

Available online on 15.11.2020 at <http://ujpr.org>**Universal Journal of Pharmaceutical Research***An International Peer Reviewed Journal*

Open access to Pharmaceutical research

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial Share Alike 4.0 License which permits unrestricted non commercial use, provided the original work is properly cited

**Volume 5, Issue 5, 2020**

Open Access

REVIEW ARTICLE

TRADITIONAL TO RECENT APPROACHES IN HERBAL MEDICINE THERAPY OF COVID-19

Mohamed S. Refaey¹, Marwa A.A. Fayed*²

Department of Pharmacognosy, Faculty of Pharmacy, University of Sadat City, Menoufia 32897, Egypt.

ABSTRACT

Coronavirus pneumonia disease (COVID-19) is a newly identified coronavirus strain that causes symptoms ranging from cold-like signs to deaths that reached millions around the world. Until this time, there is no approved vaccine has been invented for clinical use, therefore, developing an effective program for therapy is of high priority to save the lives of patients and protect others from being infected. Nature resembles a huge reservoir of anti-infectious compounds, from which innovative ideas, therapies, and products can be deduced. Chinese herbal medicine had succeeded in the treatment of other coronavirus pneumonia such as SARS, MERS and, H7N9 avian influenza which gives us hope to find the targeted remedy in the traditionally used natural herbs consumed by natives from different regions. This work aims to highlight the use of natural traditional remedies to treat viral pneumonia. This systematic review will include studies of the effects of traditional herbal medicine and its role in the treatment of COVID-19 pneumonia. Although promising results were obtained in many cases, but, only a few studies reported the fractional characterization of bioactive principles and/or mechanisms of action. It is requested that pharmaceutical industries, government agencies, and the scientific community will have a gaze at some of these plants for future research and, to find a potential drug candidates for the development of anti-SARSCoV-2 therapeutics in the near future.

Keywords: COVID-19, influenza, pneumonia, rhinovirus, SARS, traditional medicine.

Article Info: Received 6 September 2020; Revised 10 October; Accepted 25 October, Available online 15 November 2020

**Cite this article-**

Refaey MS, Fayed MAA. Traditional to recent approaches in herbal medicine therapy of COVID-19. Universal Journal of Pharmaceutical Research 2020; 5(5):71-84.

DOI: <https://doi.org/10.22270/ujpr.v5i5.491>

Address for Correspondence:

Dr. Marwa A.A. Fayed, Department of Pharmacognosy, Faculty of Pharmacy, University of Sadat City, Menoufia 32897, Egypt, E-mail: maafayed@gmail.com

INTRODUCTION

Viruses are considered as a reason for many ailments that affect humans worldwide. Most of these ailments are very complex and hard to cure, these viruses include (CV), enterovirus 71 (EV71), dengue virus (DENV), coxsackievirus, herpes simplex virus, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), influenza virus, respiratory syncytial virus (RSV) and measles virus (MV), in addition to coronavirus¹. Coronavirus (COVID-19), pandemic 2019, is considered a newly recognized type of coronavirus that causes severe illness varying from symptoms like flu and reaches to be fatal in a considerable percentage of people across the world^[1]. This represents a global challenge as cases are increasing rapidly especially critical cases with pneumonia. Recently, over 81,000 cases, with over 2700 deaths have been reported². The mortality rate is around 2%, most of whom need ICU admission while about 20.1 % have acute respiratory distress syndrome^[2]. Therefore, there is an urgent demand to find a quick

protocol and strategy for therapy for mild and severe cases. Herbal medicines and purified natural products provide a rich resource for novel remedies where some antiviral drugs have been developed and used in many herbal preparations for therapy. Traditional Chinese medicine has been widely used in China and has already played a major role in the SARS-CoV and SARS-CoV2 outbreaks³.

In addition, in terms of the composition of herbs for the treatment of paediatric COVID-19, certain herbal formulations adopt the Chinese guidelines⁴. However, compared to adults, the herbs commonly used in the proposed herbal formulations for the treatment of paediatric COVID-19 lack variety⁴. The herbs *Glycyrrhizae* root and rhizome were among the most commonly used herbs in the guidelines for adult treatment of COVID-19⁴. There is also an extensive dependence on traditional medicine in Africa⁵ and India⁵ and many of them were related to SARS-CoV therapy. The goal of this study was to systematically summarize and examine the herbs commonly used in

the treatment of coronavirus and some associated diseases in many regions of the globe to try to participate in finding a suitable therapy for this fatal virus.

In the current review paper, database searches using PubMed, Elsevier, Scopus, Google Scholar and Web of Science were performed until 10 June 2020 to provide up-to - date reported information.

Table 1: List of some Formulas used in Traditional Chinese Medicine for COVID-19.

Chinese Name	Plant Latin name	Part used
Gancao	<i>Glycyrrhiza uralensis</i> Fisch <i>Glycyrrhiza inflata</i> Batalin <i>Glycyrrhiza glabra</i> L.	Rhizome
Huangqin	<i>Scutellaria baicalensis</i> Georgi	Root
Dahuang	<i>Rheum palmatum</i> L. <i>Rheum tanguticum</i> Maxim. ex Balf. <i>Rheum officinale</i> Baill.	Rhizome
Baishao	<i>Paeonia lactiflora</i> Pall.	Root
Chenpi	<i>Citrus reticulata</i> Blanco	Fruit
Chaihu	<i>Bupleurum chinense</i> DC. <i>Bupleurum scorzonerifolium</i> Willd	Root
Jiegeng	<i>Platycodon grandiflorus</i> (Jacq.) A.DC	Root
Cangzhu	<i>Atractylodes lancea</i> (Thunb.) DC. <i>Atractylodes chinensis</i> (DC.) Koidz	Rhizome
Danggui	<i>Angelica sinensis</i> (Oliv.) Diels	Root
Shengdi	<i>Rehmannia glutinosa</i> (Gaertn.) DC	Root
Shigao	Gypsum	
Gegen	<i>Pueraria lobata</i> (Willd.) Ohwi	Root
Houpu	<i>Magnolia officinalis</i> Rehder & E. H. Wilson <i>Magnolia officinalis</i> var. <i>biloba</i> Rehder & E.H.Wilson	Bark
Chuanxiong	<i>Ligusticum chuanxiong</i> Hort.	Root
Fangfeng	<i>Saposhnikovia divaricata</i> (Turcz.) Schischk.	Root
Sbexiang	<i>Moschus berezovskii</i> Flerov. <i>Moschus sifanicus</i> Przewalski <i>Moschus moschiferus</i> Linnaeus	Musk bag
Huanglian	<i>Coptis chinensis</i> Franch. <i>Coptis deltoidea</i> C. Y. Cheng et Hsiao <i>Coptis teeta</i> Wall.	Rhizome
Qianghuo	<i>Notopterygium incisum</i> K. C. Ting ex H. T. Chang <i>Notopterygium franchetii</i> H. Boissieu	Rhizome
Xuanshen	<i>Scrophularia ningpoensis</i> Hemsl.	Root
Baizhi	<i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.	Root
Renshen	<i>Panax ginseng</i> C. A. Mey.	Root
Xionghuang	Realgar	
fuling	<i>Poria cocos</i> (Schw.)Wolf	Scleroaum
Zhiqiao	<i>Citrus aurantium</i> L.	Fruit
Maidong	<i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl.	Root
Jiangcan	<i>Beauveria assiana</i> (Bals.)Vuillant	Silkworm body
Lianqiao	<i>Forsythia suspensa</i> (Thunb.) Vahl	Fruit
Zhimu	<i>Anemarrhena asphodeloides</i> Bunge	Rhizome
Banxia	<i>Pinellia ternata</i> (Thunb.) Makino	Rhizome
Bohe	<i>Mentha haplocalyx</i> Briq.	Stem
Zhusha	Cinnabar	
Shengma	<i>Cimicifuga heracleifolia</i> Kom. <i>Cimicifuga dahurica</i> (Turcz.) Maxim. <i>Cimicifuga foetida</i> L.	Rhizome
Mahuang	<i>Ephedra sinica</i> Stapf <i>Ephedra intermedia</i> Schrenk & C.A.Mey. <i>Ephedra equisetina</i> Bunge	Stem
Zhizi	<i>Gardenia jasminoides</i> J. Ellis	Fruit
Chantui	<i>Cryptotympana pustulata</i> Fabricius	
Tianhuafen	<i>Trichosanthes kirilowii</i> Maxim. <i>Trichosanthes rosthornii</i> Harms	Root
Shengjiang	<i>Zingiber officinale</i> Roscoe	Rhizome
Xixin	<i>Asarum sieboldii</i> Miq. <i>Asarum heterotropoides</i> F. Schmidt	Rhizome
Huashi	Talcum	
Huoxiang	<i>Pogostemon amaranthoides</i> Benth.	Stem

Table 2: Chinese herbal medicines recommendation for pediatric COVID-19.

Stages	Name of herbal formula	Pattern Identification	Composition of herbal formula
Mild	Yin Qiao San	Seasonal epidemic invading the exterior-defense	# <i>Lonicerae Flos, Platycodonis Radix, Forsythiae fructus, Menthae Herba, Schizonepetae spica, Lophatheri Herba, Glycine Semen preparatum, Phragmitis Rhizoma, Arctii Semen</i>
	Xiang Su San		<i>Cyperus Rhizoma, Citrireticulatae Pericarpium, Perillae folium, Glycyrrhizae Radix et Rhizoma, Bupleuri Radix, Saposhnikoviae Radix, Cinnamomi ramulus, Osterici seu notopterygii Radix et Rhizoma</i>
Moderate	Ma Xing Shi Gan Tang + San Ren Tang	Dampness-heat blocking the lung	# <i>Ephedrae Herba, Glycyrrhizae Radix et Rhizoma, Armeniacae Semen amarum, Gypsum fibrosum, Amomi Fructus rotundus, Coicis Semen, Magnoliae Cortex, Pinelliae Rhizoma praeparatum, Talcum, Helwingiae Medulla, Stachyuri Medulla, Lophatheri Herba</i>
	Buhuan Jin Zhengqi San	Dampness-heat in the spleen and stomach	# <i>Citri Reticulatae Pericarpium, Magnoliae Cortex, Atractylodis Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Agastachis Herba, Amomi tsao-ko Fructus,</i>
Severe	Xuanbai Chengqi Tang + Ganlu Xiaodu Dan	Heat toxin blocking the lung	# <i>Gypsum fibrosum, Armeniacae Semen amarum, Rhei Radix et Rhizoma, Trichosanthis fructus, Scutellariae Radix, Talcum, Artemisiae scopariae Herba, Fritillariae cirrhosae Bulbus, Acori tatarinowii Rhizoma, Akebiae caulis, Forsythiae fructus, Agastachis Herba, Amomi fructus Rotundus, Belamcandae Rhizoma, Menthae Herba.</i>
	Not available	Intense heat toxin with blockage of bowel Qi and dysphagia	<i>Rhei Radix et Rhizoma (Enema using herbal decoction)</i>
Recovered	Liu Junzi Tang + Yu Ping Feng San	Unclear residual heat	# <i>Ginseng Radix, Atractylodis macrocephalae Rhizoma, Poria sclerotium, Citri reticulatae, Glycyrrhizae Radix et Rhizoma, Pericarpium, Saposhnikoviae Radix, Pinelliae Rhizoma, Astragali Radix</i>
	Ma Xing Shi Gan Tang*	Heat toxin fettering the lung	<i>Ephedrae Herba 4g, Anemarrhenae Rhizoma 9g, Gypsum fibrosum 20g, Armeniacae Semen amarum 10g, Phragmitis Rhizoma 10g, Coicis Semen 10g, Platycodonis Radix 6g, Lonicerae Flos 10g, Mori radices Cortex 10g.</i>
	Ma Xing Shi Gan Tang*	Epidemic toxin blocking the lung	<i>Ephedrae Herba 4g, Anemarrhenae Rhizoma 9g, Gypsum fibrosum 20g, Armeniacae Semen amarum 10g, Trichosanthis fructus 10g, Coicis Semen 10g, Rhei Radix et Rhizoma 5g, Lepidii seu descurainiae Semen 6g, Mori radices Cortex 10g, Bubali cornu 10g, Ginseng Radix 6g, Pheretima 10g.</i>
	Yin Qiao San	Wind-heat invading the lung	<i>Lonicerae Flos 15g, Schizonepetae spica 10g, Forsythiae fructus 15g, Menthae Herba 10g, Platycodonis Radix 10g, Arctii Semen 10g, Scutellariae Radix 10g, Angelicae decursivae Radix 15g, Trichosanthis pericarpium 15g, Belamcandae Rhizoma 10g, Artemisiae annuae Herba 21g, Eriobotryae folium 15g.</i>
	Ma Xing Shi Gan Tang	Wind-heat blocking the lung	<i>Ephedrae Herba 5g, Gypsum fibrosum 15g, Armeniacae Semen amarum 10g, Scutellariae Radix 10g, Angelicae decursivae Radix 15g, Trichosanthis pericarpium 15g, Belamcandae Rhizoma 10g, Pumex 20g, Eriobotryae folium 15g, Lepidii seu descurainiae Semen 10g, Artemisiae annuae Herba 21g, Pheretima 10g.</i>
Not reported	Qianjin Weijing Tang + Shangjiao Xuanpi Tang	Dampness-heat fettering the lung	<i>Phragmitis Rhizoma 15g, Coicis semen 15g, Benincasae pericarpium 15g, Armeniacae Semen amarum 10g, Trichosanthis pericarpium 15g, Scutellariae Radix 10g, Angelicae decursivae Radix 15g, Eriobotryae folium 15g, Belamcandae Rhizoma 10g, Curcumae longae Radix 15g, Artemisiae annuae Herba 21g, Lepidii seu descurainiae Semen 10g.</i>
	San Ren Tang	Dampness-heat fettering the spleen	<i>Armeniacae Semen amarum 10g, Coicis semen 15g, Amomi fructus Rotundus 5g, Pinelliae Rhizoma praeparatum 10g, Talcum 10g, Magnoliae Cortex 15g, Stachyuri Medulla Helwingiae Medulla 5g, Poria sclerotium 15g.</i>

* Originally, the name of the herbal formula was not published, and the authors named it on the basis of the Traditional Chinese Medicine Formula Dictionary. # Originally, the compositions of the herbal formula were not published, and the authors added them based on the Traditional Chinese Medicine Formula Dictionary.

The following MESH terms were used in the databases referred to above for mining results: traditional herbal medicinal plants for COVID-19, antiviral effects of coronavirus, Chinese herbal medicine, natural products for coronavirus, as well as recently reported mechanisms of action were all gathered from the online bibliographical databases. As there are no known therapies for COVID-19 infection and the production of a preventive vaccine is still under investigation. Thus, to try to minimize the mortality it causes, there is

an urgent need to develop effective antivirals for prophylaxis and effective COVID-19 infection control. The exploration of already used therapies in the treatment of this epidemic resembles a quick way to overcome this situation. This study will include a wide overall survey for the effects of traditional herbal medicine, some herbal formulae including their ingredients in addition to recent approaches for the herbal treatment of COVID-19.

Table 3: Medicinal plants reported in the treatment of COVID-19 and their mechanism of action.

Plant name	Responsive virus	Mechanism of action	References
<i>Rosa nutkana</i> C. Presl	Corona virus (CoV)	The extract was highly active against an enteric corona virus	25
<i>Amelanchier alnifolia</i> (Nutt.) Nutt. ex M.Roem.	Corona virus (CoV)	The extract was highly active against an enteric corona virus	25
<i>Houttuynia cordata</i> Thunb.	SARS-CoV	- Two primary SARS-CoV proteins, namely chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp), were inhibited. -In test animals, it increased CD4 + and CD8 + cell count, indicating its immune-stimulating effect	26
<i>Toona sinensis</i> (Juss.) M. Roem.	SARS-CoV	It inhibited SARS-CoV replication	27
<i>Rheum officinale</i> Baill., <i>Polygonum multiflorum</i> Thunb.	SARS-CoV	inhibited the interaction of SARS-CoV (S) protein and ACE2	28
<i>Cibotium barometz</i> (L.) J.Sm. and <i>Dioscorea batatas</i> Dence.	SARS-CoV	significant inhibition of SARS-CoV 3CLpro activity	29
Extracts of (<i>Anthemis hyaline</i> DC., <i>Nigella sativa</i> L., and <i>Citrus sinensis</i> (L.) Osbeck)	CoV	They decreased the replication of virus. They increased IL-8 level. Expression of the genes TRPA1, TRPC4, TRPM6, TRPM7, TRPM8 and TRPV4 changed significantly.	30
<i>Isatis indigotica</i> Fortune ex Lindl.	CoV	3CL protease inhibition	31
<i>Houttuynia cordata</i> Thunb.	CoV	Inhibition of the 3CL protease and viral polymerase.	26
Extracts of (<i>Gentiana scabra</i> Bunge, <i>Dioscorea batatas</i> Dence., <i>Cassia tora</i> L., <i>Taxillus chinensis</i> (DC.) Danser, <i>Cibotium barometz</i> (L.) J.Sm.)	CoV	3CL protease inhibition.	29
<i>Cimicifuga rhizoma</i> , <i>Meliae cortex</i> , <i>Coptidis rhizoma</i> and <i>Phellodendron cortex</i>	mouse hepatitis virus A59 (MHV-A59)	The output of MHV and intracellular viral RNA and protein expression was reduced, with EC50 values ranging from 2.0 to 27.5 g/ml. These extracts have significantly reduced the development of PEDV and less dramatically decreased the <i>in vitro</i> development of vesicular stomatitis virus (VSV).	32
<i>Sophorae radix</i> , <i>Acanthopanax cortex</i> , <i>Torilis fructus</i> and <i>Sanguisorbae radix</i>	MHV-A59	With comparable reductions in viral proteins and the development of MHV-A59, intracellular viral RNA levels were decreased. The extracts also reduced <i>in vitro</i> replication of the MHV strain of John Howard Mueller	33

The use of traditional herbal medicine for the prevention or treatment of this novel viral infection including pneumonia will be investigated. Our research was extended to include most herbs used in this aspect in most regions of the world to provide a collective review with all data required in this field. In searching for the traditionally used therapies some Chinese formulae were found listed in (Table 1) that seem to be effective⁷. It was found that *Glycyrrhizae* spp. root and rhizome is considered as one of the most used herbs in several herbal formulas followed by *Scutellariae* root and rhizome then come *Rheum* spp. These formulas were used for the treatment of

several symptoms of some patients of COVID-19 as high fever and diarrhea syndromes⁷. It was declared at a press conference in April 2020 by a Chinese official that three patent drugs of herbal constituents were approved for the treatment of COVID-19 manifestations. These include Xuebijing injections when the cases are severe in addition to Jinhuaqinggan granules and Lianhuaqingwen. After this approval, these drugs were propagated and widely used in China for the treatment of COVID-19. It was stated that these patents relieve some symptoms as fever, cough, fatigue also it decreases the risk that these cases develop to be severe but no other details were added⁸.

Table 4: Medicinal plants used in traditional medicine to treat upper respiratory viral infections.

Plant name	Responsive virus	Mechanism of action	References
Polyphenols from <i>Punica granatum</i> L.	Influenza A virus	Viral replication suppression against influenza A virus	34,35
Polyphenols of <i>Berries</i> extract	Influenza virus	Modification of immunity and improvement in the role of T cells against influenza virus and common cold	36-41
Glycyrrhizin isolated from <i>Glycyrrhiza uralensis</i> Fisch, <i>Glycyrrhiza inflata</i> Batalin and <i>Glycyrrhiza glabra</i> L.	influenza virus A2 (H2N2), H5N1 virus	Stimulation of T-cell development of interferon-gamma, immunomodulation, anti-inflammatory reduction of virus uptake by host cells against influenza A2 (H2N2), H5N1 and influenza A viruses	7,42-44
Maoto (<i>Ehedra herba</i> , <i>Cinnamomi cortex</i> , <i>Armenicae semen</i> and <i>Glycyrrhizae radix</i>)	Influenza virus	They help virus-bound natural antibodies against seasonal influenza	45,46
<i>Echinacea</i> spp.	Influenza, rhinovirus	inflammation modulators in cells infected with influenza, rhinovirus, and other respiratory viruses	17
<i>Camellia sinensis</i> (L.) Kuntze	Influenza	Influenza Increase levels of T- lymphocytes	26
<i>Potentilla arguta</i> Pursh	Syncytial virus (RSV)	Fully inhibited syncytial respiratory virus (RSV)	25
<i>Sambucus racemosa</i> L.	Syncytial virus (RSV)	completely inhibited respiratory syncytial virus (RSV)	25
<i>Ipomopsis aggregate</i> (Pursh) V.E. Grant	Parainfluenza	Good activity against parainfluenza virus type 3 was demonstrated.	25
<i>Lomatium dissectum</i> (Nutt.) Mathias & Constance	Rotavirus	The cytopathic effects of rotavirus were completely inhibited	25
Berries extract	Influenza virus	Modification of immunity and improvement in the role of T cells against influenza virus and common cold	36-41
<i>Clinacanthus siamensis</i> Bremek.	Influenza virus	Enhancement of the development of anti-influenza IgG and IgA antibodies against influenza viruses	47
<i>Punica granatum</i> L.	Influenza A virus	Suppression of Viral Replication against Influenza A virus	34,35
<i>Psidium guajava</i> L.	Influenza A (H1N1)	virucidal inhibition of viral hemagglutination against influenza A (H1N1)	48
<i>Epimedium koreanum</i> Nakai	Influenza A subtypes (H1N1, H5N2, H7N3, H9N2)	Reduction in viral replication, enhancement of type I interferon secretion and pro-inflammatory cytokines, influenza A subtype immunomodulation (H1N1, H5N2, H7N3, H9N2),	49
<i>Scutellaria baicalensis</i> Georgi	Influenza A virus	Inhibitor of neuraminidase, prevention of virus budding against Influenza A virus and common cold	50
<i>Paeonia lactiflora</i> Pall.	Influenza virus	It inhibits viral RNA and viral protein synthesis, viral hemagglutination, viral binding and penetration into host cells against influenza viruses.	51
<i>Allium sativum</i> L.	Parainfluenza, rhinovirus	-	17,52
<i>Forsythia suspense</i> (Thunb.) Vahl	RSV	-	53
<i>Geranium sanguineum</i> L.	Influenza	-	54
<i>Lonicera japonica</i> Thunb.	Influenza	-	55
<i>Pelargonium sidoides</i> DC.	Influenza Coronavirus, Coxsackie, parainfluenza Rhinovirus, RSV	-	56,57
<i>Pinus</i> spp.	Influenza	-	58,59
<i>Prunella vulgaris</i> L.	Influenza	-	60
<i>Rosmarinus officinalis</i> L.	RSV	-	61
<i>Salvia</i> spp.	Influenza	-	62
<i>Sambucus</i> spp.	Influenza (fruit) Rhinovirus (fruit) RSV (branch tip)	-	63,65
<i>Thuja</i> spp.	Parainfluenza, Influenza	-	58

Table 5: List of some secondary metabolites against viral respiratory tract infections.

Compound name	Responsive virus	Mechanism of action	References
Concanavalin A isolated from <i>Canavalia ensiformis</i> (L.)DC.	CoV	This induced hemagglutinating encephalomyelitis CoV inactivity, probably by binding to glycosylated membrane proteins that assist the virus in host cell recognition.	66
Lycorine isolated from <i>Lycoris radiata</i> (L'Hér.) Herb.	SARS-CoV	SARS-CoV with an EC ₅₀ value of 5.7 nM was inhibited	31
Emodin isolated from <i>Rheum officinale</i> Baill. and <i>Polygonum multiflorum</i> Thunb.	SARS-CoV	The interaction of the SARS-CoV(S) and ACE2 proteins with IC ₅₀ values ranging from 1 to 10 µg/mL for extracts and 200 µM for emodinamide was inhibited.	28
Tetrandrine	HCoV-OC43-infected MRC-5 human lung cells	In HCoV-OC43-infected MRC-5 human lung cells with IC ₅₀ values of 0.33, 1.01, and 0.83 µM, respectively, early stage viral-induced cell death was significantly inhibited.	67
Fangchinoline	HCoV-OC43-infected MRC-5 human lung cells	n HCoV-OC43-infected MRC-5 human lung cells with IC ₅₀ values of 0.33, 1.01 and 0.83 µM, respectively, early stage viral-induced cell death was significantly inhibited.	67
Cepharanthine	HCoV-OC43-infected MRC-5 human lung cells	n HCoV-OC43-infected MRC-5 human lung cells with IC ₅₀ values of 0.33, 1.01 and 0.83 µM, respectively, early stage viral-induced cell death was significantly inhibited.	67
8β-Hydroxyabieta-9(11),13-dien-12-one	SARS-CoV	It inhibited the activity of SARS-CoV 3CLpro with SI > 6677	68
Savinin	SARS-CoV	It inhibited the activity of SARS-CoV 3CLpro with SI > 6677	68
Betulinic acid	SARS-CoV	They were competitive SARS-CoV 3CLpro inhibitors with Ki values of 8.2 and 9.1 µM	68
Halituna isolated from marine alga <i>Halimeda tuna</i>	Coronavirus A59	It exhibited antiviral effect against murine coronavirus A59	69
Tanshinone I isolated from <i>Salvia miltiorrhiza</i> Bunge	SARS-CoV 3	This inhibited the infection and replication of SARS-CoV 3CLpro and papain-like protease (PLpro) at 1-1000 µM	70
Tannic acid isolated from black tea	SARS-CoV	Inhibitory effects were observed on SARS-CoV 3CLpro with an IC ₅₀ value of 3 µM and 3 µM, respectively.	71
3-Isotheaflavin-3-gallate isolated from black tea	SARS-CoV	Inhibitory effects were observed on SARS-CoV 3CLpro with an IC ₅₀ value of 3 µM and 7 µM, respectively.	71
Theaflavin-3,3'-digallate isolated from black tea	SARS-CoV	Inhibitory effects were observed on SARS-CoV 3CLpro with an IC ₅₀ value of 3 µM and 9.5 µM, respectively.	71
Theaflavin isolated from black tea	bovine CoV, bovine rotavirus	Bovine rotavirus and bovine corona virus infections have been neutralised.	72
Sinigrin isolated from <i>Isatis indigotica</i> Fortune ex Lindl.	SARS-CoV	An inhibitory effect on SARS-CoV 3CLpro with an IC ₅₀ value of 217µM has been shown.	73
Indigo isolated from <i>Isatis indigotica</i> Fortune ex Lindl	SARS-CoV	It showed an inhibitory effect on 3CLpro SARS-CoV with an IC ₅₀ value of 752 µM.	73
Aloe emodin isolated from <i>Isatis indigotica</i> Fortune ex Lindl	SARS-CoV	An inhibitory effect on SARS-CoV 3CLpro with an IC ₅₀ value of 8.3µM has been shown.	73
Hesperetin isolated from <i>Isatis indigotica</i> Fortune ex Lindl	SARS-CoV	An inhibitory effect on SARS-CoV 3CLpro with an IC ₅₀ value of 365 µM was seen.	73
β-sitosterol isolated from <i>Isatis indigotica</i> Fortune ex Lindl	SARS-CoV	An inhibitory effect was demonstrated on SARS-CoV 3CLpro with an IC ₅₀ value of 1210 µM.	73
Amentoflavone isolated from <i>Torreya nucifera</i> (L.) Siebold & Zucc.	SARS-CoV	It exhibited inhibitory effects with an IC ₅₀ value of 8.3µM on SARS-CoV 3CLpro.	74
Apigenin isolated from <i>Torreya nucifera</i> (L.) Siebold & Zucc	SARS-CoV	It exhibited inhibitory effects with an IC ₅₀ value of 280.8 µM on SARS-CoV 3CLpro.	74
Luteolin isolated from <i>Torreya nucifera</i> (L.) Siebold & Zucc	SARS-CoV	It exhibited inhibitory effects with an IC ₅₀ value of 20.2 µM on SARS-CoV 3CLpro.	74

Cont...

Quercetin isolated from <i>Torreya nucifera</i> (L.) Siebold & Zucc	SARS-CoV	It exhibited inhibitory effects with an IC ₅₀ value of 23.8 μM on SARS-CoV 3CLpro.	74
Myricetin	SARS-CoV	The inhibitory effect of SARS-CoV 3CLpro was 0.01-10 μMM.	75
Scutellarein	SARS-CoV	It exerted SARS-CoV 3CLpro inhibitory effect at 0.01–10 μM	75
Brousochalcone B isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Brousochalcone A isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
4-Hydroxyisolonchocarpin isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Papyriflavonol A isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both 3CLpro and PLpro of SARS-CoV. Among isolated compounds from the same plant, the highest inhibition was shown against PLpro with an IC ₅₀ value of 3.7 μM .	76
3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavane isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Kazinol A isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Kazinol B isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Brousoflavan A isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Kazinol F isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Kazinol J isolated from <i>Broussonetia papyrifera</i> (L.) L'Hér. ex Vent.	SARS-CoV	It inhibited both SARS-CoV 3CLpro and PLpro	76
Saikosaponin A	CoV-229E	It exhibited activity with an EC ₅₀ value of 8.6 μM against human CoV-229E.	77
Saikosaponin B ₂	CoV-229E	It exhibited activity with an EC ₅₀ value of 8.6, 1.7μM against human CoV-229E. Viral attachment and penetration stages were inhibited.	77
Saikosaponin C	CoV-229E	It exhibited activity with an EC ₅₀ value of 19.9 μM against human CoV-229E.	77
Saikosaponin D	CoV-229E	It exhibited activity with an EC ₅₀ value of 13.2 μM against human CoV-229E.	77
Ginsenoside Rb1 isolated from <i>Panax ginseng</i> C.A.Mey.	SARS-CoV	Antiviral activity demonstrated at 100 μM	78
Actinomycin D isolated from <i>Streptomyces parvulus</i> bacteria	CoV	At 5-25 μM with an EC ₅₀ value of 0.02 μM, the inhibited CoV attachment and penetration stages	77
Homoharringtonine	Murine coronavirus	It was the most potent alkaloid among 727 compounds with an IC ₅₀ of ~11 nM	79
Tylophorine isolated from <i>Tylophora indica</i> (Burm. f.) Merr.	CoV	Inhibited the activity of N and S proteins as well as viral replication of transmissible gastroenteritis virus enteropathogenic coronavirus	80
7-Methoxycryptopleurine isolated from <i>Tylophora indica</i> (Burm. f.) Merr.	CoV	It inhibited the activity of N and S proteins as well as viral replication of the transmissible gastroenteritis virus enteropathogenic coronavirus.	80
Cepharanthine	SARS-CoV	It inhibited the protease enzyme SARS-CoV at 0.5–10 μg / mL	81
Berberamine	HCoV-NL63	With an IC ₅₀ value of 1.48 μM, it inhibited HCoV-NL63	82
Lycorine	HCoV-OC43	Cell division was inhibited and RNA, DNA and protein synthesis were inhibited, respectively.	82
Emetine	HCoV-OC43	Cell division was inhibited and RNA, DNA and protein synthesis were inhibited, respectively.	82
Mycophenolate mofetil	HCoV-OC43	The immune suppressing effect was exerted on the CoV species	82

Cont...

Eckol isolated from <i>Ecklonia cava</i>	Porcine epidemic diarrhea coronavirus	The virus binding to porcine epidemic cells was blocked at 1-200 μM with IC_{50} values of 22.5, 18.6, 12.2, and 14.6 μM , respectively.	83
7-phloroeckol isolated from <i>Ecklonia cava</i>	Porcine epidemic diarrhea coronavirus	The virus binding to porcine epidemic cells was blocked at 1 to 200 μM with IC_{50} values of 22.5, 18.6, 12.2 and 14.6 μM , respectively.	83
Phlorofucofuroeckoln isolated from <i>Ecklonia cava</i>	Porcine epidemic diarrhea coronavirus	The virus binding to porcine epidemic cells was blocked at 1-200 μM with IC_{50} values of 22.5, 18.6, 12.2 and 14.6 μM , respectively.	83
Dieckol isolated from <i>Ecklonia cava</i>	Porcine epidemic diarrhea coronavirus	The virus binding to porcine epidemic cells was blocked at 1-200 μM with IC_{50} values of 22.5, 18.6, 12.2 and 14.6 μM respectively.	83
Procyanidin A2 isolated from <i>Cinnamomi cortex</i>	SARS-CoV	It inhibited infection with SARS-CoV at 0-500 μM	84
Procyanidin B1 isolated from <i>Cinnamomi cortex</i>	SARS-CoV	It inhibited infection with SARS-CoV at 0-500 μM	84
Cinnamtannin B1 isolated from <i>Cinnamomi cortex</i>	SARS-CoV	It inhibited infection with SARS-CoV at 0-500 μM	84
Tetra- <i>O</i> -galloyl-beta- <i>D</i> -glucose	SARS-CoV	It blocked the host cell entry of SARS-CoV at 0-10-3 mol/L	85
Luteolin	SARS-CoV	It blocked SARS-CoV's host cell entry at 0-10-3 mol/L.	85
Tetra- <i>O</i> -galloyl-beta- <i>D</i> -glucose	SARS-CoV	It blocked SARS-CoV's host cell entry at 0-10-3 mol/L.	85
Bavachinin isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
Neobavaisoflavone isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
Isobavachalcone isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
4'- <i>O</i> -methylbavachalcone isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
Psoralidin isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
Corylifol isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited papain-like protease of SARS-CoV	86
Psoralidin isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	A significant protease inhibitory effect on SARS-CoV with an IC_{50} value of 4.2 μM was observed.	28
Emodin isolated from <i>Psoralea corylifolia</i> L.	SARS-CoV	It inhibited the interaction between the protein SARS-CoV(S) and ACE2 at 0-400 μM	28
Juglanin	SARS-CoV	It blocked the SARS-CoV 3a channel with an IC_{50} value of 2.3 μM	87
Tomentin A isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
Tomentin B isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARSCoV at 0-100 μM	88
Tomentin C isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
Tomentin D isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
Tomentin E isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
3'- <i>O</i> -methyl-di-placol isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
4'- <i>O</i> -methyl-di-placol isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
3'- <i>O</i> -methyl-di-placone isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88
4'- <i>O</i> -methyl-di-placone isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0-100 μM	88

Cont...

<i>Mimulone diplacone</i> isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0–100 μ M	88
6-geranyl-4',5,7-trihydroxy-3',5'- dimethoxyflavanone isolated from <i>Paulownia tomentosa</i> Steud.	SARS-CoV	It inhibited PLpro of SARS-CoV at 0–100 μ M	88
(–)-Catechin gallate	SARS-CoV	It inhibited the SARS-CoV nanoparticle-based RNA oligonucleotide at 0.001-1 μ g/mL	89
(–)- Gallocatechin gallate	SARS-CoV	It inhibited the SARS-CoV nanoparticle-based RNA oligonucleotide at 0.001–1 μ g/mL	89
Quercetin isolated from <i>Houttuynia cordata</i> Thunb.	murine CoV	It operates at 15.63–500 μ g/mL against murine CoV.	90
Rutin isolated from <i>Houttuynia cordata</i> Thunb.	murine CoV	It operates at 15.63–500 μ g/mL against murine CoV.	90
Cinanserin (1 and 2 dpi) isolated from <i>Houttuynia cordata</i> Thunb.	murine CoV	It operates at 15.63–500 μ g/mL against murine CoV.	90
Sivestrol isolated from <i>Aglaiia foveolata</i> Pannell	HCoV-229E	With an IC ₅₀ of 40 nM, it inhibited cap-dependent viral mRNA translation of HCoV-229E at 0.6–2 μ M	91
Ferruginol isolated from <i>Sequoia sempervirens</i> (D.Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
3 β ,12-diacetoxylabieta-6,8,11,13-tetraene isolated from <i>Sequoia sempervirens</i> (D.Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Betulonic acid isolated from <i>Sequoia sempervirens</i> (D. Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Betulinic acid isolated from <i>Sequoia sempervirens</i> (D. Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Hinokinin isolated from <i>Sequoia sempervirens</i> (D. Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Savinin isolated from <i>Sequoia sempervirens</i> (D. Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Curcumin isolated from <i>Sequoia sempervirens</i> (D. Don) Endl.	SARS-CoV	It greatly inhibited replication of SARS-CoV at 0-80 μ M	92
Quabain	Gastroenterit is coronavirus (TGEV)	It lowered both viral titers and viral yields and decreased the number of copies of viral RNA to 0-3000 nM	93
Tylophorine isolated from <i>Tylophora indica</i> (Burm. f.) Merr.	CoV	It prevented viral replication in swine testicular cells infected with CoV.	80
7-methoxycryptopleurine isolated from <i>Tylophora indica</i> (Burm. f.) Merr.	CoV	Viral replication was inhibited in CoV-infected testicular swine cells	80
Tylophorine	CoV	It targeted replication of viral RNA and cellular JAK2 mediated dominant activation of NF- κ B in CoV at 0-1000 nM	94

Glycyrrhizae rhizoma is considered from the highly effective herbs widely used whatever is the stage of infection. It is approved as an antiviral herbal therapy by the China Food and Drug Administration (SFDA). Its mechanism was reported by many studies as it inhibits attachment, entry, and replication of the virus which was earlier used in treating SARS^{9,10}. In addition, *Glycyrrhizae* Radix Rhizoma possesses an anti-inflammatory effect which is useful in the treatment of lung inflammatory cases associated with COVID-19^{4,11}. A herbal formula called Qingfei Paidu Tang was recommended for the treatment of extreme

COVID-19 conditions in the Korean Guidelines, as well as its recommendation in the national Chinese guidelines for diagnosis and treatment. This formula consists of (*Ephedrae* Herba 9g, *Armeniacae* Semen *amarum* 9g, *Glycyrrhizae* Rhizoma 6g, *Gypsum fibrosum* 15~30 g, *Alismatis* Rhizoma 9g, *Cinnamomi ramulus* 9g, *Polyporus* 9g, *Poria sclerotium* 15g, *Atractylodis macrocephalae* Rhizoma 9g, *Bupleuri* Radix 16g, *Pinelliae* Rhizoma 9g, *Scutellariae* Radix 6 g, *Zingiberis* Rhizoma Recens 9g, *Farfare* Flos 9 g, *Asteris* Radix 9g, *Belamcandae* Rhizoma 9g, *Dioscoreae* Rhizoma 12g, *Asari* Herba 6g, *Aurantii*

fructus 6g, *Agastachis* Herba 9 and *Citri unshius* Pericarpium 6g). Recently, it was reported by¹², that this formula boosts immunity and decreases inflammation through its effect on the lung and spleen which are considered the pathways of COVID-19. In addition, the Korean guidelines removed the *Farfarae* Flos herb due to its safety and toxicity⁴. Ang et al., presented several herbal formulas used in traditional

medicine for pediatric COVID-19 cases (Table 2). They mentioned 13 herbal formulas approved by the Chinese guidelines which consist totally of 56 herbs. According to the authors, clusters of herbal pairs were used *Artemisiae annuae* herb and *Scutellariae* root in a cluster, *Armeniaca* seeds, and *Coicis* seeds in another and *Ephedrae* with *Gypsum fibrosum*.¹³

Table 6: List of Indian medicinal plants and their active compounds as a best therapeutic tool to treat different viral diseases.

Medicinal Plant	Active principle	Antiviral mechanism of action	Reference
<i>Acacia nilotica</i> (L.) Delile	Quercetin	Inhibition HIV-PR	
<i>Allium sativum</i> L.	Allicin	Proteolytic and hemagglutinating activity and viral replication	
<i>Andrographis paniculata</i> (Burm.f.) Nees	Andrographolide	Antiviral potential	
<i>Clitoria ternatea</i> L.	Delphinidin-3-O-glucoside	Antiviral properties	
<i>Cynara scolymus</i> L.	Cynaratriol	ACE inhibitor	
<i>Embelia ribes</i> Burm.f.	1,4- benzoquinone	Inhibition of ACE	
<i>Eugenia jambolana</i> Lam.	Ellagic acid	Protease Inhibitor	
<i>Euphorbia granulata</i> Forssk.	Gallic acid	HIV inhibitory	
<i>Gymnema sylvestre</i> (Retz.) R.Br. ex Sm.	Tartaric acid	Inhibition of viral DNA synthesis	5
<i>Hyoscyamus niger</i> L.	Hyoscyamine	Viral Inhibition and Bronchodilator	
<i>Ocimum kilimandscharicum</i> Gürke	Camphor	Inhibitory action towards HIV-1	
<i>Punica granatum</i> L.	Punicalagin	Inhibited viral Glycoprotein & Anti-HSV-1	
<i>Sphaeranthus indicus</i> L.	Tartaric acid	Inhibition of Mouse corona virus Various compositions and Herpes virus -Bronchodilation	
<i>Strobilanthes cusia</i> (Nees) Kuntze	Lupeol	Inhibitory action towards HCoV-NL63	
<i>Vitex negundo</i> L.	Sabinene	Inhibitory action against HIV	
<i>Vitex trifolia</i> L.	Casticin	Immunomodulatory & Anti-inflammatory effect on lungs	

Traditional medicine plays a major role in supplying communities with treatment in Africa. Medicinal plants such as *Artemisia annua* are known to be one of the potential therapies for COVID-19, which should be tested for effectiveness and adverse side effects. The WHO suggested testing herbs for their effectiveness and protection before conventional practice through comprehensive clinical trials is crucial^[14]. In the meantime, conventional medicine continues to be generally used across Africa. President Rajoelina estimated that 80 percent of the population of Madagascar uses 'COVID Organics'¹⁵. A biochemist researcher in traditional medicine at North-West University in South Africa, Professor Chrisna Gouws, reported about the use of *Artemisia annua* in herbal medicine "It's a very common herbal medicine. In parts of the world, it is one of the most commonly used herbs. The scientific community has been interested in

artemisinin, which is a known anti-malarial medication, since it contains"¹⁵. Collaborating with Artemi Life Inc., a US-based business and medical researchers in Denmark and Germany, the Max Planck Institute of Colloids and Interfaces, Potsdam (Germany), will be studying *Artemisia annua* extract and artemisinin derivatives in laboratory cell studies against the novel SARS-CoV-2 coronavirus¹⁵. Furthermore, there are several medicinal plants and many secondary metabolites that were reported effective against viral respiratory tract infections. For example, (Table 3) explains some of medicinal plants that possessed antiviral activity against different coronavirus types and their possible mechanism of actions. While (Tables 4 and Table 5) included various herbal medicines and different secondary metabolites which reported to have activity against causes of viral respiratory infection, specially corona virus.

Among these plants, the Lamiaceae family herbs, which have a completely different chemistry, primarily monoterpenoids. According to a previous study¹⁷ *Salvia apiana* (white sage), *S. officinalis* (garden sage), *Thymus vulgaris* (thyme), *Rosmarinus officinalis* (rosemary), and *Prunella vulgaris* (heal-all) are among the many other mints with antiviral and other beneficial effects relevant to viral respiratory infections. Generally, these are received well by patients based on taste¹⁷. Trees from two evergreen families, the Pinaceae and Cupressaceae, make up another family groups of antivirals. *Pinus spp.* (pine), *Abies spp.* (true firs), *Picea spp.* (spruces), *Thuja spp.* (cedars), and *Juniperus spp.* (junipers) resin and branch tips are all antiviral and inflammatory modulators with a respiratory tract affinity. All these groups are inflammation modulators, which is important for two reasons. The symptoms of viral respiratory infections are significantly due to immune responses to the infecting virus. More importantly, severe influenza is in part due to what has been dubbed "cytokine storm": a hyper-reaction of the immune system to certain influenza strains. Thus, inflammation-modulating herbs are significant to decrease symptoms and to prevent severe consequences, at least in the case of influenza infection. Additionally, these herbs considerably have immune-stimulating effects, running the risk of rising symptoms of viral respiratory infections or making cytokine storms worse¹⁷.

Balachandar and his colleagues reported a strategy in India to establish an effective method of viral inactivation by exploiting and infusing active compounds from naturally occurring medicinal plants into respiratory masks based on nanofiber. They listed some of the Indian medicinal plants (Table 6) that could be used as potent antiviral agents¹⁸. Moreover, Thangadurai *et al.*, reported that Siddha or Ayurvedha traditional medicine validated a polyherbal formulation Deva chooranam (DC) with proven preclinical safety and activity against HIV and may have possible activity for the prevention and management of 2019-nCoV infection. This herbal formula includes three medicinal herbs: *Cedrus deodara* (Devadaru), *Cinnamomum tamala* (Lavanga pathiri) and *Alpinia galanga* (Arathai)¹⁹.

RECENT APPROACHES FOR TREATMENT

Recently, a study published by Ren *et al.*, showed that 574 prescriptions with the key words "Warm diseases (Wenbing)", "Pestilence (Wenyi or Yibing)" or "Epidemic diseases (Shiyi)" were obtained among 96606 classical prescriptions.⁷ Meanwhile, among the 574 prescriptions, there were 40 forms of Chinese Medicines (CMs), 36 CMs-pairs, 6 triple-CMs-groups, with high frequency. Also, the primary targets of SARS-COV-2, namely 3CL protease (Mpro) and angiotensin-converting enzyme 2 (ACE2), were used to dock the main constituents from the 40 kinds by the Ligand FitDock method. The COVID-19 targets were docked with a total of 66 higher frequency compounds distributed in 26 forms of CMs, of which Gancao (*Glycyrrhizae Radix et rhizoma*), Dahuang (*Rhei radix*

et rhizome), HuangQin (*Scutellariae radix*) and Chaihu (*Bupleuri radix*) contained more potential compounds. In addition, the results of the network pharmacology showed that pairs of Chinese medicines HuangQin (*Scutellariae radix*) and Gancao (*Glycyrrhizae radix et rhizoma*) might interact with targets for immune and inflammatory diseases⁷.

In another study conducted by Chen *et al.*, two key proteins, 3C-like protease (3CLpro) and angiotensin-converting enzyme 2 (ACE2), could be used as targets for active constituents *in silico* screening that stop SARS-COV-2 replication and proliferation, profit from rapid SARS-COV-2 sequencing coupled with molecular modelling based on the genomes of associated viral proteins^{20,21}. Owis *et al.*, reported that ten flavonoids that were isolated from *Salvadora persica* L. aqueous extract showed remarkable binding stability at the N3 binding site of main protease of the COVID-19 to different degrees when compared with darunavir, a COVID-19 main protease inhibitor. The isolated and identified flavonoids were similar in structure which gave the opportunity to deduce the relation between their structure and the affinity to the receptors of the N3 binding site. The findings showed that the fundamental flavonol as a nucleus itself possesses an activity, in addition, the presence of rutinose in position 3 in this nucleus and the absence of O-CH₃ group in ring B may be an explanation for improving the binding stability²². According to Khattab *et al.*, cathepsins and furin, may be used for developing broad-spectrum anti-SARS-CoV therapies which target multiple viral and non-viral proteins²³. A recent study by Qamar and his colleagues analyzed the 3CLpro sequence of CoV-19, developed its 3D homology model, and screened it against a library of medicinal plant containing 32,297 possible anti-viral phytochemicals/ traditional Chinese medicinal compounds and selected the top nine hits that may inhibit the action of SARS-CoV-2 3CLpro and therefore virus replication²⁴. These compounds were 5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethyl allyl) isoflavone, myricitrin, methyl rosmarinate, 3,5,7,3',4',5'-hexahydroxy flavanone-3-O-β-D-glucopyranoside, (2S)-eriodictyol 7-O-(6'-O-galloyl)-β-D-glucopyranoside, calceolarioside B, myricetin 3-O-β-D-glucopyranoside, licoleafol and amaranthin with docking scores -16.35, -15.64, -15.44, -14.42, -14.41, -14.36, -13.70, -13.63 and -12.67, respectively, compared to nelfinavir (-12.20), prulifloxacin (-11.32) and colistin (-11.73).

CONCLUSION

From the above reviewed studies, it is evident that different countries around the world have abundance of antiviral plants resources based on scientific findings. There are several medicinal plants traditionally used by the local people of many countries all over the world to treat coronavirus. However, there is a great deficiency to find enough studies considering the chemistry and pharmacological effects of these herbal plants. Therefore, carrying detailed ethnomedicinal studies is of great demand to discover novel active principles

with promising activity against this fatal virus. Besides, very few herbs have been screened *in vitro* and *in vivo* against viruses including coronavirus, so, pharmaceutical industries and/or government agencies should support more research activities in this area in order to utilize these antiviral medicinal plants for a solution against the global fatal illness (COV-19) or any threaten viral infections.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

AUTHORS' CONTRIBUTIONS

The two authors shared the research ideas, collected data, wrote the article, revised the article grammatical correction and reviewed the whole article.

REFERENCES

- Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. *J Trad Complement Med* 2014; 4: 24-35 <https://doi.org/10.4103/2225-4110.124335>
- Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. In: Springer; 2020 <https://doi.org/10.1186/s13054-020-2818-6>
- Hensel A, Bauer R, Heinrich M, Spiegler V, Kayser O, Hempel G, Kraft K. Challenges at the Time of COVID-19: opportunities and innovations in antivirals from nature. *Planta Med* 2020. <https://doi.org/10.1055/a-1177-4396>
- Ang L, Lee HW, Choi JY, Zhang J, Lee MS. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. *Integ Med Res* 2020; 9: 100407. <https://doi.org/10.1016/j.imr.2020.100407>
- Africa news. Coronavirus - Africa: World Health Organization (WHO) supports Scient Prov Trad Med. In: 2020.
- Balachandar V, Mahalaxmi I, Kaavya J, et al. COVID-19: emerging protective measures. *Eur Rev Med Pharmacol Sci* 2020; 24: 3422-3425. https://doi.org/10.26355/eurrev_202003_20713
- Ren X, Shao X-X, Li X-X, et al. Identifying potential treatments of COVID-19 from Traditional Chinese Medicine (TCM) by using a data-driven approach. *J Ethnopharmacol* 2020;258: 112932 <https://doi.org/10.1016/j.jep.2020.112932>
- Yang Y. Use of herbal drugs to treat COVID-19 should be with caution. *Lancet (London, England)* 2020 [https://doi.org/10.1016/S0140-6736\(20\)31143-0](https://doi.org/10.1016/S0140-6736(20)31143-0)
- Li T, Peng T. Traditional Chinese herbal medicine as a source of molecules with antiviral activity. *Antiviral Res* 2013; 97: 1-9. <https://doi.org/10.1016/j.antiviral.2012.10.006>
- Chen F, Chan K, Jiang Y, Kao R, Lu H, Fan K, Cheng V, Tsui W, Hung I, Lee T. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* 2004; 31: 69-75. <https://doi.org/10.1016/j.jcv.2004.03.003>
- Yang X-L, Liu D, Bian K, Zhang D-D. Study on *in vitro* anti-inflammatory activity of total flavonoids from *Glycyrrhizae Radix* et *Rhizoma* and its ingredients. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi. China J Chinese Mat Med* 2013; 38: 99-104. PMID: 23596884
- Zhao J, Tian S, Yang J, Liu J, Zhang W. Investigating the mechanism of Qing-Fei-Pai-Du-Tang for the treatment of novel coronavirus pneumonia by network pharmacology. *Chinese Trad Herb Drugs* 2020; 51.
- Ang L, Lee HW, Kim A, Lee JA, Zhang J, Lee MS. Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines. *Complement Ther Clin Pract* 2020; 39: 101174. <https://doi.org/10.1016/j.ctcp.2020.101174>
- Brazzaville. WHO supports scientifically-proven traditional medicine. In: 2020
- Gikandi H. Madagascar defends coronavirus herbal remedy. In: 2020.
- Seeberger PH. *Artemisia annua* to be tested against coronavirus. In: 2020.
- Yarnell E. Herbs for Viral Respiratory Infections. *Alter Complement Ther* 2018; 24: 35-43 <https://doi.org/10.1089/act.2017.29150.eya>
- Balachandar V, Mahalaxmi I, Kaavya J, et al. COVID-19: emerging protective measures. *Euro Rev Med Pharmacol Sci* 2020; 24: 3422-3425 https://doi.org/10.26355/eurrev_202003_20713
- Thangadurai K J, GRa YM. Scientific validation of Siddha herbal formulation Deva Chooranam against novel Coronavirus (2019-nCoV/COVID-19). *Int J Rec Sci Res* 2020; 11: 37006-37010. <https://doi.org/10.24327/ijrsr.2020.1101.5040>
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* 2020; 395: 507-513 [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)
- Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *Bio Rxiv* 2020. <https://doi.org/10.1101/2020.02.03.931766>
- Owis AI, El-Hawary MS, El Amir D, et al. Molecular docking reveals the potential of *Salvadora persica* flavonoids to inhibit COVID-19 virus main protease. *RSC Advances* 2020; 10: 19570-19575. <https://doi.org/10.1039/D0RA03582C>
- Sayed AM, Khattab AR, Aboul Magd AM, et al. Nature as a treasure trove of potential anti-SARS-CoV drug leads: a structural/mechanistic rationale. *RSC Advances* 2020; 10: 19790-19802. <https://doi.org/10.1039/D0RA04199H>
- Qamar MT, Alqahtani SM, Alamri MA, Chen LL. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *J Pharm Anal* 2020. <https://doi.org/10.1016/j.jpha.2020.03.009>
- Jassim SAA, Naji MA. Novel antiviral agents: a medicinal plant perspective. *J Appl Microbiol* 2003; 95: 412-427 <https://doi.org/10.1046/j.1365-2672.2003.02026.x>
- Lau KM, Lee KM, Koon CM, et al. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *J Ethnopharmacol* 2008; 118: 79-85. <https://doi.org/10.1016/j.jep.2008.03.018>
- Chen C-J, Michaelis M, Hsu H-K, et al. *Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication. *J Ethnopharmacol* 2008; 120: 108-111. <https://doi.org/10.1016/j.jep.2008.07.048>
- Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antivir Res* 2007; 74: 92-101. <https://doi.org/10.1016/j.antiviral.2006.04.014>
- Wen CC, Shyur LF, Jan JT, et al. Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. *J Tradit Complem Med* 2011; 1: 41-50. [https://doi.org/10.1016/s2225-4110\(16\)30055-4](https://doi.org/10.1016/s2225-4110(16)30055-4)
- Ulasli M, Gurses SA, Bayraktar R, et al. The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Mol Biol Repor* 2014; 41: 1703-1711. <https://doi.org/10.1007/s11033-014-3019-7>
- Li S-y, Chen C, Zhang H-q, et al. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antivir Res* 2005; 67: 18-23

- <https://doi.org/10.1016/j.antiviral.2005.02.007>
32. Kim HY, Shin HS, Park H, et al. *In vitro* inhibition of coronavirus replications by the traditionally used medicinal herbal extracts, *Cimicifuga rhizoma*, *Meliae cortex*, *Coptidis rhizoma*, and *Phellodendron cortex*. J Clin Virol 2008; 41: 122-128. <https://doi.org/10.1016/j.jcv.2007.10.011>
 33. Kim HY, Eo EY, Park H, et al. Medicinal herbal extracts of *Sophorae radix*, *Acantho panacis cortex*, *Sanguisorbae radix* and *Torilis fructus* inhibit coronavirus replication *in vitro*. Antivir Ther 2010; 15: 697-709. <https://doi.org/10.3851/IMP1615>
 34. Sundararajan A, Ganapathy R, Huan L, et al. Influenza virus variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. Antivir Res 2010; 88: 1-9. <https://doi.org/10.1016/j.antiviral.2010.06.014>
 35. Haidari M, Ali M, Casscells III SW, Madjid M. Pomegranate (*Punica granatum*) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomed 2009; 16: 1127-1136. <https://doi.org/10.1016/j.phymed.2009.06.002>
 36. Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. J Inter Med Res 2004; 32: 132-140. <https://doi.org/10.1177/147323000403200205>
 37. Roschek Jr B, Fink RC, McMichael MD, et al. Elderberry flavonoids bind to and prevent H1N1 infection *in vitro*. Phytochem 2009; 70: 1255-1261. <https://doi.org/10.1016/j.phytochem.2009.06.003>
 38. Ikuta K, Mizuta K, Suzutani T. Anti-influenza virus activity of two extracts of the blackcurrant (*Ribes nigrum* L.) from New Zealand and Poland. Fukush J Med Sci 2013; 59: 35-38. <https://doi.org/10.5387/jms.59.35>
 39. Ikuta K, Hashimoto K, Kaneko H, et al. Anti-viral and anti-bacterial activities of an extract of blackcurrants (*Ribes nigrum* L.). Microbiol Immunol 2012; 56: 805-809. <https://doi.org/10.1111/j.1348-0421.2012.00510.x>
 40. Sekizawa H, Ikuta K, Mizuta K, Takechi S, Suzutani T. Relationship between polyphenol content and anti-influenza viral effects of berries. J Sci Food Agri 2013; 93: 2239-2241. <https://doi.org/10.1002/jsfa.6031>
 41. Nantz MP, Rowe CA, Muller C, et al. Consumption of cranberry polyphenols enhances human $\gamma\delta$ -T cell proliferation and reduces the number of symptoms associated with colds and influenza: a randomized, placebo-controlled intervention study. Nutri J 2013; 12: 161. <https://doi.org/10.1186/1475-2891-12-161>
 42. Utsunomiya T, Kobayashi M, Pollard RB, Suzuki F. Glycyrrhizin, an active component of licorice roots, reduces morbidity and mortality of mice infected with lethal doses of influenza virus. Antimicrob Agen Chemother 1997; 41: 551-556. PMID: 9055991
 43. Michaelis M, Geiler J, Naczk P, et al. Glycyrrhizin inhibits highly pathogenic H5N1 influenza A virus-induced pro-inflammatory cytokine and chemokine expression in human macrophages. Medical Microbiol Immunol 2010; 199: 291-297. <https://doi.org/10.1007/s00430-010-0155-0>
 44. Wolkerstorfer A, Kurz H, Bachhofner N, Szolar OH. Glycyrrhizin inhibits influenza A virus uptake into the cell. Antivir Res 2009; 83: 171-178. <https://doi.org/10.1016/j.antiviral.2009.04.012>
 45. Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. J Infect Chemother 2012; 18: 534-543. <https://doi.org/10.1007/s10156-012-0378-7>
 46. Nagai T, Kataoka E, Aoki Y, et al. Alleviative effects of a Kampo (a Japanese herbal) medicine Maoto (Ma-Huang-Tang) on the early phase of influenza virus infection and its possible mode of action. Evid-Based Complement Alter Med 2014; 2014. <https://doi.org/10.1155/2014/187036>
 47. Wirotasangthong M, Nagai T, Yamada H, Amnuoyopol S, Mungmee C. Effects of *Clinacanthus siamensis* leaf extract on influenza virus infection. Microbiol Immunol 2009; 53: 66-74. <https://doi.org/10.1111/j.1348-0421.2008.00095.x>
 48. Sriwilaijaroen N, Fukumoto S, Kumagai K, et al. Antiviral effects of *Psidium guajava* Linn (guava) tea on the growth of clinical isolated H1N1 viruses: Its role in viral hemagglutination and neuraminidase inhibition. Antivir Res 2012; 94: 139-146. <https://doi.org/10.1016/j.antiviral.2012.02.013>
 49. Cho W-K, Weeratunga P, Lee B-H, et al. Epimedium koreanum Nakai displays broad spectrum of antiviral activity *in vitro* and *in vivo* by inducing cellular antiviral state. Viruses 2015; 7: 352-377. <https://doi.org/10.3390/v7010352>
 50. Ding Y, Dou J, Teng Z, et al. Antiviral activity of baicalin against influenza A (H1N1/H3N2) virus in cell culture and in mice and its inhibition of neuraminidase. Arch Virol 2014; 159: 3269-3278. <https://doi.org/10.1007/s00705-014-2192-2>
 51. Ho J-Y, Chang H-W, Lin C-F, et al. Characterization of the anti-influenza activity of the Chinese herbal plant *Paeonia lactiflora*. Viruses 2014; 6: 1861-1875. <https://doi.org/10.3390/v6041861>
 52. Weber ND, Andersen DO, North JA, et al. *In vitro* virucidal effects of *Allium sativum* (garlic) extract and compounds. Planta Med 1992; 58: 417-423. <https://doi.org/10.1055/s-2006-961504>
 53. Tang W, Eisenbrand G. *Forsythia suspensa* (Thunb.) Vahl. In, Chinese Drugs of Plant Origin: Springer; 1992: 515-519.
 54. Serkedjieva J, Gegova G, Mladenov K. Protective efficacy of an aerosol preparation, obtained from *Geranium sanguineum* L., in experimental influenza infection. Die Pharma- An Inter J Pharma Sci 2008; 63: 160-163. <https://doi.org/10.1691/ph.2008.7617>
 55. Ding Y, Cao Z, Cao L, et al. Antiviral activity of chlorogenic acid against influenza A (H1N1/H3N2) virus and its inhibition of neuraminidase. Sci Rep 2017; 7: 45723. <https://doi.org/10.1038/srep45723>
 56. Theisen LL, Muller CP. EPs® 7630 (Umckaloabo®), an extract from *Pelargonium* sidosides roots, exerts anti-influenza virus activity *in vitro* and *in vivo*. Antivir Res 2012; 94: 147-156. <https://doi.org/10.1016/j.antiviral.2012.03.006>
 57. Michaelis M, Doerr HW, Cinatl Jr J. Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium* sidosides, on replication of a broad panel of respiratory viruses. Phytomed 2011; 18: 384-386. <https://doi.org/10.1016/j.phymed.2010.09.008>
 58. Won JN, Lee SY, Song DS, Poo HY. Antiviral activity of the plant extracts from *Thuja orientalis*, *Aster spathulifolius*, and *Pinus thunbergii* against influenza virus A/PR/8/34. J Microbiol Biotech 2013; 23: 125-130. <https://doi.org/10.4014/jmb.1210.10074>
 59. Watanabe K, Momose F, Handa H, Nagata K. Interaction between influenza virus proteins and pine cone antitumor substance that inhibits the virus multiplication. Biochem Bioph Res Comm 1995; 214: 318-323. <https://doi.org/10.1006/bbrc.1995.2290>
 60. Tian L, Wang Z, Wu H, et al. 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 2011; 137: 534-542. <https://doi.org/10.1016/j.jep.2011.06.002>
 61. Shin H-B, Choi M-S, Ryu B, et al. Antiviral activity of carnosic acid against respiratory syncytial virus. Virol J 2013; 10: 303. <https://doi.org/10.1186/1743-422X-10-303>
 62. Bang S, Li W, Ha TKQ, et al. Anti-influenza effect of the major flavonoids from *Salvia plebeia* R. Br. via inhibition of influenza H1N1 virus neuraminidase. Nat Prod Res 2018; 32: 1224-1228. <https://doi.org/10.1080/14786419.2017.1326042>

63. Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, et al. Inhibition of several strains of influenza virus *in vitro* and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. *J Alter Complement Med* 1995; 1: 361-369.
<https://doi.org/10.1089/acm.1995.1.361>
64. McCutcheon A, Roberts T, Gibbons E, et al. Antiviral screening of British Columbian medicinal plants. *J Ethnopharmacol* 1995; 49: 101-110.
[https://doi.org/10.1016/0378-8741\(95\)90037-3](https://doi.org/10.1016/0378-8741(95)90037-3)
65. Glatthaar-Saalmüller B, Rauchhaus U, Rode S, et al. Antiviral activity *in vitro* of two preparations of the herbal medicinal product Sinupret® against viruses causing respiratory infections. *Phytomed* 2011; 19: 1-7.
<https://doi.org/10.1016/j.phymed.2011.10.010>
66. Islam MT, Sarkar C, El- Kersh DM, et al. Natural products and their derivatives against coronavirus: A review of the non- clinical and pre- clinical data. *Phytother Res* 2020.
<https://doi.org/10.1002/ptr.6700>
67. Kim DE, Min JS, Jang MS, et al. Natural Bis-Benzylisoquinoline Alkaloids-Tetrandrine, Fangchinoline, and Cepharanthine, inhibit human Coronavirus OC43 Infection of MRC-5 Human Lung Cells. *Biomol* 2019; 9.
<https://doi.org/10.3390/biom9110696>
68. Wen CC, Kuo YH, Jan JT, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem* 2007; 50: 4087-4095.
<https://doi.org/10.1021/jm070295s>
69. Koehn FE, Sarath GP, Neil DN, Cross SS. Halitunal, an unusual diterpene aldehyde from the marine algae *Halimeda tuna*. *Tetrahed Lett* 1991; 32: 169-172
[https://doi.org/10.1016/0040-4039\(91\)80845-W](https://doi.org/10.1016/0040-4039(91)80845-W)
70. Park JY, Kim JH, Kim YM, et al. Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. *Bioorg Med Chem* 2012; 20: 5928-5935.
<https://doi.org/10.1016/j.bmc.2012.07.038>
71. Chen CN, Lin CP, Huang KK, et al. Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3, 3'-digallate (TF3). *Evid-Based Complement Alter Med* 2005; 2: 209-215. <https://doi.org/10.1093/ecam/neh081>
72. Clark K, Grant P, Sarr A, et al. An *in vitro* study of theaflavins extracted from black tea to neutralize bovine rotavirus and bovine coronavirus infections. *Veter Microbiol* 1998; 63: 147-157.
[https://doi.org/10.1016/s0378-1135\(98\)00242-9](https://doi.org/10.1016/s0378-1135(98)00242-9)
73. Lin C-W, Tsai F-J, Tsai C-H, et al. Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. *Antivir Res* 2005; 68: 36-42
<https://doi.org/10.1016/j.antiviral.2005.07.002>
74. Ryu YB, Jeong HJ, Kim JH, et al. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. *Bioorg Med Chem* 2010; 18: 7940-7947.
<https://doi.org/10.1016/j.bmc.2010.09.035>
75. Yu MS, Lee J, Lee JM, et al. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. *Bioorg Med Chem Lett* 2012; 22: 4049-4054. <https://doi.org/10.1016/j.bmcl.2012.04.081>
76. Park JY, Yuk HJ, Ryu HW, et al. Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. *J EnzyInhib Med Chem* 2017; 32: 504-512. <https://doi.org/10.1080/14756366.2016.1265519>
77. Cheng PW, Ng LT, Chiang LC, Lin CC. Antiviral effects of saikosaponins on human coronavirus 229E *in vitro*. *Clin Exper Pharmacol Physiol* 2006; 33: 612-616.
<https://doi.org/10.1111/j.1440-1681.2006.04415.x>
78. Wu CY, Jan JT, Ma SH, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceed Nat Acad Sc* 2004; 101: 10012-10017.
<https://doi.org/10.1073/pnas.0403596101>
79. Cao J, Forrest JC, Zhang X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antivir Res* 2015; 114: 1-10
<https://doi.org/10.1016/j.antiviral.2014.11.010>
80. Yang CW, Lee YZ, Kang IJ, et al. Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. *Antivir Res* 2010; 88: 160-168.
<https://doi.org/10.1016/j.antiviral.2010.08.009>
81. Zhang CH, Wang YF, Liu XJ, et al. Antiviral activity of cepharanthine against severe acute respiratory syndrome coronavirus *in vitro*. *Chinese Med J* 2005; 118: 493.
82. Shen L, Niu J, Wang C, et al. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. *J Virol* 2019; 93: e00023-00019.
<https://doi.org/DOI:10.1128/JVI.00023-19>
83. Kwon H-J, Ryu YB, Kim Y-M, et al. *In vitro* antiviral activity of phlorotannins isolated from *Ecklonia cava* against porcine epidemic diarrhea coronavirus infection and hemagglutination. *Bioorg Med Chem* 2013; 21: 4706-4713.
<https://doi.org/10.1016/j.bmc.2013.04.085>
84. Zhuang M, Jiang H, Suzuki Y, et al. Procyanidins and butanol extract of Cinnamomi Cortex inhibit SARS-CoV infection. *Antivir Res* 2009; 82: 73-81
<https://doi.org/10.1016/j.antiviral.2009.02.001>
85. Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol* 2004; 78: 11334-11339.
<https://doi.org/10.1128/JVI.78.20.11334-11339.2004>
86. Kim DW, Seo KH, Curtis-Long MJ, et al. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of *Psoralea corylifolia*. *J Enzym Inhib Med Chem* 2014; 29: 59-63.
<https://doi.org/10.3109/14756366.2012.753591>
87. Schwarz S, Sauter D, Wang K, et al. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. *Planta Med* 2014; 80: 177-182
<https://doi.org/10.1055/s-0033-1360277>
88. Cho JK, Curtis-Long MJ, Lee KH, et al. Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of *Paulownia tomentosa*. *Bioorg Med Chem* 2013; 21: 3051-3057.
<https://doi.org/https://doi.org/10.1016/j.bmc.2013.03.027>
89. Roh C. A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. *Inter J Nanomed* 2012; 7: 2173
<https://doi.org/10.2147/IJN.S31379>
90. Chiow K, Phoon M, Putti T, et al. Evaluation of antiviral activities of *Houttuynia cordata* Thunb extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. *Asian Pac J Trop Med* 2016; 9: 1-7.
<https://doi.org/10.1016/j.apjtm.2015.12.002>
91. Müller C, Schulte FW, Lange-Grünweller K, et al. Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses. *Antivir Res* 2018; 150: 123-129. <https://doi.org/10.1016/j.antiviral.2017.12.010>
92. Wen CC, Kuo YH, Jan JT, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem* 2007; 50: 4087-4095.
<https://doi.org/10.1021/jm070295s>
93. Yang CW, Chang HY, Lee YZ, et al. The cardenolide ouabain suppresses coronavirus replication via augmenting a Na⁺/K⁺-ATPase-dependent PI3K-PDK1 axis signaling. *Toxicol App Pharmacol* 2018; 356: 90-97.
<https://doi.org/10.1016/j.taap.2018.07.028>
94. Yang CW, Lee YZ, Hsu HY, Shih C, et al. Targeting coronavirus replication and cellular JAK2 mediated dominant NF-κB activation for comprehensive and ultimate inhibition of coronavirus activity. *Sci Rep* 2017; 7: 1-13.
<https://doi.org/10.1038/s41598-017-04203-9>