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Prospection of antiviral compounds from forest plants under ongoing SARS-COV-2 pandemic

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Abstract

The COVID-19 pandemic is due to the spread of SARS-CoV-2, a virulent infectious coronavirus which created severe threats to the public health systems and global socioeconomic impact. It spreads over 221 countries and territories around the world and has reported a total of 130,954,934 confirmed cases with a death toll of 2,853,007. An indepth understanding of SARS-CoV-2 virus in terms of structure, variants, mechanism of infection, spread and impacts is needed to develop strategies to eradicate it. It is the condition that, India is facing second wave of SARS-CoV-2 spread in major cities like Mumbai, Delhi and Chennai. Since historic epidemics, most of the antiviral medicines are mainly developed based on medicinal plants with the aid of ethnobotanical records. Conventional medicine along with dietary therapy could be a complementary therapeutic measure to prevent and manage SARS-CoV-2 infections. Herbal drugs from medicinal and aromatic plants are major source for the development of novel antiviral drugs. Exploration of plants with numerous bioactive compounds of therapeutic importance remains mostly scanty. Identifying potential natural plant sources constitute an alternate to contain and prevent SARS-CoV-2 infection either by being a viricidal or by boosting the immune system is need of the hour. In order to prevent and contain the severe respiratory infections associated with the COVID 19 pandemic in the absence of potential medicines against the SARS-CoV-2 virus, search for antiviral compounds from natural resources gains importance. This article aimed to provide comprehensive list of plants and their active compounds of antiviral properties which would pave a way to develop herbal drug to prevent and contain SARS-CoV-2 infection.

1. Introduction

The exponential spread of the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a serious global threat to human health. Severe acute respiratory syndrome (SARS) is a respiratory illness caused by SARS-CoV-2 (Drosten *et al*., 2003; Ksiazek *et al*., 2003; Peiris *et al*., 2003b; Poutanen *et al*., 2003). This febrile respiratory illness was initially described in early 2003 (Chan-Yeung and Yu, 2003; Donnelly *et al*., 2003; Lee *et al*., 2003; Peiris *et al*., 2003a; Tsang *et al*., 2003). The potential to cause life-threatening respiratory failure and rapid transmission placed SARS-CoV-2 in public health emergency of international concern (PHEIC) list (Al-Qahtani, 2020). In the last two decades, the world has faced three important outbreaks of very pathogenic CoVs, including the emergence of SARS-CoV between 2002 and 2003, Middle East Respiratory Syndrome (MERS-CoV) in the year 2012 till date and now COVID-19 is the 3rd deadliest coronavirus pandemic. The coronavirus disease 2019 (COVID-19) pandemic (previously known as 2019-nCoV) was first discovered in the city of Wuhan, China, at the end of December 2019. In a very short period, an outbreak of apparent idiopathic pneumonia had become the COVID-19 pandemic and countries worldwide are comprehensively trying to find preventative measures or cure against the acute resolving disease COVID-19. This pandemic situation warrants us to develop novel antiviral drugs immediately to control and prevent the spread of SARS-CoV-2.

India predominantly relied on plant-based medications under different domain names like Ayurveda, Siddha, Unani, *etc*. Though, the advent of allopathic medicines has cornered the prevalence of plant-based treatments, the current pandemic emphasizes the need for revisiting those plants and studying those using advanced tools and approaches. Technological interventions are the need-of-the-time to dissect the medicinal value of plants for identifying suitable phytocompounds that could serve as potential molecules in treating SARS-CoV-2. In this present scenario, exploration of plants with bioactive molecules of antiviral property for the development of novel drug is much needed. Several antiviral active compounds from medicinal plants against some notable viral pathogens including coronavirus (CoV), coxsackie virus (CV), dengue virus (DENV), entero virus 71 (EV71), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), influenza virus, measles virus (MV), and respiratory syncytial virus (RSV) have been discovered, however, nature and composition of those plants and their mode of actions are not available for drug development. The age-old antimalarial drug chloroquine (Cq), introduced in 1945 and its analogue hydroxychloroquine (Hcq) could be potent therapeutic agents against COVID-19 (Tripathy *et al*., 2020). Quinine an alkaloid obtained from the bark of *Cinchona officinalis* has been used in the treatment of malaria since the 1960s (Achan *et al*., 2011). In SARS-CoV-2, Hcq in combination with

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azithromycin found to be more effective in reducing the viral load (Gautreta *et al*., 2020). Similarly, glycyrrhizin, a saponin isolated from *Glycyrrhiza glabra* roots is reported to be effective against SARS-CoV by inhibiting viral replication (Cinatl *et al*., 2003b). As an RNA virus, 2019-nCoV may have the same functional proteins to process virus replication and assembly to human immuno-deficiency virus (HIV). As a result, HIV protease inhibitors may also be effective for 2019-nCov. Currently, the combination of lopinavir/ritonavir (LPV/R), which has been proven effective in SARS-CoV and MERS-CoV, has been recommended for treatment in 2019-nCoV. It is also reported that around 35 drugs and vaccines are under clinical trials for amelioration of COVID-19. AYUSH, Ministry of Health, GOI, New Delhi has recommended various traditional formulations for both preventive and symptomatic management of COVID-19 (Table 1) with add on interventions to conventional care from Ayurvedha, Siddha, Unani, and Homeopathy. There are around 25 plant species reported to have inhibitory activity on ACE, IL and other proteins such as Transmembrane protease, serine 2 (TMPRSS2); 3-chymotrypsin-like protease (3CLpro); spike, RNA-dependent RNA polymerase (RdRp), and papain like protease (PLpro) which would lead to develop drug for SARS-CoV-2. This review throws the state of knowledge on the antiviral compounds from medicinal plants under ongoing SARS-COV-2 pandemic.

Table 1: This table depicts the Indian medicinal plants and its usage provided by the AYUSH, Government of India as a therapeutic approach for COVID-19

Indian medicinal plant	Form of extract	Trade name	Indian traditional medical practice	Preparation	Recommended usage	Effective against
Preventive and prophylactic						
Tinospora cordifolia	Aqueous	Samshamanivati	Ayurveda	Samshamanivati 500 g with warm water	Twice a day for 15 days	Chronic fever
Andrographis paniculata	Aqueous	Nilavembukudineer	Siddha	Nilavembukudineer 60 ml decoction	Twice a day for 14 days	Fever and cold
Cydonia oblonga	Aqueous	Behidanaunnab	Unani	Behidana-3 g Unnab-5 Nos	Twice a day for 14 days	Antioxidant, immunemodulatory antiallergic, smooth muscle relaxant, anti-influenza activity.
Zizyphus jujube *Cordia myxa*	Sapistan			Sapistan -9 Nos Boil these 3 in 250 ml water, boil it until it remains half and filter it.		
Arsenicum album 30	Tablet	*Arsenicum album* 30	Homeopathy		Daily once in empty stomach for 3 days (should be presented after 1 month till the infection persist).	Effective against SARS-CoV-2, immunemodulator.
Symptomatic management for COVID-19						
Ayush-64	Tablet	–	Ayurveda	–	2 tablets twice a day	Respiratory infection
Agastya haritaki	Powder	Agasthya rasayanam	Ayurveda	5 gm in warm water	Twice a day	Upper respiratory infection
Anuthaila	Oil	Sesame oil	Ayruveda	-	2 drops in each nostril daily morning	Respiratory infection
Adathodai manapagu	Aqueous	*Adathodai manapagu*	Siddha	-	10 ml twice a day	Fever
Bryonia alba	Tablet	Bryonia	Homeopathy	-	-	Reducing lung inflammation

Rhustoxicodendron	Tablet	Rhustox	Homeopathy	-	-	Viral infection
Atropa belladonna	Tablet	Belladonna	Homeopathy	-	-	Asthma and chronic lung diseases.
Bignonia sempervirens	Tablet	Geisemium	Homeopathy	-	-	Asthma
Eupatorium perfoliatum	Tablet	*Eupatorium perfoliatum*	Homeopathy	-	-	Respiratory symptoms
Add on interventions to the conventional care						
Vishasura kudineer	Tablet	Polyherbal formulation	Siddha	Decoction 60 ml	Twice a day	Fever
Kabasura kudineer	Tablet	Polyherbal formulation	Siddha	Decoction 60 ml	Twice a day	

(Ref: AYUSH Ministry of Health Corona Advisory - D.O. No. S. 16030/18/2019 - NAM).

2. Genomic organization and virus structure

Coronavirus (COVs) are encased in a positive stranded RNA that comes into the coronavirinae subfamily. In addition, the genetic material is surrounded by nucleocapsid proteins in the nucleus and envelope that contain four proteins, such as spike proteins, envelope proteins, and membrane proteins. The genome of the CoVs range is long from 26 to 32 kilobase, which is perhaps the largest known RNA virus.

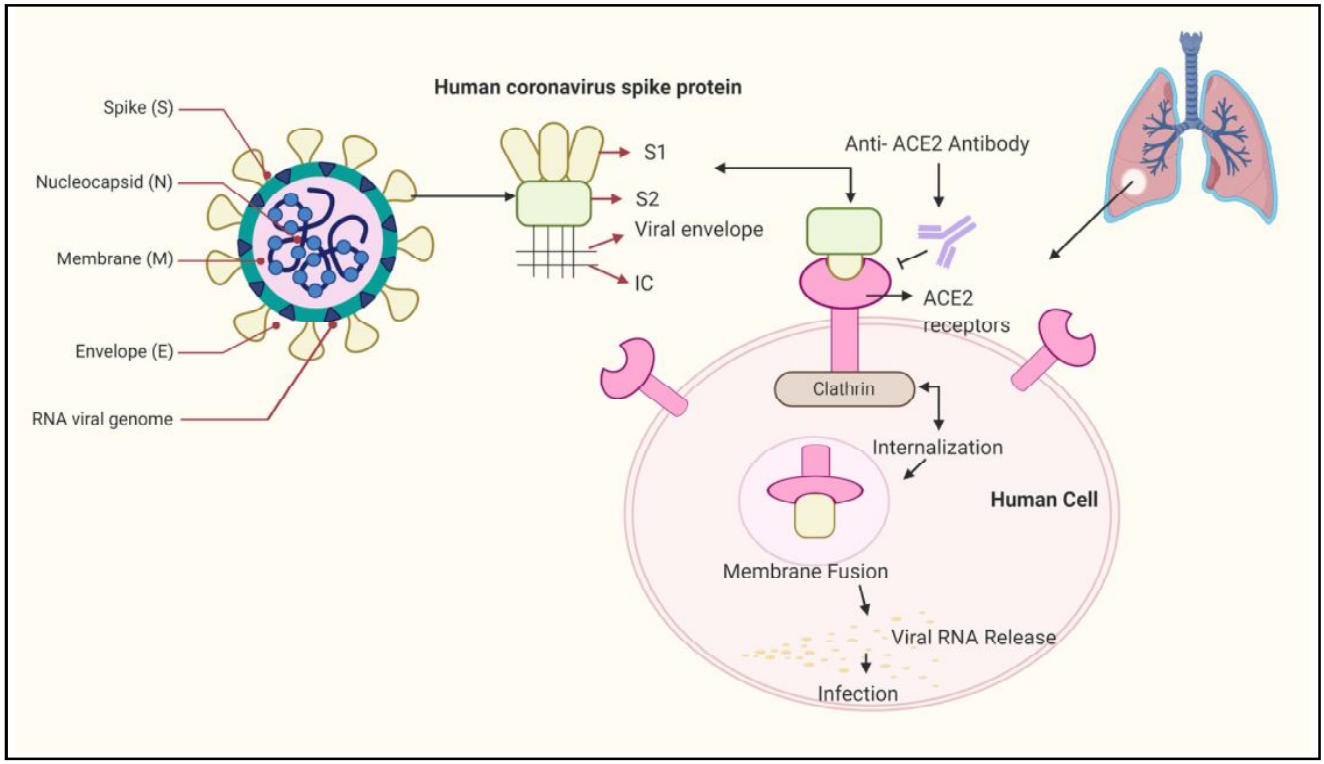

Figure 1: Mode of action of coronavirus (CoV). (Source: Vellingiri *et al.*, 2020).

Among the viral structure, the S protein has a major role in binding the virus to the host receptor cells. S protein has two subunits which are the S1 receptor-binding subunit and S2 the membrane fusion subunit; where the earlier one attached itself to the ACE2 receptor of the human host cell and the S2 subunit internalizes and creates the membrane fusion among the viral subunit and the ACE2 receptors. This leads to the release of the viral RNA into the host cell and results into respiratory infection.Therefore, exploration of biologically active compounds to inhibit the SARS-CoV-2 spike protein into ACE2 receptor is the main priority (Figure 1).

Coronaviruses are present in a number of bat and bird species that are thought to serve as natural hosts. Molecular clock dating coronavirus analyzes suggest that the most recent common ancestor of these viruses was about 10,000 years ago. This relatively young age contrasts dramatically with the ancient evolutionary past of

their supposed natural hosts, which started to diversify. It is found that the time for all coronaviruses common to the most recent ancestor is possibly much greater (millions of years) than the period previously inferred. In early 21st Century, severe acute respiratory coronavirus syndrome (SARS-CoV) and Middle East respiratory coronavirus syndrome (MERS-CoV) are the two major and highly infectious and pathogenic bat borne coronaviruses posed severe threats to humans.

3. Coronavirus cases in India

India's coronavirus tally rose to 4.37 million with a single-day spike of 89,706 infections, while the death toll crossed the 73,890 mark with 1115 fresh fatalities, according to the Union Health Ministry data. The recoveries surged to 3.39 million pushing the recovery rate to 78 per cent. Meanwhile, Indian companies have asked the Russian Direct Investment Fund (RDIF) to provide the technical details of phase 1 and phase 2 clinical trials of Russia's coronavirus vaccine, the world's first registered vaccine against the infection. However, countries like India using dietary therapy and herbal medicines to prevent SARS-CoV-2 infections could be a complementary COVID-19 therapy, while drugs remain under development. Hence, the present review provides an insight into look at antiviral compounds from medicinal plants for the development of drugs for SARS-CoV-2 (Table 2).

Table 2: List of selected clinical trials for the amelioration of COVID-19 specific drugs and vaccines

S.No.	Study	Drug	Status	Organizaion
1.	Evalution of the efficacy and safety of sarilumab in hospitalized patients with COVID-19	Sarilumab	Recruiting	Regeneron study site New York, United States
2.	Study to evalute the safety and antiviral activity of remdesivir in participants with severe coronavirus disease (COVID-19)	Remdesivir	Recruiting	Hoag Memorial Hospital Presbyterian Newport Beach, Californi, United States: Stanford Hospital, Stanford, California, United States: Providence Regional Medical Centre Everett, Everett, Washington, United States
3.	Fingolimod in COVID-19	Fingolimod 0.5 mg	Recruiting	Wan-Jin Chen Fuzhou, China
4.	The clinical study of carrimycin on treatment patients with COVID-19	Carrimycin Lopinavir/ ritonavir tablets or arbidol or chloroquine phosphate	Not recruiting	-
5	Efficacy and safety of corticosteriods in COVID-19	Methylprednisolone	Recruiting	Hubei Province Hospital of Integrated Chinese and Western Medicine Wuhan, Hubei, China Yichang First People s Hospital Yuchang, Hubei, China Renmin Hospital of Wuhan University Wuhan, China
6	Mild/moderate 2019 nCoV remdesivir	Remdesivir	Recruiting	Jin Yin-tan Hospital. Wu Han, Hubei, China
7	Adaptive COVID-19 treatment trial	Remdesivir	Recruiting	National Institutes of Health Clinical Center, National Institute of Allergy and Infectious Disease Laboratory of Immunoregulation, Clinical Research Section. Bethesda, Maryland, United State University of Nebraska Medical Center Infectious Diseases. Omaha, Nebraska, United States. University of Texas Medical Center Infectious Disease. Galveston, Texas, United States Providence Sacred Heart Medical Center Spokane, Washington, United states

8	Severe 2019-nCoV remdesivir RCT	Remdesivir	Recruiting	Bin Cao Beijing, Benijing, China
9	Nitric oxide gas inhalation for severe acute respiratory syndrome in COVID-19.	Nitric oxide gas	Not yet recruiting	-
10	Efficacy and safety of IFN- '2' in the treatment of novel coronavirus patients	Recombinant human interferons - '1'	Not yet recruiting	-
11	Evaluting and comparing the safety and efficacy of ASCO9/ritonavir and lopinavir/ ritonavir for novel coronavirus infection	ASCO9/ritonavir group Lopinavir/ritonavir group	Not yet recruiting	
12	Safety and immunogenicity study of 2019-nCoV vaccine (MRNA-1273) to prevent SARS-CoV-2 infection	mRNA-1273	Not yet recruiting	Kaiser Permanente Washington Health Research Institute Vaccines and Infectious Diseases
13	Glucocorticoid therapy for novel coronavirus critically III patients with severe acute respiratory failure	Methylprednisollone	Recruiting	Medical ICU, Peking Union Medical College Hospital Beijing, Beijing China
14	Lopinavir/ ritonavir, ribavirin and IFN-beta combination for nCoV	Lopinavir/ritonavir Ribavirin Interferon beta-1B	Recruiting	University of Hong Kong, Queen Marry Hospital Hong Kong, Hong Kong
15	Efficacy of chloroquine and lopinavir / ritonavir in mild/general novel coronavirus (COVID-19) infections: A prospective, open-label, multicenter randomized controlled clinical study	Chloroquine Lopinavir / ritonavir	-	The Fifth Affiliated Hospital Sun Yat-Sen University
16	A study for the efficacy of hydroxychloroquine for mild and moderate COVID-19 infectious diseases	Hydroxychloroquine	-	The Second Affiliated Hospital of Chongqing Medical University
17	A prospective, randomized, open-label, parallel controlled trial for the preventive effect of hydroxchlo-roquine on medical personnel after exposure to COVID-19	Hydroxychloroquine	-	Renmin Hospital of Wuhan University
18	The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19): multicenter randomized, open-label controlled trial	Carrimycin	-	Beijing Youan Hospital, Capital Medical University
19	A prospective clinical study for recombinant human interferon alpha infection in highly exposed medical staffs	Recombinant humaninterferon alpha 1b	-	Chinese PLA General Hospital
20	A pilot study of sildenafil in COVID-19	Sildenafil citrate	Recruiting	Department and Institute of Infectious Disease, Wuhan Hubei, China
21	Comparison of lopinavir/ ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19)	Lopinavir/ ritonavir hydroxychloroquine sulfate	Recruiting	Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of Korea

22	The efficacy and safety of thalidomide combined with low-dose hormones in the treatment of severe COVID-19	Thalidomide	Not yet recruiting	-
23	Various combination of protease inhibitors, oseltamivir, favipiravir, and chloroquine for treatment of COVID-19: A randomized control trial.	Oral	Not yet recruiting	Subsai Kongsaengdao, Bangkok, Thailand
24	Chloroquine prevention of coronavirus diseas (COVID-19) in the healthcare setting	Chloroquine	Not yet recruiting	-
25	Favipiravir combined with tocilizumab in the treatment of coronavirus disease 2019	Favipiravir combined with tocilizumab	Recruiting	Anhui Medical University Affiliated First Hospital, Hefei, Anhui, China Guiqjang Wang, Beijing, Beijing, China Peking University First Hospital, Beijing, China
26	Trial treatment for COVID-19 in hospitalized adults	Remdesivir Lopinavir/ ritonavir interferon beta-1A	Not yet recruiting	-
27	Randomized controlled trial of losartan for patients with COVID-19 losartan requiring hospitalization	Losartan	Not yet recruiting	Hennepin Country Medical Center, Minneapolis, Minnesota, United States M Health Fairview University of Minnesota, Medical Center, Minneapolis, Minnesota, United States University of Minnesota Medical Center, Minneapolis, Minnesota, United States
28	Evaluation of ganovo (danoprevir) combined with ritonavir in the treatment of novel coronavirus infection	Ganovo with ritonavir +/- Interferon	Recruiting	The Ninth Hospital of Nanchang Nanchang, Jiangxi, China
29	Eculizumab (soliris) in COVID-19 infected patients	Eculizumab	Initiated	-
30	Expanded access remdesivir (RDV; GS-5734™)	Remdesivir	Initiated	-
31	Norwegian coronavirus disease 2019 study	Hydroxychloroquine sulfate	Not yet recruiting	-
32	Post-exposure prophylaxis for SARS-coronavirus-2	Hydroxychloroquine	Recruiting	University of Minnesota Medical Center, Minneapolis, Minnesota, United States
33	The efficacy and the safety of pirfenidone capsules in the treatment of severe new coronavirus pneumonia (COVID-19)	Pirfenidone	-	Third Xizngya Hospital of Central South University

Source: Vellingiri *et al.* (2020)

Many researchers have determined the inhibitory ability of various active compounds from natural resources. Compounds such as asiatic acid, andrographolide, apigenin, brazilein, brazilin, catechin, curcumin, gingerol, hesperidin, hesperetin, kaemferol, luteolin, myricetin, naringenin and quercetin against the target protein of COVID-19, particularly ACE2, TMPRSS2, RdRp, 3CLpro and PLpro through molecular docking studies by evaluating the binding energy between the active compound and the target proteins are well known (Laksmiani *et al*., 2020). Laksmiani *et al*. (2020) reported few active chemical compounds in medicinal plants showed excellent affinity towards target protein proved that they can be used as antivirals against SARS-CoV-2. The active compounds from *Caesalpinia sappan* L. such as brazilein and brazilin had an excellent affinity towards ACE2. Hesperidin from Citrus sp. to TMPRSS2 with most negative value of docking score and lower binding energy value than drugs such as arbidol, chloroquine, camostatmesylate, remdesivir and lopinavir that used as inhibitor agent to COVID-19 (Laksmiani *et al*., 2020). Hence, the aforementioned medicinal plants could be a potential source of antivirals to develop drugs against SARS-CoV-2 through inhibiting ACE2, TMPRSS2, RdRp and protease (3CLpro and PLpro) that interfered the process of virus infection which causing pneumonia (Laksmiani *et al*., 2020). Glycyrrhizin isolated from *Glycyrrhiza glabra* roots was found effective in preventing the SARS-CoV replication (Cinatl *et al*., 2003a); myricetin from *Myrica rubra*, scutellarein from *Scutettaria baicalensis* and *Asplenium belangeri* are known to inhibit the ATPase activity of SARS-CoV helicase nsP13 (Yu *et al*., 2020); amentoflavone, quercetin, luteolin and apigenin from *Torreya nucifera* (Ryu *et al*., 2010) and emodin, sinigrin and hesperetin extracted from *Isatis indigotica* (Lin *et al*., 2005) have inhibit 3CLpro function. Water extract of *Houttuynia cordata* has antiviral activity against SARS-CoV due to its inhibitory effect on 3C-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) of the virus; lycorine from *Lycoris radiate* (Li *et al*., 2005); 13 mannose-binding lectins identified to possess a robust anti-coronaviral activity (Keyaerts *et al*., 2007). Another lectin, agglutinin isolated from *Galanthus nivalis*, was effective against FCoV when administered in combination with a synthetic drug nelfinavir (Hsieh *et al*., 2010). Recently, resveratrol (trans-3, 5, 42-trihydroxystilbene) a natural stilbene derivative present in abundance in *Vitis vinifera*, *Polygonum cuspidatum*, and as *Vaccinium macrocarpon* showed inhibition of MERS-CoV infection (Lin *et al*., 2017).

Sivaraman and Pradeep (2020) and Vellingiri *et al*. (2020) had underlined the positive side of this plant-based concoction that keeps the infection levels at bay. Identification of the antiviral mechanisms from these natural agents has helped to understand how and where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus-host-specific interactions. It has been shown that natural plants (Table 3) contain antiviral activities to coronaviruses (McCutcheon *et al*., 1995) and the mechanism of action is to inhibit viral replication (Vlietinck and Vanden Berghe, 1991; Jassim and Naji, 2003). The Table 3 provides ethnobotanical details with respect to SARS - severe acute respiratory syndrome, MERS-Middle East respiratory syncytial virus, ARVI-Acute respiratory viral infections.

Table 3: List of ethnobotanicals and their mode of action against CoV

S. No.	Plant source	Mechanism of action	Target	Virus	References
1	*Acacia nilotica*	Inhibition	-	HIV-PR	Mishra *et al*., 2014
2	*Allium sativum*	Proteolytic and hemagglutinating activity and viral replication	-	SARS	Keyaerts *et al*., 2004
3	*Andrographis paniculata*	Suppression	NLRP3, Capase-1, and IL-1]	SARS-COV and likely SARS-COV-2	Liu *et al*., 2020a, 2020b
4	*Boerhaavia diffusa*	Inhibition	ACE	-	Prathapan *et al*., 2013; Khan and Kumar, 2019
5	*Clerodendrum inerme*	Inactivation	Ribosome	SARS-CoV-2	Olivierir *et al*., 1996
6	*Clitoria ternatea*	Metalloproteinase inhibitor	ADAM17	-	Maity *et al*., 2012
7	*Coriandrum sativum*	Inhibition	ACE	-	Pandey *et al*., 2011
8	*Cynara scolymus* *Cassia occidentalis* *Cascinium fernestratum*	Inhibition	ACE	-	Prathapan *et al*., 2013; Khan and Kumar, 2019
9	*Embelia ribes*	Inhibition	ACE	-	Prathapan *et al*., 2013; Khan and Kumar, 2019
10	*Eugenia jambolana*	Inhibition	Protease	-	Otake *et al*., 1995
11	*Euphorbia granulata*	Inhibition	-	HIV-1PR	Mishra *et al*., 2014
12	*Glycyrrhiza glabra*	Inhibition of viral replication: Modulaton of membrane fluidity	-	SARS; HIV-1	Akamatsu *et al*., 1991; Cinatl *et al*., 2003a; Fiore *et al*., 2008
13	*Gymnema sylvestre*	Inhibition of viral DNA synthesis	-	-	Vimalanathan *et al*., 2009; Arun *et al*., 2014

14	*Hyoscyamus niger*	Inhibition and Bronchodilator	Ca2+	-	Gilani *et al*., 2008
15	*Ocimum lilimandscharicum*	Inhibition	-	HIV-1	Thayilseema and Thyagarajan, 2016
16	*Ocimum sanctum*	Inhibition	-	HIV-1	Rege and Chewdhary, 2014
17	*Punica granatum*	Inhibition	ACE	-	Prathapan *et al*., 2013; Khan and Kumar, 2019
18	*Salacia oblonga*	Suppression	Angio tensin II, ATI Signal	-	He *et al*., 2011
19	*Sambucus ebulus*	Inhibition	-	Enveloped virus	Ganjhu *et al*., 2015
20	*Solanum nigrum*	-	-	HIV-1	Yu, 2004
21	*Sphaeranthus indicus*	Inhibition	-	Mouse coronavirus and Herpesvirus	Galani *et al*., 2010 Tiwari and Khosa, 2009; Vimalanathan *et al*., 2009
22	*Strobilanthes callosa*	Blocking	-	HCoV-NL63	Tsai *et al*., 2020
23	*Strobilanthes cusia*	Blocking	-	HCoV-NL63	Tsai *et al*., 2020
24	*Vitex negundo*	Inhibition	-	HIV-1	Nair, 2012
25	*Vitex trifolia*	Reduction	-	SARS-CoV	Liou *et al*., 2018

Note: HIV-IPR: Human Influenza Virus -1 Protease; SARS; Severe Acute Respiratory Syndrome; SARS-CoV: Severe Acute Respiratory Syndrome-Coronavirus; ACE-Angiotensin converting enzyme; HIV-1; Human Influenza Virus-1; gp120; Envelope Glycoprotein 120; CD4; Cluster of Differentiation; HCoV-NL63; Human coronavirus Nl62; RNA ; Ribonucleic acid; MHV-A59; Mouse Hepatitis Virus-A59; Ca2+: Calcium ion; NLRP3: NLR Family Pyrin Domain Containing 3; ATI-Angiotensin 1; HCoV-NL63: Human Coronavirus-NL63.

Table 4: Bioproducts against CoV

Extracts or preparations	Test system	Test dose/ concentration	Proposed mechanism	IC50 or EC50 value	References
Lycorisradiata	SARS-CoV	10^{-1} – 10^{-4} mg/ml	Undefined	2.4 ± 0.2 µg/ml	Li *et al*., 2005
Artemisia lingua	SARS-CoV	10^{-1} – 10^{-4} mg/ml	Undefined	34.5 ± 2.6 µg/ml	Li *et al*., 2005
Pyrrosia lingua	SARS-CoV	10^{-1} – 10^{-4} mg/ml	Undefined	43.2 ± 14.1 µg/ml	Li *et al*., 2005
Lindera aggregate	SARS-CoV	10^{-1} – 10^{-4} mg/ml	Undefined	88.2 ± 7.7 µg/ml	Li *et al*., 2005
Isatis indigotica	SARS-CoV	1-500 µg/ml	3CL protease inhibition	-	Li *et al*., 2005
Extract of *Rheum officinale* and *Polygonumm ultiflorum*	SARS-CoV	0-100 µg/ml	Inhibits the interaction of SARS-CoV S protein and ACE2.	1 to 10 µg/ml	Ho, Wu, Chen, Li, and Hsiang, 2007
Houttuynia cordata aq. Extract	SARS-CoV	0-400 µg/ml	3CL protease and viral polymerase inhibition	-	Lau *et al*., 2008
Herbal extracts (*Gentiana scabra, Dioscorea batatas, Cassia tora, Taxillus chinensis, Cibotium barometz*)	SARS-CoV	25-200 µg/ml	3CL protease inhibition	39 µg/mL and 44 µg/mL (Two extracts of *Cibo-tiumbarometz*)	Wen *et al*., 2011
Anthemis hyaline, *Nigella sativa* and *Citrus sinensis* extracts	Coronavirus infected HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule Ia cells inoculated with MHV-A59 (Mouse hepatitis virus-A59)	1/50 and 1/100 dilution of ethanolic extract (100 g/200 ml)	Increased IL-8 level, Significantly changed the expression of TRPA1,TRPC4, TRPM^, TRPM7, TRPM8 and TRPV4 genes	-	Ulasli *et al*., 2014

4. Natural products inhibiting virulence effect of CoV infection

Nature provides a vast library of chemicals to explore and develop drugs for treatment of various ailments including viral diseases (Denaro *et al*., 2019). Natural products and their derivatives are used in folk medicine will have always played a crucial role in drug development process against various diseases, which resulted in screening of such agents to combat emergent mutants of coronavirus (Ganjhu *et al*., 2015). There is a vast scope for herbal medicines in the view of nutraceuticals market (Williamson *et al*., 2020). Interestingly, the acceptability and, therefore, research on plant based drugs are growing on a daily basis. Some natural products have been found to exhibit their antiviral activity through the inhibition of viral replication (Moghadamtousi *et al*., 2015; Oliveira *et al*., 2017). Apart from plant derived compounds (Jardim *et al*., 2018), several marine natural products (Wang *et al*., 2014) as well as biotechnologically produced compounds (Neumann and Neumann Staubitz, 2010) are also reported for their antiviral properties against different viruses. Along this line, *Nigella sativa* demonstrated its inhibitory activity against hepatitis C virus (Oyero *et al*., 2016). General mechanism for antiviral activity of most of the natural products is inhibition of viral replication and some natural products (*e.g*., lycorine, homoharringtonine, silvestrol, ouabin, tylophorine and 7 methoxycryptopleurine) have interacted with important virulent viral proteins (Table 4).The natural compounds, procyanidin A2, procyanidin B1, and cinnamtannin B1, isolated from *Cinnamomi cortex* inhibited SARS-CoV infection at 0-500 µM (Zhuang *et al*., 2009). On the other hand, tetra *O* galloyl beta D glucose, luteolin, and tetra *O* galloyl beta D glucose blocked the host cell entry of SARS-CoV at $0–10^{-3}$ mol/l (Yi *et al*., 2004). In another study, bavachinin, neobavaisoflavone, isobavachalcone, 4' *O* methylbavachalcone, psoralidin, and corylifol isolated from *Psoralea corylifolia* inhibited papain like protease of SARS-CoV (Kim *et al*., 2014). Interestingly, psoralidin exhibited a strong protease inhibitory effect on SARS-CoV with an IC_{50} value 4.2 µM, whereas emodin, rhein, and chrysin inhibited interaction of SARS-CoV (S) protein and ACE2 at 0-400 µM (Ho *et al*., 2007). Listed in Table 4 are crude extracts and Table 5 are isolated compounds that display activity against CoV. In addition, a good number of natural products with anti coronavirus activity are the major constituents of some common dietary supplements, which can be exploited to improve the immunity of the general population in certain epidemics. Lin *et al*. (2014) reported a good number of herbal medicines have shown potential antiviral activity.

Table 5: Efficacy of secondary metabolites and their derivatives against CoV infection

Compounds (Biological source)	Test system mechanism	Dose concentration	Proposed	IC_{50} or EC_{50} value	References
Aloe emodin (*Isatis indigotica*)	SARS-CoV	1-100 µg/ml	3CL protease inhibition	8.3 µM	Lin *et al*., 2005
Amentoflavone (*Torreya nucifera*)	SARS-CoV	1-1000 µM	3CL protease inhibition	8.3 µM	Ryu *et al*., 2010
Apigenin (*Torreya nucifera*)	SARS-CoV	1-1000 µM	3CL protease inhibition	280.8 µM	Ryu *et al*., 2010
Bavachinin (*Psoralea corylifolia*)	SARS-CoV	1-150 µM	Inhibitors of papain like protease (PLpro).	38.4 ± 2.4 µM	Kin *et al*., 2014
Berbamine	HCoV-NL63	0-20 µM	Undefined	1.48 µM	Kin *et al*., 2019
Beta-sitosterol (*Isatis indigotica*)	SARS-CoV	1-100 µg/ml	3CL protease inhibition	1210 µM	Lin *et al*., 2005
Betulonic acid	SARS-CoV	0-10 µM	Inhibition of replication	0.63 µM	Wen *et al*., 2007
Betulonic acid	SARS-CoV	8-80 µM	3CL protease inhibition	10 µM	Wen *et al*., 2007
Betulonic acid	SARS-CoV	8-80 µM	3CL protease inhibition	>100 µM	Wen *et al*., 2007
Broussochalcone A (*Broussonetia papyrifera*)	3-chymotrypsin -like and papain -like coronavirus cysteine proteases	0-200 µM	Protease inhibition	-	Park *et al*., 2017
(-) Catechingallate and (-) Gallocatechingallate	SARS-CoV	0.001-1 µg/ml	Inhibition of nanoparticle-based RNA oligonucleotide	-	Roh, 2012

Cepharanthine	SARS-CoV	0.5-10 µg/ml	Protease inhibition	9.5 µg/ml	Zhang *et al*., 2005
Cepharanthine	HCoV-OC43-infected MRC-5 human lung cells	2-20 µM	Undefined	0.83 ± 0.07 µM	Kim *et al*., 2019
Cinanserin (1dpi) (*Houttuynia cordata*)	Murine CoV	500-15.63 µg/ml	Undefined	31.25 µg/ml	Chiow *et al*., 2016
Cinanserin (2dpi) (*Houttuynia cordata*)	Murine CoV	15.63-500 µg/ml	Undefined	62.50 µg/ml	Chiow *et al*., 2016
Cinnamtannin B1 (*Cinnamomi cortex*)	SARS-CoV	0-500 µM	Inhibition of pseudovirus infection	32.9 ± 3.9 µM	Zhuang *et al*., 2009
Chrysin (5,7-dihydroxy-flavone)	SARS-CoV	0-400 µM	Inhibited interaction of SARS-CoV (S) protein and ACE2	-	Ho *et al*., 2007
Concanavalin A	-	-	Lose the haemaagglutina-tion properties of the virus envelope and acause datransient interference with infectivity	-	Greig and Bouillant, 1977
Corylifol (*Psoralea corylifolia*)	SARS-CoV	1-150 µM	Inhibitors of papain like protease (PLpro)	32.3 ± 3.2 µM	Kim *et al*., 2014
Curcumin	SARS-CoV	8-80 µM	Inhibition of 3CL protease	40 µM	Wen *et al*., 2007
Dieckol (*Ecklonia cava*)	Porcine epidemic diarrhea CoV	1-200 µM	Inhibition of viral replication	14.6 ± 1.3 µM	Kwon *et al*., 2013
Diplacone (*Paulownia tomentosa*)	SARS-CoV	0-100 µM	Inhibition of papain like protease	10.4 ± 0.16 µM	Chow *et al*., 2013
3ß,12-diacetoxyabieta-6,8,11,13-tetraene	SARS-CoV	0-10 µM	Inhibition of replication	1.57 µM	Wen *et al*., 2007
1-(4,5-Dihydroxy-3-hydroxymethylcy-clopente-2-enyl)-1H-1,2,4-triazole-3-carboxylic acid amide	SARS-CoV	-	Undefined	21 µM	Cho *et al*., 2006
1-(4,5-Dihydroxy-3-hydroxymethylcy-clopente-2-enyl)-1H-1,2,4-triazole-3-carboxylic acid amide	SARS-CoV	-	Undefined	47 µM	Cho *et al*., 2006
Eckol (*Ecklonia cava*)	Porcine epidemic diarrhea CoV	1-200 µM	Blockage of the binding of virus to cells	22.5 ± 2.2 µM	Cho *et al*., 2013
Emetine	HCoV-OC43, HCoV-NL63,MERS-CoV and MHV-A59	0-5 µM	Inhibited RNA,DNA and Protein synthesis	0.30,1.43, 0.34 and 0.12 µM	Shen *et al*., 2019
Emodin (1,3,8-trihyd-roxy-6-methylanthra-quinone)	SARS-CoV	0-400 µM	Inhibited interaction of SARS-CoV (S) protein and ACE2	200 µM	Ho *et al*., 2007
Fangchinoline	HCoV-OC43-infected MRC-5 human lung cells	2-20 µM	Undefined	1.01 ± 0.07 µM	Kim *et al*., 2019
Ferruginol	SARS-CoV	0-10 µM	Inhibition of replication	1.39 µM	Wen *et al*., 2007
6-geranyl-4',5-7-trihy-droxy-3',5'-dimethoxy-flavanone (*Paulownia tomentosa*)	SARS-CoV	0-10 µM	Inhibition of replication	13.9 ± 0.18 µM	Cho *et al*., 2013
Halituna (*Halimeda tuna*)	Murine coronavirus A59	-	Undefined	-	Koehn *et al*., 1991

Hesperetin (*Isatis indigotica*)	SARS-CoV	1-100 µg/ml	3CL protease inhibition	365 µM	Lin *et al*., 2005
Hexachlorophene	Murine CoV (MHV-2aFLS)	0-10 µM	Undefined	1.2 µM	Cao *et al*., 2015
Hinokinin	SARS-CoV	8-80 µM	3CL protease inhibition	>100 µM	Wen *et al*., 2007
Homoharringtonine	Murine CoV (MHV-2aFLS)	0-70 nM	Undefined	12nM	Cao *et al*., 2015
4-Hydroxyisolon-chocarpin (*Broussonetia papyrifera*)	3-chymotrypsin-like and papain-like coronavirus cysteine proteases	0-200 µM	Protease inhibition	-	Park *et al*., 2017
Hygromycin B (*Streptomyces hygroscopicus*)	Mouse hepatitis virus (MHV-A59)	0-1 µM/kg	Reduced virus replication and necrotic liver foci	-	Macintyre *et al*., 1991
8ß-hydroxyabieta -9(11),13-dien-12-one	SARS-CoV	0-10 µM	Inhibition of replication	1.47 µM	Wen *et al*., 2007
Indigo (*Isatis indigotica*)	SARS-CoV	1-100 µg/ml	3CL protease inhibition	752 µM	Lin *et al*., 2005

5. Conclusion

COVID-19 a newly emerged upper respiratory tract viral respiratory disease caused by the coronavirus, Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) is identified from China, in December 2019, spreads rapidly across worldwide. A novel coronavirus disease (COVID-19) is zoonotic and also transmitted from human-to-human rapidly leading to pandemic responsible for the current global health crisis. COVID-19 spreads over 221 countries and territories around the world with total confirmed cases of 130 million and 2.84 million deaths. While drugs remain under development, using conventional medicines along dietary therapy are recommended by AYUSH, Govt. of India to prevent and boost immunity to tackle SARS-CoV-2 infections. Exploration of antiviral compounds from medicinal plants to develop drugs for SARS-CoV-2 is highly warranted.

6. Solution strategy to combat COVID-19

The spectrum of symptoms associated with COVID-19 ranges from difficulties in breathing and other respiratory conditions to critical conditions including kidney failure, heart attack and sometimes even death and, therefore, the following strategies have been recommended to avoid spread of COVID-19.

- Avoiding International and domestic travels to spread the infection from severely affected areas/countries.
- Individuals are likely to be infected by others who have been inflicted with the virus. The disease can spread from person-to -person *via* small droplets from nose or mouth when a person with COVID-19 coughs or exhales; these particles in the air, settle on surfaces in the environment further infecting people who breathe these particles or touch these places and then touch their body parts, and hence 6 feet physical distance is recommended (WHO, 2020).
- Reports suggest that older persons and persons with pre-existing medical conditions (such as high blood pressure, heart disease, lung disease, cancer or diabetes) appear to develop serious illness more often than others, and hence co-morbid patients must be treated with utmost care.
- Also, it has been reported that some of the Asian populations are more susceptible to acquire this COVID-19 infection when compared to the other races populations, needs special attention.
- National Institute of Health (NIH) has mentioned that SARS-CoV-2 could survive for upto 3 h maximum as aerosols to a maximum of three days on surfaces.
- Slowing the spread of the COVID-19 cases will significantly reduce the strain on the healthcare system of the country by limiting the number of people who are severely sick by COVID-19 and need hospital care.
- So, it is time for all the citizens to join hands together to fight against coronavirus by practicing self-hygiene and physical distancing.
- WHO is coordinating efforts to develop medicines to prevent and treat COVID-19.
- India as a front runner developed an indigenous COVID vaccine COVAXIN along with COVISHIELD (the Oxford-AstraZeneca vaccine) and started vaccination campaign on 16th January, 2021. As of 31st March 2021, India's vaccination programme has given 65.1 million doses of vaccine with 9.3 million Indians having had two doses, and targeted to vaccinate 30 crores in near future.

7. Dietary therapy and herbal medicine could be used against COVID-19 in the following four ways

- Diet or supplement for infection prevention and immunity strengthening.
- Application as antiviral agent on masks.
- Air disinfection agent to stop aerosol transmission of the virus.
- Surface sanitizing agent to afford a disinfected environment.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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