Journal of Medicinal Herbs and Ethnomedicine 2023, 9: 1-17
doi: 10.25081/jmhe.2023.v9.7340
https://updatepublishing.com/journal/index.php/jmhe

Review Article

ISSN: 2455-0485

Antiviral medicinal plants of India as a potential tool against COVID-19: A review with ethno scientific evidence

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Received: October 20, 2022
Revised: December 05, 2022
Accepted: December 08, 2022
Published: March 23, 2023

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ABSTRACT

Indian traditional medicinal systems are one of the oldest therapeutic systems in the world. Medicinal and aromatic plants play a dominant role in Indian traditional medicinal systems. Traditionally, many medicinal plants are used in India for their therapeutic relevance so much so that they have acquired a significant role in Indian religion as well. Many of these plants have proven antiviral effects. This review documents up-to-date information about many such medicinal herbs used in India which have got pharmacological significance in fighting viral infections. These plants surely have the potential to provide protection against Covid-19. The review presents a list of such plants along with their chemical ingredients and possible modes of action against the respective viral diseases. All information has been obtained by consulting the databases of Scopus, PubMed, Science Direct, Elsevier, Springer and relevant research papers and reports on COVID-19. The cited medicinal plants are used extensively in India as herbal remedies. The use of these plants is validated in light of research papers citing their ethnobotanical uses, important active principles and modes of action of the of medicinally important natural products. The plants listed have great potential to fight COVID-19 and other viral infections. Many of these are immunity boosters providing strength to the body to control the onset of diseases.

KEYWORDS: COVID-19, Medicinal herbs, Viral diseases, Herbal remedy, Immunity boosters, Active principle

INTRODUCTION

While medicinal plants have been used to treat viral infections in the past, the effort of the Boots drug company (Nottingham, England) to screen 288 plants for anti-influenza activity was the first recognized step in the production of antiviral agents (Chantrill *et al.*, 1952). Since then, more than 90 drugs from various functional groups have been approved for the treatment of viral infections, including Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV), Hepatitis C virus (HCV) and influenza virus (DeClercq & Li, 2016). The production of safe and novel antiviral drugs has been necessitated by the high prices and adverse side effects of synthetic drugs. Herbal extracts have emerged as a novel option for the development of antiviral drugs that target various stages of the virus replication cycle. Many of the currently available medicines for microbial infections are derived from plants. One/fourth of the widely used medicines contain at least one active compound derived from plants (Farnsworth & Soejarto, 1991). Ethnobotanical sources also corroborate the fact that the various traditional medicines used in India are mainly obtained from medicinal plants (Ahvazi *et al.*, 2007).

Introduction to Coronavirus

Coronavirus has been described as a pathogen that causes disease and death as a result of massive alveolar damage and progressive respiratory failure. According to the WHO report, Coronavirus pandemic has globally affected more than 100 million people and killed more than 2904686 people as of 8th April 2021.Coronavirus disease, 2019 has been abbreviated and named as COVID-19 by WHO on 11th February 2020. A simple Google search suggests there is an upsurge in the number of Coronavirus related papers (almost 30.44 times) published in scientific journals in 2020 (Figure 1). This pandemic has caused havoc worldwide, affecting almost more than half of the entire human world population due to its contagious nature and high transmission rate.

Coronavirus belongs to the Coronaviridae family of Nidovirales order. Coronavirus (CoV) are microscopic virus particles with an encapsulated positive single-stranded RNA of 26-32 kb (largest RNA genome), infecting humans as well as animals. It is divided into alpha, beta, gamma and delta subgroups and almost all the known human targeting CoVs belong to either the alpha subgroup i.e., Human CoV-NL63 and CoV-229E or the beta subgroup i.e., Human CoV-OC43, HKU1 (Human Coronavirus), SARS-CoV (Severe acute respiratory syndrome-coronavirus), MERS-CoV (Middle East respiratory syndrome-coronavirus) and the recently emerging SARS-CoV-2 (Lu *et al.*, 2015). In 2002-2003, the first 'Severe Acute Respiratory Syndrome' (SARS-CoV) epidemic was caused by Coronavirus in Guangdong, China and approximately 10 years later 'Middle East Respiratory Syndrome' (MERS-CoV) outbreak occurred in the Middle East in 2012. Further, by the end of 2019, Wuhan in China witnessed the flare-up of novel Coronavirus (nCov-19) which has been currently keeping the world on its toes with its global outbreak in 2020. The International Committee on Taxonomy of Viruses (ICTV) named it as SARS-CoV-2 (Zhang *et al.*, 2020).

Origin and Transmission

The initial outbreak of coronavirus reported from the Hunan market of Wuhan in China leads to the presumption of an intermediate animal source for respective viral attacks in humans (Andersen *et al.*, 2020). Bats are the reservoir of many viruses including SARS-CoV and MERS-CoV (Hu *et al.*, 2015). It was observed that the genetic constitution of SARS-CoV-2 is similar to CoV RATG of bats by 96.2% and 79.5% identical to SARS-CoV (Guo *et al.*, 2019). Although $RATG_{13}$ is approximately 96% similar to SARS-CoV-2, divergence in the receptor binding domain of the spike leads to inefficacy in binding to human Angiotensin-converting enzyme 2 (ACE2) receptors present in the cells of the respiratory tract (Andersen *et al.*, 2020).

Clinical Symptoms

Symptoms of Coronavirus differ from one person to another. Probably, depending on the immunity and medical history, a person may show mild to severe symptoms proving to be fatal or asymptomatic (Guan *et al.*, 2020). The common symptoms of COVID-19 include fever, sore throat, dry cough, muscle pain, and shortness of breath; sometimes, symptoms like nausea and diarrhea are also observed. Severe symptoms lead to lung and kidney damage and can prove to be fatal (Chen *et al.*, 2020). The incubation period of the virus is 2-14 days after being exposed to the virus. Older people along with people suffering from diabetes, cardiovascular disease, respiratory problems and other medical problems tend to develop more severe symptoms (By CDCP 2019).

Structure of Coronavirus

Coronaviruses are encapsulated particles with a central core of nucleocapsid proteins enclosing a single-stranded positive RNA and the surface envelope embedded with 'spikes' i.e., glycoprotein projections. The spikes play an important role in attachment to the host cell receptors (Tyrrell & Myint, 1996). In addition to receptor binding, spikes play an important role in virus-host membrane integration, antibody neutralization and mediating entrance of viruses into the host. The spike glycoprotein is trimeric in nature with a single unit of S protein (Ou *et al.*, 2020). The receptor-binding domain (RBD) of S protein binds to the human angiotensin-converting enzyme (hACE2) (Wrapp *et al.*, 2020) present in epithelial cells of lung alveoli and noticed in absorptive cells lining the small intestine as well (Hamming *et al.*, 2004).

Comparison of SARS-CoV and SARS-CoV-2 also implies that the latter is evolved to bind more strongly to the ACE2 receptor. The receptor binding domain has conserved regions of antigen for antibodies to interact and thus serves as a potential target for cross-reactive antibody therapy against coronavirus (Lan *et al.*, 2020). Protease, papain-like protease (PLpro) from the coronavirus causes severe acute respiratory syndrome (SARS-CoV). This is a unique protease because it is not only responsible for processing the viral poly protein into its functional units but it is also capable of cleaving ubiquitin and ISG15 conjugates and plays a significant role in helping SARS-CoV evade the human immune system (Ratia *et al.*, 2008). SARS-CoV-2 shows 77.5% and 50% sequence homology with SARS-CoV and MERS-CoV respectively (Kim *et al.*, 2020). Due to these similarities, medicinal plants and their derivative compounds which have been used to treat SARS-CoV and MERS-CoV can also be used as potent inhibitors of SARS- CoV-2. Another important aspect of the Coronavirus which may serve as the most probable drug target is the Main Protease, also called 3CLpro. Upon transcription, the coronavirus genome produces a polypeptide that undergoes enzymatic cleavage to result in a non-structural protein constituting the viral replication machinery. 3-chymotrypsin like protease (3CLpro) produces its cleavage activity at 11 different sites of the polypeptide (Anand *et al.*, 2003).

With the main protease being the major drug target so far and along with the current development and clinical trials of a drug or vaccine, the best way to cope with the nCoV-19 without any major side effects is to rely on the medicinal plants which constitute a holistic effect of various compounds from boosting immunity to treating infections. Thus, medicinal plants can serve as a potential source to deal with this novel coronavirus due to active compounds like flavonoids such as quercetin which can degrade dengue virus envelope protein (Mir *et al.*, 2016), protease inhibiting compounds (Majumdar, 2013) which may inhibit 3CLpro, terpenoids etc. and show effective antiviral activity (UlQamar *et al.*, 2016). Also, the compounds obtained from medicinal plants against nCoV-19 can be used as a potential source to design a virus-targeting drug. In this review, we focus on the phytochemicals derived from various medicinal plants which are used in India as antiviral agents that can also serve as the potential therapeutic source against novel coronavirus.

Natural Medicine to Control Virus

In the development of human civilization, medicinal plants always played a critical role. Plants have been used for thousands of years to prevent epidemics, treat health disorders and control diseases besides providing a variety of nutritional foods. The

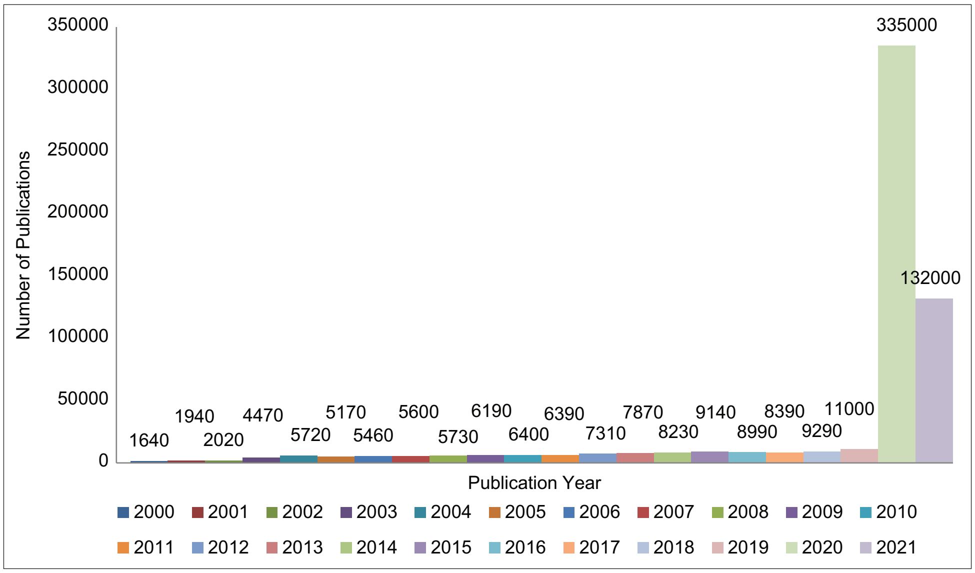

Figure 1: Year-wise publications in scientific journals once "Coronavirus" was entered as a keyword (In total, 187810 articles were found collectively)

two important traditional systems of medicine, Traditional Indian Medicine (TIM) i.e., Ayurveda, and Traditional Chinese Medicine (TCM) system are used extensively for the treatment of diseases (Patwardhan *et al.*, 2005). All 6 systems of medicine that are recognized in India, *viz*., Ayurveda, Yoga, Siddha, Unani, Naturopathy and Homeopathy, depend a lot on the use of medicinal plants and their chemical components (Ravishankar & Shukla, 2007). Among all these systems, medicinal plants are traditionally being used as primary health care against many diseases. Hence, medicinal plants are very rightly called as "backbone of traditional medicine." About 3.3 million people utilize medicinal plants in less developed countries on a regular basis (Davidson–Hunt, 2000). Plants-based therapies rely on different kinds of secondary metabolites produced by the plants which are responsible for their biological activities. These metabolites possess antiviral, antibacterial, antioxidant, anti-inflammatory and antispasmodic effects. Table 1 enlists several vegetables, fruits and medicinal plants commonly used in India for antiviral effects with Solanaceae and Zingiberaceae contributing a maximum number of antiviral plants followed by Euphorbiaceae, Acanthaceae, Rutaceae, Fabaceae and Lamiaceae (Figure 2). Many of these plants are also used as ethnomedicine in different parts of the world (Table 2).

The compound called withanone isolated from *Withania somnifera* (L.) Dunal may inhibit novel Coronavirus-19 by disrupting the interaction between host ACE 2 and viral spike-protein Receptor Binding Domain (RBD) (Varshney *et al.*, 2020). Another compound Withaferin A (WA), an active compound isolated from *W. somnifera* act against H1N1 influenza (Cai *et al.*, 2015). This compound also inhibits herpes simplex virus (HSV) (Grover *et al.*, 2011). Roots of *W. somnifera* are also used against β-amyloid (1–42)-induced cytotoxicity in HIV-1Ba-L (clade B) infection (Kurapati *et al.*, 2016).

Similarly, *Ocimum sanctum* L. and *Azadirachta indica* A. Juss., the two high-value important medicinal plants have exceptionally significant antimicrobial activity. Due to their excessive use in Indian systems of medicine, these plants have acquired very high religious significance in Hinduism, the age-old religion in India. Natural compounds from *O. sanctum* (Tulsi) and *A. indica* (Neem) have high binding efficacy against SARS-CoV-2 targets (Kumar, 2020). Oleanolic acid, methyl eugenol and ursolic acid show high binding potential with surface spike glycoprotein and RNA polymerase in SARS-CoV-19. Epoxy-azadiradione, gedunin show efficacy against m-protease of SARS-CoV-19. Active compounds from *O. sanctum* also inhibit replication and protein synthesis in the Swine flu H_1N1 virus (Joshi, 2014). Tulsi strengthens the immune response by enhancing both cellular and humoral immunity by boosting the cell-mediated immune responsiveness and gamma-aminobutyric acid (GABA) (Mukherjee *et al.*, 2005). Eugenol and other essential oils from *O. sanctum* considerably improve immune response due to immuno-stimulating effects (Sen, 1993). *A. indica* bark is known to block the entry of Herpes Simplex Virus (HSV) (Tiwari *et al.*, 2010). Two compounds from neem namely, rutin and tiplasinin have been used against influenza strains (Ahmad *et al.*, 2015).

Tinocordiside, berberine, magnoflorino and isocolumbinare the naturally occurring compounds isolated from *Tinospora cordifolia* (Willd.) Miers (Giloy) have the potential to inhibit the 4 key targets (surface glycoprotein, receptor binding domain, RNA-dependent RNA polymerase and main protease) in SARS-CoV-2 (Sagar & Kumar, 2020). Active compounds isolated from Giloy can also be used against Herpes Simplex Virus-1 (HSV-1) (Pruthvish & Gopinatha, 2018). Giloy was also used as a potent inhibitor against H1N1 flu due to its immunostimulant property (Yasmin *et al.*, 2020). Besides the above-mentioned compounds, agglutins from *Nicotiana tabacum* L. (tobacco), *Urtica dioica* L. (stinging needle) and *Morus nigra* L. (Black mulberry) are also reported to inhibit viral attachment in case of SARS-CoV (Keyaerts *et al.*, 2007).

Table 1: Plants with antiviral potential

S. No.	Vernacular Name	Scientific Name	Family	Key compound	Viral disease	Mode of action	References
1	*Bhui* Amla	*Phyllanthus amarus* Schumach. & Thonn.	*Phyllanthaceae*	Quercetin, Ellagicacid, Rutin, luteolin, kaempferol, quinic acid, andursolic acid	AIDS	Inhibit HIV replication (blocking the interaction of HIV-1 gp120 with its primary cellular receptor CD4)	Notka *et al.*, 2004
					Hepatitis B	Inhibition of mRNA transcription	Lee *et al.*,1996
					Hepatitis C	Inhibition of mRNA transcription	Ravikumar *et al.*, 2011
2	Chankapiedra	*Phyllanthus niruri* L.	Euphorbiaceae	Nirurin, ent-norsecurin, Quercetin, rutin, astragalin, isoquercitrin, kaempferol-4-rhamnopyranoside	Hepatitis B	Inhibits DNA polymerase, binds to the surface antigen of hepatitis B virus	Venkateswaran *et al.*, 1987
3	Amla	*Emblica officinalis* Gaertn.	Euphorbiaceae	EGCG, theaflavin digallate, resveratrol (RV), hydroxytyrosol	Influenza A	Reduction of plasma membrane, accumulation of nucleoprotein (NP) at the late stage of the replication cycle	Liu *et al.*, 2011
4	Kalmegh	*Andrographis paniculata* (Burm. f.) Nees	Acanthaceae	Andrographolide, neoandrographolide	Dengue fever	Inhibit replication and pyrimidine biosynthesis	Tang *et al.*, 2012
					Herpes simplex virus 1	Not determined (ND)	Wiart *et al.*, 2005
					Influenza A	block binding of virus on RBC receptors	Chen *et al.*, 2009
5	Haldi	*Curcuma longa L.*	Zingiberaceae	Curcumin	HIV	Inhibition of HIV-1 and HIV-2 proteases	Sui *et al.*, 1993
					Influenza	Inhibition of haemagglutination	Chen *et al.*, 2010
					Herpes simplex virus (1&2)	Reduction of replication	Kutluay *et al.*, 2008; Zandi *et al.*, 2010;
					Coxsackievirus	Replication inhibition through UPS dysregulation	Si *et al.*, 2007
					Hepatitis B	Suppression of HBV replication by increasing the p53 level	Kim *et al.*, 2009
					Human papilloma virus (HPV)	Inhibition expression of viral oncoproteins of E6 and E7	Divya & Pillai, 2006
					Japanese encephalitis virus (JEV)	Reduction in production of infective viral particles	Dutta *et al.*, 2009
					Severe acute respiratory syndrome (SARS)	Inhibition expression of Mpro protease	Kim *et al.*,2008
6	Indian saffron	*Curcuma zanthorrhiza* Roxb.	Zingiberaceae	Demethoxycurcumine,	Hepatitis B	Reduction of replication	Devaraj *et al.*, 2010
7	White Himalayan Rue	*Boenninghausenia albiflora* (Hook.) Rchb. ex Meisn.	Rutaceae	Leptodactylone, rutarensin, rutamarin	SARS-CoV	Not determined	Yang *et al.*, 2007
					Kaposi's sarcoma-associated herpesvirus (KSHV)	Replication inhibition	Xu *et al.*, 2014
8	Nargis	*Narcissus tazetta* L.	Amaryllidaceae	Narcissus tazetta lectin (NTL) protein	Influenza A and B	Replication inhibition	Ooi *et al.*, 2010
9	Orchid	*Listera ovata* (L.) R.Br.	Orchidaceae	Lectins-mannose-specific protines	HIV	Inhibit virus cell binding	van Damme *et al.*, 1994
					SARS-CoV	ND	Keyaerts *et al.*, 2007
10	Adrak	*Zingiber officinale* Rosc.	Zingiberaceae	Gingerol, β-sitosterol shogaol, dehydrogingerdione	Chikungunya	Replication inhibition	Kaushik *et al.*, 2020
					HIV	Inhibiton of Reverse Transcriptase (RT) enzyme	Kharisma *et al.*, 2018
					COVID-19	Inhibition expression of Mpro protease	Rathinavel *et al.*, 2020

(*Contd...*)

Table 1: (*Continued*)

S. No.	Vernacular Name	Scientific Name	Family	Key compound	Viral disease	Mode of action	References
11	Giloy	*Tinospora sinensis* (Lour.) Merr.	Menispermaceae	Berberine, Isocolumbin, Magnoflorine Tinocordiside	SARS-CoV-2	Inhibition expression of viral protease (6Y84) and RNA dependent RNA polymerase (6M71)	Sagar *et al.*, 2020
					Influenza A	Inhibition expression of viral protease	Saikia *et al.*, 2019
					HIV	ND	Gupta *et al.*, 2010
12	Mulathee	*Glycyrrhiza glabra* L.	Fabaceae	Glycyrrhizin, Licorice, Glycyrrhizic acid	JEV	Inhibition of viral replication	Badam, 1997
					HIV	Inhibition of viral replication	De Clercq, 2000
					Herpes Simplex type I	Inhibition of viral replication	Pompei *et al.*, 1979
13	Ashwagandha	*Withania somnifera* L.Dunal	*Solanaceae*	Withaferin-A, Withanone	Herpes Simplex type I	Inhibit virus cell binding	Kambizi *et al.*, 2007
					HIV 1 and 2	Inhibition expression of viral protein	Asres *et al.*, 2001
					SARS-CoV-2	Inhibition expression of viral protease	Kumar *et al.*, 2020
14	Gheekumari	*Aloe vera* (L.) Burm.f.	Asphodelaceae	aloin A , aloin B, elgonica dimer A, feralolide, isoaloeresin D, aloeresin E	HSV-1 & 2	Inhibition of viral replication	Zandi *et al.*, 2007
15	Neem	*Azadirachta indica* A. Juss.	Meliaceae	kaempferol-3-Orutinoside, rutin, hyperoside, epicatechin, quercetin	Dengue virus	Inhibition expression of viral protease (NS2B-NS3pro)	Dwivedi *et al.*, 2021
					Coxsackie virus B	ND	Badam *et al.*,1999
					poliovirus type 1 (PV-1)	Inhibition of replication of PV-1	Faccin-Galhardi *et al.*, 2012
					HCV	Inhibition expression of viral protease (NS3/4A)	Ashfaq *et al.*, 2016
16	Jamun	*Syzygium cumini* (L.) Skeels	Myrtaceae	Caffeic acids, Citronellol, Eugenol, Ferulic acids, Kaempferol	Influenza (H5N1)	ND	Ramya *et al.*, 2012; Sood *et al.*, 2012
17	Purple coneflower	*Echinacea purpurea* (L.) Moench	Asteraceae	cichoric acid	HSV-1&2	Inhibition of replication	Thompson, 1998
					HIV	Cytochrome P450 (CYP) 3A and P-glycoprotein activity	Robinson, 1998; Penzak *et al.*, 2010
					Influenza A	Influence activity of Cytochrome P450 and P- Glycoprotine in human	Pleschka *et al.*, 2009
18	Elderberry	*Sambucus nigra L.*	Adoxaceae	Kaempfero, Quercetin, Catechin, Epicatechin, Cyanidin-3-rutinoside	HIV	Inhibition expression of viral protease	Uncini *et al.*, 2005
					Influenza A& B	Inhibit virus-cell binding	Serkedjieva *et al.*, 1990; Roschek*et al.*, 2009
					SARS-CoV	Inhibition of replication	Keyaerts *et al.*, 2007
19	Tulsi	*Ocimum sanctum* L.	Lamiaceae	Eugenol, methyl eugenol, caryophyllene, cirsilineol, cirsimaritin, rosmarinic, Quercetin	HSV-1 & 2	ND	Jadhav *et al.*,2012
					New Castle Disease virus (NDV)	ND	Jayati *et al.*, 2013
					HSV 2	Inhibition of replication	Chiang *et al.*, 2005
20	Chakrphool	*Illicium angustisepalum* A.C. Sm.	Schisandraceae	cis- and trans-anethole, α-pinene, farnesol, β-phellandrene, α-terpineol, llicinone A 23-dioic acid	Newcastle disease virus (NDV)	ND	Alhajj *et al.*, 2020
					HIV	ND	Song *et al.*, 2007
					HSV	Inhibition of replication	Astani *et al.*, 2011
					SARS-CoV-2	Inhibition expression of viral protease (Mpro)	Silva *et al.*, 2020

(*Contd...*)

Table 1: (*Continued*)

S. No.	Vernacular Name	Scientific Name	Family	Key compound	Viral disease	Mode of action	References
21	Shatavari	*Asparagus racemosus* Willd.	Asparagaceae	Asparanin A, Muzanzagenin, Asparagamine A, Rutin, Shatavarin, Tinocordiside, 20-βHydroxy Ecdysone	HIV-1	Inhibit virus cell binding (glycoprotein gp120/41 and the cellular receptor protein CD4)	Panvilai *et al.*, 2020
					SARS-CoV-2	Inhibition expression of viral protease	Borse *et al.*, 2020
22	Saag	*Spinacia oleracea* L.	Chenopodiaceae	Kaempferol	SARS-CoV-2	Inhibition expression of viral protease (Mpro)	Talleii *et al.*, 2020
23	Ban tulsi	*Origanum vulgare* L.	Lamiaceae	caffeoylquinic acids, C-glycosides, 2,5-dihydroxybenzoic acid, rosmarinic acid, luteolin	Animal herpesviruses	ND	Fernandes *et al.*, 2012
					Influenza (H1N1)	ND	Vimalanathan & Hudson, 2012
					Coxsackie virus B3	ND	Zhang *et al.*, 2014
24	Pyaz	*Allium cepa* L.	Liliaceae	Quercetin Hexadecanoic acid Tricosane Isopropyldithioisopropane	HSV-1	Inhibition expression of viral protease	Romeilah *et al.*, 2010
					Adenoviruses (ADV)	ND	Chen *et al.*, 2011
25	Shimla mirch	*Capsicum annuum* L.	Solanaceae	β-ionone camphor thymol benzoic acid	Newcastle disease virus (NDV)	ND	Eggink *et al.*, 2012; Hanif *et al.*, 2016;
26	Sweet orange	*Citrus sinensis* (L.) Osbeck	Rutaceae	Myricetin, Naringenin, Naringin, Neryl-acetate, Pcymene, Quercetin, Rutin, Scutellarein, Stigmasterol, Subaphyllin	coronavirus (CoV)	Inhibition of replication and expression of TRP genes	Sathya & Gopalakrishnan, 2013; Ulasli *et al.*, 2014
27	Kushmul	*Berberis lycium* Royle	Berberidaceae	Baberine Chenabine, Diphenolic, Palmatine, Gilgitine, Jhelumine, Kara-koramine	Hepatitis C	ND	Ikram, 1975; Yousaf *et al.*, 2018
28	Chaay	*Camellia sinensis* (L.) Kuntze	Theaceae	Epigallocatechin-3-Gallate (EGCG), Epicatechin Gallate (ECG), Epigallocatechin (EGC)	Infectious Laryngotrachietis Virus (ILTV)	ND	Zaher *et al.*, 2008
					Feline calicivirus (FCV)	Suppression the level of ROS	Oh *et al.*, 2013
					Influenza A (H1N1)	Inhibition of replication	Ling *et al.*, 2012
					HIV-1	ND	Li *et al.*, 2011
					Enterovirus 71 (EV71)	Inhibition of replication	Ho *et al.*, 2009
					HSV-1	ND	De Oliveira *et al.*, 2013
29	Lahsun	*Allium sativum* L.	Alliaceae	Alliin, Allicin, E-Ajoene	Human cytomegalovirus (HCMV)	Inhibition of replication	Zhen *et al.*, 2006
					Influenza B	ND	Tsai *et al.*, 1985
30	*Calamus*/ Ghorbach	*Acorus calamus L.*	Araceae	Tatanan, b-asarone, a-asarone	Dengue virus (DENV)	Inhibition of RNA replication	Rajput *et al.*, 2014
					SARS CoV2/COVID 19	Inhibition expression of viral protease (Mpro)	Krishnasamy *et al.*, 2020
31	Papita	*Carica papaya* L.	Caricaceae	Chlorogenic acid, 5, 7-dimethoxycoumarin kaempferol quercetin	Dengue virus	Inhibition expression of viral protease (NS2B-NS3 serine protease)	Senthilvel *et al.*, 2013; Sharma *et al.*, 2019
					SARS CoV2/COVID 19	Inhibition expression of viral protease (Mpro)	Yang *et al.*, 2020
32	Aam	*Mangifera indica* L.	*Anacardiaceae*	Mangiferin	HSV-2	Inhibition of replication	Zhu *et al.*, 1993
					HIV	ND	Guha *et al.*, 1996
33	Mungna/ saijna	*Moringa oleifera* Lam.	Moringaceae	niazimicin, niazirin, beta-sitosterol, kaempferide	NDV	ND	Chollom *et al.*, 2012
					HIV	Inhibition of replication	Nworu *et al.*, 2013
34	Mokoi	*Solanum nigrum* L.	Solanaceae	Rutin, Gallic acid, Protocatechuic acid	Hepatitis C	Inhibition expression of viral protease (NS3)	Javed *et al.*, 2011
					HIV-1	Inhibition of replication	Yu, 2004

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Table 1: (*Continued*)

S. No.	Vernacular Name	Scientific Name	Family	Key compound	Viral disease	Mode of action	References
35	Babul	*Acacia nilotica* (L.) Delile	*Fabaceae*		Hepatitis C	Inhibition expression of viral protease (NS3-4A protease)	Rehman *et al.*, 2011
36	Sankuppi	*Clerodendrum inerme* (L.) Gaertn.	Verbenaceae	cirisimaritin, pectolinarigenin, apigenin	SARS CoV	Inhibition expression of Ribosome	Olivieri *et al.*, 1996
37	Arus	*Justicia adhatoda* L.	Acanthaceae	alpha-Sitosterol, Amrinone, Pentadecanoic Acid, Stigmasterol	Influenza	Inhibition of viral attachment and/or viral replication	Chavan & Chowdhary, 2014
38	Isabgol	*Plantago major* L.	Plantaginaceae	caffeic acid, chlorogenic acid, Luteolin,	Adenoviruses (ADV)	Inhibition of viral attachment and/or viral replication	Chiang *et al.*, 2002
				p-coumaric acid	HSV-1 & 2	Enhancing secretion of interferon-γ	Chiang *et al.*, 2003
39	Harad	*Terminalia chebula* Retz.	Combretaceae	chebumeinin A, chebumeinin B, Ellagic acid, Gallic acid,	Hepatitis B	Inhibition of replication	Chung *et al.*, 1997
				Chebulic acid	Hepatitis C	Inhibition expression of viral protease (NS3-4A protease)	Ajala *et al.*, 2014

Table 2: Ethnobotanical uses of plants

S. No.	Scientific Name	Ethnobotanical uses	References
1	*Phyllanthus amarus* Schumach. & Thonn.	In jaundice paste or fresh roots are given orally.	Balakrishnan *et al.*, 2009
		Whole plant is taken as an antimalarial.	Upadhyay *et al.*, 2010
2	*P. niruri* L.	The fresh roots powder for jaundice.	Singh, 1986
		Decoction of dried leaves is taken orally for indigestion and used in bath for fever.	Weniger *et al.*, 1986
3	*Emblica officinalis* Gaertn.	Leaf juice are used in dysentery and gonorrhea.	Narayan & Singh, 2017
4	*Andrographis paniculata* (Burm. f.) Nees	Paste of leaves is applied externally on bitten site of scorpion sting and snakebites.	Samy *et al.,* 2008
		Leaf extract is applied for various skin allergies.	Thomas *et al.*, 2013
5	*Curcuma longa L.*	Paste of leaves used for asthma.	Velayudhan *et al.*, 2012
		One glass of milk with two teaspoons turmeric powder used in cold and influenza.	Bouzabata & Boukhari, 2014
6	*C. zanthorrhiza* Roxb.	Tuberous root sap used for heartburn.	Sujarwo & Caneva, 2015
		Rhizome used for stomachache.	Rahayu & Andini, 2019
7	*Boenninghausenia albiflora* (Hook.) Rchb. ex Meisn.	Leaves are used to kill the bed bug.	Singh, 2008
		Leaves are used for cuts.	Singh *et al.*, 2014
8	*Narcissus tazetta* L.	Flower and bulb juice taken with milk for skin disease and wounds.	Gürdal & Kültür, 2013
		Whole plant used for blood purification.	Khan *et al.,* 2015
9	*Listera ovata* (L.) R.Br.	Tincture of tubers used for externally skin tone.	Tamm, 1972
		Whole herb is boiled and used for indigestion.	Shapoo *et al.*, 2013
10	*Zingiber officinale* Rosc.	Rhizome powder paste used for cough and vomiting.	Ahmad *et al.*, 2018
		Rhizome powder used for muscular pain.	Kumar & Pandey, 2015
11	*Tinospora sinensis* (Lour.) Merr.	Stem part used in gonorrhea and chlamydia.	Acharya & Pokhrel, 2006
		Extract of its stem along with bark of *Alstonia scholaris* (L.) R. Br. is taken twice a day for Dysentery.	Saha *et al.*, 2014
12	*Glycirrhiza glabra* L.	Stem and root decoction used for cold, stomach pain, back pain and bone fractures.	Nasab & Khosravi, 2014
		Root decoction used for Pectoralgia.	Dolatkhahi *et al.*, 2014
13	*Withania somnifera* L.Dunal	Whole plant used for bronchitis and ulcer.	Jabeen *et al.*, 2010
		Leaves are applied on tumour glands.	Rashid & Marwat, 2006
14	*Aloe vera* (L.) Burm.f.	Leaf pulp is used to promote menstrual flow and mixed leaf pulp in turmeric powder and applied on eyes to relieve eyes pain.	Shende *et al.*, 2014
15	*Azadirachta indica* A. Juss.	Fresh leafy twigs are used for spraying cow's urine inside the hut to keep away insect and mites.	Ayyanar *et al.*, 2010
		Juice made from young leaves mixed with excess water of boil rice used in worm.	Anisuzzaman *et al.*, 2007
16	*Syzygium cumini* (L.) Skeels	Leaves paste used for indigestion.	Ayyanar & Ignacimuthu, 2011
		Its bark is used as digestive.	Nadkarni & Nadkarni, 1976
17	*Echinacea purpurea* (L.) Moench	Leaves and flower powder used for influenza.	Korkmaza *et al.*, 2016
		The roots used to treat blood poisoning, snake poisoning, skin disease.	Kumar & Ramaiah, 2011

(*Contd...*)

Table 2: (*Continued*)

S. No.	Scientific Name	Ethnobotanical uses	References
18	*Sambucus nigra* L.	Flowers are used for inflammation, lowers fever and colds.	Jarić *et al.*, 2007
		Leaves and inner bark have also been used for their purgative, emetic, diuretic, topical emollient, expectorant, and diaphoretic action.	Kultur, 2007
19	*Ocimum sanctum* L.	Leaf juice used for glaucoma, cataract, chronic conjunctivitis & other painful eye diseases.	Surkar *et al.*, 1994
		Leaves used for skin disease.	Jain *et al.*, 2010
20	*Spinacia oleracea* L.	Whole plant used for asthma and leprosy.	Kumar & Singh, 2019
		Seeds used for fevers, inflammation of the liver and jaundice.	Kumar & Singh, 2019
21	*Origanum vulgare* L.	Whole plant Used in bronchitis, colic and diarrhea.	Tiwari*et al.*, 2016
		Leaves Flowering branches used for Cold and flu.	Polat & Satıl, 2012
22	*Allium cepa* L.	Bulbus used for sprain and edema.	Ugulu, 2011
		Bulbus used as Tonic and for colds, cough.	Singh & Singh, 2009
23	*Capsicum annuum* L.	Fruits used for snakebite, scarlatina.	Ishtiaq *et al.*, 2007
		Fruits are eaten during loss of appetite, indigestion and to 'purify blood'.	Kichu *et al.*, 2015
24	*Citrus sinensis* (L.) Osbeck	Peels and fruits used as mosquito repellant.	Obata & Aigbokhan, 2012
		Leaf decoction used for cold.	Camejo-Rodrigues *et al.*, 2003
25	*Berberis lycium* Royle	Fresh leaves decoction is taken orally for Jaundice.	Abbasi *et al.*, 2013
		Roots decoction used for diabetes and body pain.	Ahmad *et al.*, 2018
26	*Camellia sinensis* (L.) Kuntze	Root, flower decoction used for hypertension and coughing.	Au *et al.*, 2008
		Leaves used for Hepatitis.	Amiri & Joharchi, 2013
27	*Allium sativum* L.	Bulbils extract used for Bee bite and high blood pressure.	Bulut & Tuzlaci, 2015
		Bulbils extract used for treating whooping cough in children.	Jarić *et al.*, 2015
28	*Acorus calamus L.*	Roots used for pneumonia and cough.	Hossan *et al.*, 2009
		Roots used for snake bite, liver disorder and cold.	Balakumbahan *et al.,* 2010
29	*Carica papaya* L.	Roots and leaves used for typhoid, stomach upset, malaria and diarrhea.	Saotoing *et al.,*2011
		Fruits and decoction of leaves used for constipation.	Abe & Ohtani, 2013
30	*Mangifera indica* L.	Kernels of mango used for diarrhoea.	Sairam *et al.*, 2003
		Leaves are inhaled to get relief from throat infections.	Narayanan *et al.*, 2011
31	*Moringa oleifera* Lam	Leaves and seeds are used for diabetes, anemia and high blood pressure.	Abe & Ohtani, 2013
32	*Solanum nigrum* L.	Leaves extract used for washing painful eyes.	Abbasi *et al.*, 2013
		Leaves and fruits are used as liver tonic.	Singh *et al.*, 2014
33	*Acacia nilotica* (L.) Delile	Dysentery, asthma and stomachache.	Rashid *et al.*, 2015
		Gum used in cough, bark used for diarrhea.	Hussain *et al.*, 2008
34	*Clerodendrum inerme* (L.) Gaertn.	Leaf paste is used in fever.	Partha, 2014
		Bathing with the leaf decoction is claimed to be effective against fever.	Bhandary *et al.*, 1995
35	*Justicia adhatoda* L.	Whole plant used for jaundice and hepatitis.	Abbasi *et al.*, 2009
		Crushed leaves applied on chest for pneumonia treatment.	Vijayan, 2007
36	*Plantago major* L.	Leaves and roots are used for wound healing.	Azizi & Keshavarzi, 2015
		Leaf used for coughs, stomach ulcers and insect bites.	Jarić *et al.*, 2015
37	*Terminalia chebula* Retz	Seeds and fruits for indigestion.	Sahu *et al.*, 2013
		Fruits used for intestinal ulcer.	Ayyanar & Ignacimuthu, 2011

Similarly, andrographolide from *Andrographis paniculata* (Burm. f.) Nees (green chireta) can be used as a potent inhibitor of the main protease of SARS-COV-2 (Mpro) (Enmozhi *et al.*, 2020). Bis-andrographolide ether and 6 other compounds isolated from the aerial parts of *A. paniculata* showed anti-HIV and cytotoxic activity as well (Niranjan *et al.*, 2005). Andrographolide inhibits the production of mature viral particles(Pongtuluran *et al.*, 2015). Compounds *viz*., α- Hederin and Nigellidine isolated from another medicinal plant cum Indian spice, *Nigella sativa* L. (Kalonji), might inhibit the activity of COVID-19 by acting on the main protease (Mpro) (Bouchentouf & Missoum, 2020). Besides, the *N. sativa* mixture is also found to have virucidal activity as it reduces viral load significantly along with the symptoms of HIV infection (Onifade *et al.*, 2013). *N. sativa* modulates the pro and anti-inflammatory cytokines and acts as a balancing factor between Th1/Th2 lymphocytes (Gholamnezhad *et al.*, 2014).

Glabrin B, shinpterocarpin, glabridin, glycyrrhetic acid, hispaglabridin A, licochalcone A, prenyllicoflavone, apioside A, liquiritigenin, isoliquiritin, liquiritinapioside, shinflavanone and isoliquiritigenin like phytochemicals isolated from *Glycyrrhiza glabra* L. (Yashtimadhu) act against SARS-CoV-2 main protease (Mpro). Glycyrrhetic acid, apioside, glabridin, liquiritinapioside, shinpterocarpin and shinflavanone are the key phytochemicals isolated from *G. glabra* that act against human ACE2 receptor and their different protein residues which are involved in the interaction (Maurya, 2020). Glycyrrhizin, an active compound of liquorice roots is found to inhibit the

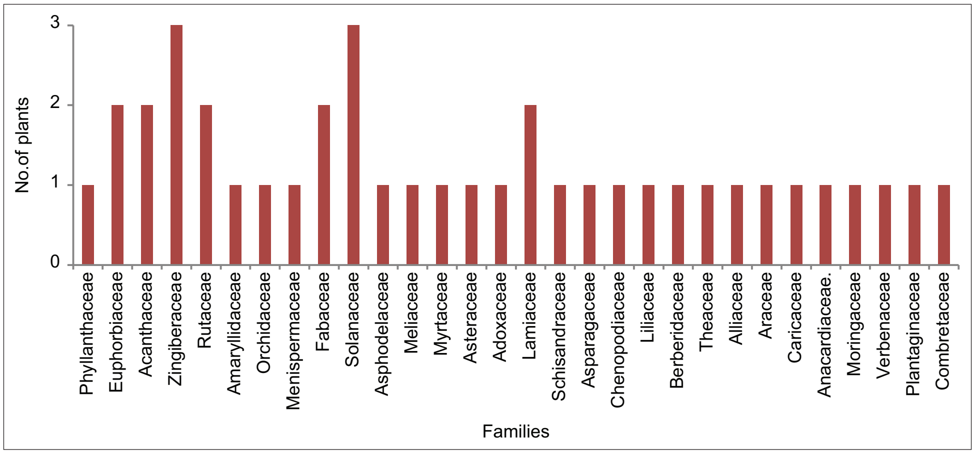

Figure 2: Percent (%) contribution of reported plant families as source of antiviral compounds

replication of the SARS-associated virus (Cinatl *et al.*, 2003). Glycyrrhizin (GL) is also used in infection against the influenza A virus (IAV) (Wolkerstorfer *et al.*, 2009). Likewise, essential oils *viz.*, allyldisulfide and allyltrisulfide account for 51.3% of total essential oils isolated from *Allium sativum* L. (Garlic), have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2 (Thuy *et al.*, 2020). All these compounds have huge potential to be used as potent inhibitors against SARS-CoV-2. *A. sativum* and *A. cepa* L. (onion) contain organosulphur compounds like quercetin and allicin which are also associated with the inhibition of viral infection. Quercetin shows effect on entry and attachment of Enterovirus and Influenza virus. This compound also inhibits RNA polymerase which is necessary for viral infection. Organosulphur compounds allicin, diallyl trisulphide and ajoene are the main chemical compounds that are responsible for the antiviral activity of garlic (Sharma, 2019). Chemical compounds present in garlic are also used in the treatment of cancer, diabetes, atherosclerosis and hyperlipidemia (Gebreyohannes & Gebreyohannes, 2013).

Astragalin, lupeol and nictoflorin isolated from *Nyctanthes arbor-tristis* L. (Harsingar) and aloenin and aloesin from *Aloe barbadensis* Miller can also be used as inhibitors of COVID-19 protease (Srivastava *et al.*, 2020). *Aloe* polysaccharides (APS) extracted from *A. vera* leaves inhibit the replication of the H1N1 subtype influenza virus (Sun *et al.*, 2018). Punicafolin from *Phyllanthus emblica* L. (Indian gooseberry), amaroswerin from *Swertia chirata* Buch.-Ham. ex Wall (Chirayta), heptacosanol from *Eclipta prostrata* L. (Bhringraj) have binding affinity for inhibition of spike protein. Amarogentin from *S. chirata*, azadirachtin and rutin from *A. indica*, phyllanemblinin A from *P. emblica* L. also inhibits M-Pro protein in case of COVID-19 (Ranjan, 2020).

One of the major phytoconstituents isolated from *Rheum emodii* Wall. (Indian Rhubarb) i.e., emodin is also reported to have an inhibitory effect on the interaction of SARS-CoV. It has been also found that emodin blocks both the binding of the SARS-CoV S protein to ACE2 and the infectivity of the S- protein (Bilal *et al.*, 2013). Theaflavin, an active compound isolated from *Camellia sinensis* (L.) Kuntze (tea plant) could also be used against SARS-CoV-2 as it binds with RNA-dependent RNA polymerase of COVID-19 (Lung *et al.*, 2020). Catechin from *C. sinesis* (green tea) and curcumin from *Curcuma longa* (turmeric) also have a dual binding affinity. Both these molecules bind to ACE2 and viral S-protein. Curcumin binds directly to the receptor binding Domain (RBD) of viral S-protein. Catechin binds with ACE2 and S-protein (Jena *et al.*, 2020). Curcumin also inhibits Chikungunya and Zika virus replication. Curcumin mainly works by interfering with virus cell binding (Mounce *et al.*, 2017) and shows inhibition against Influenza virus infection and exhibit haemagglutination activity (Chen *et al.*, 2010).

Dandelion, *Taraxacum officinale* (L.) Weber ex F.H.Wigg, inhibits the influenza virus infection by inhibiting the viral polymerase activity and the reduction of the virus nucleoprotein (NP) RNA (He *et al.*, 2011). Likewise, 6-gingerol extracted from the rhizome of *Zingiber officinale* Roscoe have a binding affinity with various COVID-19 viral proteins and thus could be used as a potential choice to treat COVID-19 (Rathinavel *et al.*, 2020). Fresh ginger by stimulating mucosal cells to secrete Interferon-beta (IFN-β), also contributes to counteracting viral infection (San *et al.*, 2013). Leaves of *Olea europaea* L. (olive) also show inhibitory activity against the influenza virus (Nekooeian, 2006). Olive leaves inhibit the replication of HIV, cell to cell transmission and acute infection (Lee-Huang *et al.*, 2003).

Medicinal Plants used to Enhance Immunity

Besides, fighting the infection, another strategy to overcome the deadly virus is to strengthen the body's immune system. There are several plants in Indian traditional systems of medicine that are used as excellent immunity boosters. Different formulations are made using these plants or these are used in raw form individually or in combinations to augment immunity.

Infact, viral and bacterial infections attack the immunity system of the host. Many of the vitamins and proteins play an important role to fight these infectious agents. Among the vitamins, vitamin C (ascorbic acid) plays an important role in enhancing immunity. Ascorbic acid is essential for the stimulation of immune response by acting as an animmunostimulant, anti-inflammatory, antiviral and antibacterial nutrient supplement (Sorice *et al.*, 2014). Citrus fruits (lemon and oranges), tomato, papaya, strawberry, green chillies, pepper, mango etc. are some of the vitamin C rich fruits. Similarly, *Tinospora cordifolia* (Willd.) Miers (Guduchi) is a rich source of vitamin C and effective in inhibiting the growth of bacteria and has a tremendous ability to boost immunity (Saha & Ghosh, 2012). *Emblica officinalis* Gaertn. (Amla) also contains a high amount of natural vitamin C and, therefore, is used extensively in raw as well as processed forms as an immunostimulant in India. *Picrorhiza kurroa* Royle ex Benth. (Kutki) also possesses the ability to stimulate a humoral response by acting on various levels of immune mechanisms such as antibody production (Hussain *et al.*, 2013). Pectins from *Centella asiatica* L. (Brahmi) also showed immunostimulating activities (Wang *et al.*, 2003).

Plant Based Immunity Booster Drugs Developed in India

Ministry of AYUSH, India, made a herbal formulation named 'AyushKwath' or 'AyushKudineer' or 'AyushJoshanda'. This mixture consists of *Piper nigrum* L. (Krishna Marich), *Cinnamomum verum* J. Presl bark (Dalchini), *O. sanctum* leaves (Tulsi), dry *Z. officinale* Rosc. (Sunthi) and is used as an immunity booster. Trikatu, as per Ayurvedic's Bhaisajya Ratnawali is a mixture of three bitter herbs, consisting of dried fruits of *Piper nigrum* L. (Maricha), *P. longum* L. (Peepli) and *Z. officinale* Roscoe (Sunthi) (Kaushik & Trikatu, 2018). Triphala composed of *Terminalia chebula* Retz., *T. belerica* Wall and *Phyllanthus emblica* L. is used as an immunomodulator, antibacterial, radioprotective, antioxidant, anti-stress, antimutagenic, chemoprotective, anticancerous and anti-inflammatory herbal medicine (Baliga *et al.*, 2012). Tablet Divya Swasari Ras (DSR) is a unique combination of various plant parts, namely, galls of *Pistacia integerrima* J.L. Stewart ex Brandis (Zebrawood/Karkatashringi), fruits of *Glycyrrhiza glabra* L. (Liquorice/Mulethi), the bark of *Cinnamomum zeylanicum* Blume (Cinnamon/Dalchini), fruits of *Cressa cretica* L. (Salt Cresse/Rudanti), rhizomes of *Z. officinale*, fruits of *P. nigrum* L.(Maricha/Black pepper), fruits of *P. longum* L. (Long pepper/ Pippali), roots of *Anacyclus pyrethrum* L. and buds of *Syzygium aromaticum* (L.) Merr. & L.M.Perry (Cloves/Lavanga). It is used to protect against allergic airway inflammation and possesses a potential therapeutic option for viral and allergic asthma management (Balkrishna *et al.*, 2020).

Chyawanprash, an ayurvedic mixture of many herbs is a powerful immunity booster formulation that is used in India since time immemorial for fighting general debility and body rejuvenation for delaying the ageing process (Gupta *et al.*, 2017). Chyawanprash consists of several ingredients like *Sida cordifolia* Linn. (bala), *Tribulus terrestris* Linn. (Gokshur), *Aegle marmelos* Correa (Bael), *W. somnifera* (Aswagandha), *P. longum* Linn. (Pippali), *Emblica officinalis* (Amla), *Asparagus racemosus* (Shatavari), *C. asiatica* (Brahmi) and *Eugenia caryophyllus* Linn (Sharma *et al.*, 2019).

From ancient times, plants are used for therapeutic purposes in many civilizations across the globe. Even today, plants serve as the foundation for many pharmaceuticals. As a relief to a variety of illnesses, the use of medicinal plants is a traditional practice among different ethnic groups. However, this information is rarely documented and often passed down orally from generation to generation. When a traditional healer dies without passing on his experience to the next generation, the world loses hundreds of years of invaluable therapeutic knowledge. This ethnobotanical knowledge is highly significant and must be prioritised for preservation. Undoubtedly, the ethnobotanical know how of traditional systems of medicines helped a lot in boosting the immunity of people in the prevailing COVID era. However, the scientific base of this must be clinically evaluated for therapeutic effectiveness. Table 2 lists the ethnobotanical applications of plants used as antiviral agents in various scientific studies.

CONCLUSION

Traditional Indian medicinal practices relied solely on medicinal plants and even today, the potential of phytochemicals obtained from medicinal plants in curing diseases cannot be denied. Research is advancing, with the worldwide increase in the number of people affected by coronavirus, in the field of isolating and analyzing the phytochemicals that possess antiviral activity and to elucidate their mode of action. A considerable number of medicinal plants and their phytochemicals have been investigated for antiviral activity. Also, the immune-boosting effect of bioactive compounds obtained from these medicinal plants provides a holistic approach to cure various infections. With the ongoing evolution of various viruses resulting in increased resistance against the current drug therapy, the phytochemicals obtained from plants can be a significant potential source of therapy to treat various viral infections including the infection caused by changing strains of coronavirus. Many promising herbal treatments exist for viral diseases with proof of their efficacy and safety in advanced clinical trials. Through this article, we try to summarize and consolidate most of the commonly available potential Indian medicinal plant sources that can be used against viral infections especially the challenging strains of COVID-19. However, a lot of work still remains to be done to determine optimal treatments, doses, and formulae for those herbal preparations. Researches need to proceed in the direction of drug formation from phytochemicals against COVID-19. Besides, the pharmacodynamic and pharmacokinetic mechanisms of action of bioactive compounds derived from these medicinal plants on the structure and function of novel coronavirus needs to be studied as well.

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