46(3).
Sornpet, B., Potha, T., Tragoolpua, Y., Pringproa, K., 2017. Antiviral activity of five Asian medicinal pant crude extracts against highly pathogenic H5N1 avian influenza virus. Asian Pacific Journal of Tropical Medicine 10 (9), 871–876. https://doi.org/10.1016/j.apjtm.2017.08.010.
Speranza, J., Miceli, N., Taviano, M.F., Ragusa, S., Kwiecień, I., Szopa, A., Ekiert, H., 2020. Isatis tinctoria l.(woad): a review of its botany, ethnobotanical uses, phytochemistry, biological activities, and biotechnological studies. Plants 9 (3), 298.
Tanemoto, R., Okuyama, T., Matsuo, H., Okumura, T., Ikeya, Y., Nishizawa, M., 2015. The constituents of licorice (Glycyrrhiza uralensis) differentially suppress nitric oxide production in interleukin-1β-treated hepatocytes. Biochemistry and biophysics reports 2, 153–159.
Tang, W., Eisenbrand, G., 1992. Anemarrhena Asphodeloides Bge Chinese Drugs of Plant Origin. Springer, pp. 105–108.
Tang, Y.-R., Zeng, T., zafar, S., Yuan, H.-W., Li, B., Peng, C.-Y., Wang, S.-C., Jian, Y.-Q., Qin, Y., Choudhary, M.I., Wang, W., 2018. Lonicerae flos: a review of chemical constituents and biological activities. Digital Chinese Medicine 1 (2), 173–188. https://doi.org/10.1016/S2589-3777(19)30022-9.
Tian, L., Wang, Z., Wu, H., Wang, S., Wang, Y., Wang, Y., Xu, J., Wang, L., Qi, F., Fang, M., Yu, D., Fang, X., 2011. Evaluation of the anti-neuraminidase activity of the traditional Chinese medicines and determination of the anti-influenza A virus effects of the neuraminidase inhibitory TCMs in vitro and in vivo. J. Ethnopharmacol. 137 (1), 534–542. https://doi.org/10.1016/j.jep.2011.06.002.
Trombetta, D., Occhiuto, F., Perri, D., Puglia, C., Santagati, N.A., Pasquale, A.D., Saija, A., Bonina, F., 2005. Antiallergic and antihistaminic effect of two extracts of Capparis spinosa L. flowering buds. Phytother Res. 19 (1), 29–33. https://doi.org/10.1002/ptr.1591.
ul Qamar, M.T., Alqahtani, S.M., Alamri, M.A., Chen, L.-L., 2020. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Journal of pharmaceutical analysis.
Ullah, I., Shinwari, Z.K., Khalil, A.T., 2017a. Investigation of the cytotoxic and antileishmanial effects of Fagonia indica L. extract and extract mediated silver nanoparticles (AgNPs). Pakistan J. Bot. 49 (4), 1561–1568.
Ullah, I., Wakeel, A., Shinwari, Z.K., Jan, S.A., Khalil, A.T., Ali, M., 2017b. Antibacterial and antifungal activity of isatis tinctoria l.(brassicaceae) using the micro-plate method. Pakistan J. Bot. 49 (5), 1949–1957.
van Beek, T.A., Joulain, D., 2018. The essential oil of patchouli, Pogostemon cablin: a review. Flavour Fragrance J. 33 (1), 6–51.
Wagner, H., Bauer, R., Melchart, D., Staudinger, A., 2016. Fructus Arctii–Niubangzi Chromatographic Fingerprint Analysis of Herbal Medicines Volume IV. Springer, pp. 19–26.
Wagner, H., Bauer, R., Melchart, D., Xiao, P.-G., Staudinger, A., 2015a. Radix et Rhizoma Glycyrrhizae–Gancao Chromatographic Fingerprint Analysis of Herbal Medicines Volume III. Springer, pp. 43–53.
Wagner, H., Bauer, R., Melchart, D., Xiao, P.-G., Staudinger, A., 2015b. Radix Platycodonis–Jiegeng Chromatographic Fingerprint Analysis of Herbal Medicines Volume III. Springer, pp. 255–265.
Wahedi, H.M., Ahmad, S., Abbasi, S.W., 2020. Stilbene-based natural compounds as promising drug candidates against COVID-19. J. Biomol. Struct. Dyn. 1–10.
Wang, F., Jiang, Y.P., Wang, X.L., Lin, S., Pu, P.B., Zhu, C.G., Wang, S.J., Yang, Y.C., Shi, J.G., 2013. Chemical constituents from flower buds of Lonicera japonica. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica 38 (9), 1378–1385.
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., Xiao, G., 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 30 (3), 269–271. https://doi.org/10.1038/s41422-020-0282-0.
Wen, C.-C., Kuo, Y.-H., Jan, J.-T., Liang, P.-H., Wang, S.-Y., Liu, H.-G., Lee, C.-K., Chang, S.-T., Kuo, C.-J., Lee, S.-S., Hou, C.-C., Hsiao, P.-W., Chien, S.-C., Shyur, L.-F., Yang, N.-S., 2007. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J. Med. Chem. 50 (17), 4087–4095. https://doi.org/10.1021/jm070295s.
Whitehead, A., Simpson, C., Willcox, M., Webley, F., Hay, A.D., Butler, C., Yao, L., Wrixon, E., Bell, M., Bostock, J., Little, P., Griffiths, G., Moore, M., 2019. HATRIC: a study of Pelargonium sidoides root extract EPs®7630 (Kaloba®) for the treatment of acute cough due to lower respiratory tract infection in adults—study protocol for a double blind, placebo-controlled randomised feasibility trial. Pilot and Feasibility Studies 5 (1), 98. https://doi.org/10.1186/s40814-019-0478-6.
Worldometer, 2020. Coronavirus. https://www.worldometers.info/coronavirus/. (Accessed 16 July 2020).
Wu, C.-Y., Jan, J.-T., Ma, S.-H., Kuo, C.-J., Juan, H.-F., Cheng, Y.-S.E., Hsu, H.-H., Huang, H.-C., Wu, D., Brik, A., Liang, F.-S., Liu, R.-S., Fang, J.-M., Chen, S.-T., Liang, P.-H., Wong, C.-H., 2004. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc. Natl. Acad. Sci. U.S.A. 101 (27), 10012. https://doi.org/10.1073/pnas.0403596101.
Wu, Y.-N., Wang, W., Yao, G.-D., Jiang, X.-F., Zhang, Y., Song, S.-J., 2018. Antioxidant phenolic acids from the leaves of Armeniaca sibirica. J. Asian Nat. Prod. Res. 20 (10), 969–976. https://doi.org/10.1080/10286020.2017.1373101.
Xu, S., Xu, X., Yuan, S., Liu, H., Liu, M., Zhang, Y., Zhang, H., Gao, Y., Lin, R., Li, X., 2017. Identification and analysis of amygdalin, neoamygdalin and amygdalin amide in different processed bitter almonds by HPLC-ESI-MS/MS and HPLC-DAD. Molecules 22 (9), 1425.
Yamada, P., Iijima, R., Han, J., Shigemori, H., Yokota, S., Isoda, H., 2010. Inhibitory effect of acteoside isolated from Cistanche tubulosa on chemical mediator release

and inflammatory cytokine production by RBL-2H3 and KU812 cells. Planta Med. 76 (14), 1512–1518. https://doi.org/10.1055/s-0030-1249775.

Yang, H.J., Park, S., Pak, V., Chung, K.R., Kwon, D.Y., 2011. Fermented Soybean Products and Their Bioactive Compounds. Soybean and health, 978-953.

Yarmolinsky, L., Huleihel, M., Zaccai, M., Ben-Shabat, S., 2012. Potent antiviral flavone glycosides from Ficus benjamina leaves. Fitoterapia 83 (2), 362–367. https://doi.org/10.1016/j.fitote.2011.11.014.

Yarnell, E., 2017. Herbs for viral respiratory infections. Alternative Compl. Ther. 24 (1), 35–43. https://doi.org/10.1089/act.2017.29150.eya.

Yeh, C.F., Wang, K.C., Chiang, L.C., Shieh, D.E., Yen, M.H., San Chang, J., 2013. Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. J. Ethnopharmacol. 148 (2), 466–473.

Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., Zhang, H., Luo, H., Zhu, L., Jiang, P., Chen, L., Shen, Y., Luo, M., Zuo, G., Hu, J., Duan, D., Nie, Y., Shi, X., Wang, W., Han, Y., Li, T., Liu, Y., Ding, M., Deng, H., Xu, X., 2004. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 78 (20), 11334. https://doi.org/10.1128/JVI.78.20.11334-11339.2004.

Yoo, D.-G., Kim, M.-C., Park, M.-K., Song, J.-M., Quan, F.-S., Park, K.-M., Cho, Y.-K., Kang, S.-M., 2012. Protective effect of Korean red ginseng extract on the infections by H1N1 and H3N2 influenza viruses in mice. J. Med. Food 15 (10), 855–862.

Youssouf, M.S., Kaiser, P., Tahir, M., Singh, G.D., Singh, S., Sharma, V.K., Satti, N.K., Haque, S.E., Johri, R.K., 2007. Anti-anaphylactic effect of Euphorbia hirta. Fitoterapia 78 (7), 535–539. https://doi.org/10.1016/j.fitote.2007.06.003.

Yu, J.Q., Wang, Z.P., Zhu, H., Li, G., Wang, X., 2016. Chemical constituents of Lonicera japonica roots and their anti-inflammatory effects. Yao xue xue bao = Acta pharmaceutica Sinica 51 (7), 1110–1116.

Yu, M.-S., Lee, J., Lee, J.M., Kim, Y., Chin, Y.-W., Jee, J.-G., Keum, Y.-S., Jeong, Y.-J., 2012. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg. Med. Chem. Lett 22 (12), 4049–4054. https://doi.org/10.1016/j.bmcl.2012.04.081.

Zhang, W.-M., Huang, W.-Y., Chen, W.-X., Han, L., Zhang, H.-D., 2014a. Optimization of extraction conditions of areca seed polyphenols and evaluation of their antioxidant activities. Molecules 19 (10), 16416–16427.

Zhang, Z., Xiang, L., Bai, D., Fu, X., Wang, W., Li, Y., Liu, H., Pan, J., Li, Yn, Xiao, G.G., 2014b. Treatment with Rhizoma Dioscoreae extract has protective effect on osteopenia in ovariectomized rats. Sci. World J. 2014.

Zhao, W., Deng, A.J., Du, G.H., Zhang, J.L., Li, Z.H., Qin, H.L., 2009. Chemical constituents of the stems of Ephedra sinica. J. Asian Nat. Prod. Res. 11 (2), 168–171. https://doi.org/10.1080/10286020802573552.

Zhou, W., Yin, A., Shan, J., Wang, S., Cai, B., Di, L., 2017. Study on the rationality for antiviral activity of Flos Lonicerae Japonicae-Fructus Forsythiae herb couple preparations improved by chito-oligosaccharide via integral pharmacokinetics. Molecules 22 (4), 654.

Zou, H., He, T., Chen, X., 2019. Tetrandrine inhibits differentiation of proinflammatory subsets of T helper cells but spares de novo differentiation of iTreg cells. Int. Immunopharm. 69, 307–312.