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Efficacy of traditional Indian medicinal plants against COVID-19: A review

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Abstract

The world is yet to recover from the current global pandemic, now known as COVID-19, caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome related Coronavirus 2) or novel coronavirus. SARS-CoV-2 is extremely contagious and transmits all over the world rapidly by human to human interactions to become the first pandemic of this century. The current COVID-19 pandemic damages economies of the developing and advanced countries, create a social imbalance, and causes fatality of thousands of people. However, efficient antiviral medications are lacking against SARS-CoV-2 till now. Some synthetic drugs have gained attention, but they are currently under evaluation and have major side effects. Besides, natural compounds contribute to the diverse chemical reservoir, many of which, showcasing antiviral activity. It makes them ideal candidates against SARS-CoV-2 treatment and prevention. These antiviral phytochemicals can inhibit the enzymes of SARS-CoV-2 that are necessary for viral reproduction and infection. The Scopus, Google Scholar, ScienceDirect, PubMed, and WHO websites have been searched for papers using the keywords coronavirus, COVID-19, SARS, MERS, in addition to traditional herbal medicine, remedy, and plants. Most of the publications focused on polar compounds. In this review, we reported that the current knowledge about Indian medicinal plant extracts identified as inhibitors of SARS-CoV-2. This review aims to speed up research of anti Covid-19 bio-products which have no side effects and safe for patients.

Viral infections have always been a severe threat to mankind, and many new viral diseases causing critical health problems are reported over the times throughout the globe. COVID-19 is a contagious viral infection caused by a novel type of pathogenic Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2). This novel coronavirus (CoVs) infection has turned into a pandemic situation worldwide, as declared by the World Health Organization (WHO) on March 11, 2020, and continuously affecting the world's population (Andersen[3]). As of October 22, 2021, the pandemic had caused 242,348,657 infections, followed by 4,927,723 deaths worldwide (WHO[31]). The rapid increase in COVID-19 cases across the world calls for the development of COVID-19 treatment on a priority basis. CoVs belong to the Coronaviridae family; genetically they are divided into four major genera: i. Alpha coronavirus, ii. Beta coronavirus, iii. Gamma coronavirus, iv. Delta coronavirus. Among all recognized CoVs, mainly Alpha coronaviruses and Beta coronaviruses can infect humans[3].

Three epidemics have been reported in the last two decades, all of which have been caused by beta coronaviruses, namely SARS (2002-03), MERS (2012), and SARS-CoV-2. SARS-CoV-2 emerged on 31st December 2019 as a respiratory disease; it can also infect internal organs and gradually cause the failure of an organ. The first core center of Covid-19 was Wuhan city, Hubei located in South China (Andersen[3]). Since the reporting of the first case of COVID-19 in India on January 30, 2020, over 167,695 active cases and 454,712 deaths (October 25, 2021) have already been confirmed by the ministry of health and family welfare, India[13]. Presently, antiviral drugs are not available for COVID-19. It is difficult to develop broad range antiviral medicines because viruses like SARS-CoV-2 can frequently mutate their genetic materials, and invariably gain resistance against any particular drug. Many type new strains have been discovered in the many countries with a novel genetic mutation. The Centre for Mathematical Modelling of Infectious Diseases (at the London School of Hygiene and Tropical Medicine) reported that the new strain is 56% more transmissible and contagious than the other variant (Wise[32]). However, some synthetic antiviral medications have shown effectiveness, such as hydroxychloroquine, remdesivir, arbidol lopinavir, ritonavir, etc. But these synthetic compounds sometimes cause severe side effects, which are harmful to our health. Although a few potential vaccine candidates have shown some efficacy in triggering some immune responses, it is unclear whether the vaccines will provide any form of long term protection without any side effects. However, antiviral herbal medicines can reduce side effects and open new avenues for novel antiviral drug development. Besides, many more potent drugs, based on the natural compound structure, which exhibits the intended activity, can be produced (Bhuiyan[4]).

In the drug discovery pathway, natural products have carried an important role since ancient times. People have been utilizing diverse types of traditional medicines against contagious diseases globally. These may also contain anti hCoV (human Coronavirus) active compounds. Many researchers have discovered bioactive compounds useful for SARS-CoV-2 treatment due to their antiviral

activity. Furthermore, traditional Indian medicines (TIM) have been very popular as therapeutic medication and might play a significant role in SARS-CoV-2 infection prevention[20].

Globally, half of all drugs were mimic or derived from natural compounds. Recently Wan[29] reported that COVID-19 patients were successfully treated by traditional Chinese medicine (TCM) alone or in addition to western medicine. In this review, we discuss the broad spectrum of phytochemicals against SARS-CoV-2 from different plant species. We mainly highlight active ingredients from Indian traditional medicinal plants that may lead to the possible discovery of effective COVID-19 treatment.

2. Genetic organization of SARS-CoV-2:

SARS-CoV-2 belongs to subgenus Sarbecovirus of the genus Betacoronavirus (Order: Nidovirales, Family: *Coronaviridae*). Complete genome sequence analysis of SARS-CoV-2 shows ~79% similarity with SARS-CoV and ~50% similarity with Middle East respiratory syndrome coronavirus (MERS-CoV); however, the virus has more resemblances (89.1%) in nucleotide sequence with bat SARS like coronaviruses. SARS-CoV-2 is an enveloped RNA virus having a diameter of 80–120 nm and has a single stranded, positive sense RNA of 29903 bp length. Genes for replicase *ORF1ab* with 16 predicted non-structural proteins, and 4 structural proteins, such as *spike* glycoprotein (S), *envelope* (E*), membrane* (M), and *nucleocapsid* (N) are sequentially arranged from 52 to 32 in the viral genome (Mercatelli and Giorgi[17]). Angiotensin-converting enzyme type 2 (ACE2), encoded by *the ACE2* gene, is the receptor protein in humans for the SARS-CoV-2 like SARS-CoV. However, the rapid transmission of SARS-CoV-2 from one human to another lies in the fact that it binds to the ACE2 receptor more effectively (10-20 fold) than SARS-CoV. The spike protein interacts with the ACE2 receptor for virus entry into the host. The host transmembrane protease serine type 2 (TMPRSS2) is responsible for activation of spike protein by cleavage and virus fusion with the host cell membrane. Also, Main protease (M^{pro}) or 3 chymotrypsin like protease ($3CL^{pro}$) and PL^{pro} (papain like protease) help in viral replication by cleaving virus polypeptide at 11 sites and transforming them into mature non-structural proteins (NSPs)[3].

3. Drug repurposing for treatment of Covid-19 :

There is no specific treatment recommended for asymptomatic or symptomatic Covid-19 patients by the World Health Organization. However, WHO[33], in order to search for effective COVID-19 therapeutics, launched an international clinical trial in the name of the SOLIDARITY trial. The results of the Solidarity Trial published on 15 October 2020 reported that only corticosteroids had been proven effective against severe and critical COVID-19, whereas redeliver, hydroxychloroquine, lopinavir/ritonavir, and interferon had little or no effect in hospitalized patients. However, we still report these drugs in our study which is summarized in Table 1.

Table 1. The existing antiviral drugs used for COVID-19 treatment are as follows

Therapeutic agent	Traditional use	Mechanism of action
Lopinavir/ritonavir (Kaletra™)	Used in HIV-1 treatment	Lopinavir, a protease inhibitor, inhibits assembly of virus particles. Ritonavir decelerates the metabolism of lopinavir by inhibiting CYP3A enzymes[8].
Favipiravir (Favilavir or Avigan)	Used against influenza A, Ebola and Lassa and other RNA viruses	Guanine analogue that acts as RNA- dependent RNA polymerase inhibitor of RNA viruses[10].
Remdesivir (GS-5734)	Used in Ebola, MERS, SARS, and other RNA virus diseases.	Adenine nucleotide analogue prodrug that suppresses viral replication[1].
Corticosteroids	Effective against asthma, allergic rhinitis, and many inflammatory diseases.	Reduce lung inflammation and suppress the immune system (Russell[22]).
Chloroquine phosphate and hydroxychloroquine (a chloroquine analog)	Effective against malaria, chronic Q fever, autoimmune and viral diseases.	Hydroxychloroquine inhibits viral entry by increasing endosomal pH; whereas chloroquine phosphate hinders terminal phosphorylation of receptors (ACE2) of SARS-CoV [2].
Umifenovir (Arbidol™)	Used for treatment of influenza viruses.	Inhibits virus entry by interrupting virus and cell membrane fusion by inhibiting clathrin-mediated endocytosis[5].

4. Historical role of Indian medicinal plants on drug discovery :

In the pharmaceutical industry, bioactive natural products play a significant role in new drug development. India has always been called the repository of medicinal plants because of the different types of agro climatic zone. People from the Indian subcontinent regions are well acquainted with traditional medicinal plants through ayurvedic medicines and ethnopharmacology since the prehistoric period (above 2000 years ago)[23]. Ayurveda is the oldest practice in the Indian medicine system, and currently, a lot of importance has been given to it. Ayurvedic medicines have become an alternative to conventional drugs for their effortless accessibility, minimum, or no side effects, and low cost. Until recently, knowledge about TIM, including the importance of medicinal plants and formulation, were scripted within some books such as Ayurveda Materia Medica[9] and Indian Materia Medica[18].

Approximately 85% of traditional medicines are derived from plant sources. Traditional medicinal plants have a long standing old history with numerous indigenous communities. Indigenous remedial practices have been culturally received throughout all

aspects of human culture and also environmental evolution[6]. India always represents one of the famous emporia of ethnobotanical profusion because of hugely diversified ethnic groups, and abundant biological sources are present here. Bose[6] reported from Jalpaiguri, West Bengal 115 types of medicinal plants which are used as allopathic medications for treatment purposes such as cut and wounds, cough and cold, skin diseases, pain, inflammation, bone fracture, stomachache, abdominal disorder, jaundice, and liver problems, fever, and many more. Likewise, many other Indian regions are also known as a medicinal plants resource factory such as Darjeeling Himalaya of West Bengal, Himalayan state of Uttarakhand, North East India, Maharashtra, Theni districts (Western Ghats) of Southern India, Tamil Nadu, Assam, Madhya Pradesh, Uttaranchal, etc. Previously reported the Indian medicinal plants effectively prevent many chronic diseases like cancer, dysentery, Parkinson's, neuropathic pain, asthma, HIV infections, and many others[27]. Research on these traditional medicinal plants might provide some potential bioactive compounds, and leads to new drug development to fight against the deadly disease.

5. Role of Indian Medicinal plants to deactivate SARS-CoV-2 :

Different medicinal plants are a great source of phytochemicals (polyphenols, alkaloids, lipids, and sterols) with a wide range of biological activity. The trend in medicine and biotechnology shows that the use of natural compounds has increased considerably in recent times. Recently, Srivastava[28] reported that derivatives of Indian Herbal Plants promisingly deactivate protease of SARS-CoV-2, *in silico* studies. Divya[11] suggested that South Indian medicinal plants could be used in SARS-CoV-2 treatment. Likewise, many other researchers have reported diverse types of bioactive derivatives from medicinal plants that promisingly inhibit SARS-CoV-2 activity which summarized in Table-2. To this end, we can say that the Indian medicinal plants traditionally used in ethnopharmacological treatment may hold the key to the current global crisis. Exploring Indian Medicinal plants compounds through additional research combining with standard medicine may provide solutions to diminish the multiple drug resistance virus strains like SARS-CoV-2.

Table-2. Antiviral activity of Indian medicinal plants against SARS-CoV-2.

Name of the plant	Active compounds	Target site(s)	Inhibition mechanism
Nyctanthes arbor-tristis L.	Nictoflorin ($C_{27}H_{30}O_{15}$), Astragalin ($C_{21}H_{20}O_{11}$), Lupeol ($C_{25}H_{26}O_4$)	M^{pro} (Srivastava[28])	Viral replication
Aloe barbadensis Miller	Aloenin ($C_{19}H_{22}O_{10}$), Aloesin ($C_{19}H_{22}O_9$)	M^{pro} (Srivastava[28])	Viral replication
	Aloeemodin ($C_{15}H_{10}O_5$), Aloin ($C_{21}H_{22}O9$), Chrysophanol ($C_{15}H_{10}O_4$) Catechin ($C_{15}H_{14}O_6$), Aloin A ($C_{21}H_{22}O_9$), Isoaloresin, Quercetin ($C_{15}H_{10}O_7$)	$3CL^{pro}$, Spike glycoprotein ACE2 and RdRp (Pandit[19])	Viral replication and attachment to host cell

Tinospora cordifolia (Thunb.) Miers	Berberine ($C_{28}H_{18}NO_4$), Sitosterol (C29H50O); Choline ($C_5H_{14}NO$), Tetrahydropalmatine ($C_{21}H_{25}NO_4$), Octacosanol ($C_{28}H_{58}O$)	$3CL^{pro}$ (Srivastava[28])	Viral replication, transcrition
	Corydine ($C_{20}H_{23}NO_4$), Cordioside ($C_{26}H_{34}O_{12}$), Cordiofolioside A, Tinosporin ($C_{20}H_{22}O_6$)	$3CL^{pro}$, Spike glycoprotein ACE2 and RdRp (Pandit[19])	Viral replication and attachment to host cell
	Tinocordiside ($C_{21}H_{32}O_7$)	$3CL^{pro}$ (Shree[26])	Viral replication
	Tinosponone ($C_{19}H_{22}O_5$), Xanosporic acid ($C_{28}H_{24}O_{11}$), Cardiofolioside B, Tembetarine ($C_{20}H_{26}NO_4$)	M^{pro} (Krupanidhi[14])	Viral replication, transcription
Curcuma longa L.	Curcumin ($C_{21}H_{20}O_6$), Bisdemethoxycurcumin ($C_{19}H_{16}O_4$), Demethoxycurcumin ($C_{20}H_{18}O_5$), Tetrahydrocurcumin ($C_{21}H_{24}O_6$)	$3CL^{pro}$, Spike glycoprotein ACE2 and RdRp (Srivastava[28])	Viral replication
	Curcumin derivative Cur2	PL^{pro} (Goswami[12])	Viral replication
Azadirachta indica A. Juss.	Nimbin ($C_{30}H_{36}O_9$); Nimolicinol ($C_{28}H_{34}O_7$)	M^{pro} (Srivastava[28])	Viral replication
	Azadiradionolide ($C_{28}H_{34}O_6$)	NSP9 (Parida[20])	Viral replication
Withania somnifera (L.) Dunal (Parida[20])	Withanolide ($C_{28}H_{38}O_6$), Withaferin A ($C_{28}H_{38}O_6$); Withanoside V ($C_{40}H_{62}O_{14}$), Somniferine ($C_{36}H_{36}N_2O_7$); 27-Deoxy-14-hydroxywithaferin A ($C_{28}H_{38}O_6$), 17-Hydroxywithaferin ($C_{28}H_{38}O_6$)	$3CL^{pro}$	Viral replication, transcription
	27-Hydroxywithanone ($C_{28}H_{38}O_7$), Deoxywithastramonolide ($C_{28}H_{38}O_6$), 27 Deoxywithaferin A ($C_{28}H_{38}O_5$), 2,3-Dihydrowithaferin A ($C_{28}H_{40}O_6$)	Spike	Viral replication and entry to host cell (21)
	27-Hydroxywithanolide B ($C_{28}H_{38}O_6$), Anaferine ($C_{13}H_{24}N_2O$)	NSP10	Viral replication and entry to host cell
	12-Deoxywithastramonolide ($C_{28}H_{38}O_6$)	NSP12 (RNA Binding Site)	Replicative enzyme and entry to host cell
	Anaferine ($C_{13}H_{24}N_2O$)	NSP16	Methyl-transferase activity
	27-Hydroxywithanolide B ($C_{28}H_{38}O_6$), 12-Deoxywithastramonolide ($C_{28}H_{38}O_6$)	NSP9 (RNA-binding protein)	Viral replication
	Somniferine ($C_{36}H_{36}N_2O_7$)	NSP15	Endo-ribonuclease activity
	2,3-Dehydrosomnifericin ($C_{28}H_{40}O_7$), Withanolide B ($C_{28}H_{38}O_5$), 24,25-dihydrowit-	NSP3	Viral replication and entry to host

	hanolide D ($C_{28}H_{40}O_6$), 27-Deoxy-14-hydroxywithaferin A ($C_{28}H_{38}O_6$)		cell
Zingiber officinale Roscoe	Gingerol ($C_{17}H_{26}O_4$), Shogaol ($C_{17}H_{24}O_3$)	M^{pro} (Srivastava[28])	Viral replication
	8-Gingerol (C19H30O4), 10-Gingerol ($C_{21}H_{34}O_4$), 6-Gingerol ($C_{17}H_{26}O_4$)	PLpro (Goswami[12])	Viral replication
Allium cepa L.	Quercetin ($C_{15}H_{10}O_7$)	M^{pro} (Srivastava[28])	Viral replication
Ocimum sanctum L.	Ursolic acid ($C_{30}H_{48}O_3$), Apigenin ($C_{15}H_{10}O_5$); Vicenin ($C_{27}H_{30}O_{15}$), Isorientin 4´-O-glucoside 2"-O-p-hydroxybenzoagte ($C_{34}H_{34}O_{18}$)	$3CL^{pro}$ (Shree[26])	Viral replication
Cannabis sativa L.	Cannabidiol ($C_{21}H_{30}O_2$)	M^{pro} (Srivastava[28])	Viral replication
	Cannabinoid, cannabidiol ($C_{21}H_{30}O_2$)	Serine protease TMPRSS2, Spike glycoprotein-ACE2 (Wang[30])	Gene expression
Piper nigrum L.	Piperine ($C_{17}H_{19}NO_3$)	M^{pro} (Srivastava[28])	Viral replication
Rhododendron arboreum Sm.	Epicatechin gallate ($C_{22}H_{18}O_{10}$), 5-O-Feruloylquinic acid ($C_{17}H_{20}O_9$), Quercetin-O-rhamnoside ($C_{21}H_{20}O_{11}$), 5-O-Coumaroyl Dquinic acid, Kaempferol ($C_{15}H_{10}O_6$),Epicatechin ($C_{15}H_{14}O_6$), Quercetin ($C_{15}H_{10}O_7$)	M^{pro} (Lingwan[15])	Viral replication, transcription
Silybum marianum (L.) Gaertn.	Silybin ($C_{25}H_{22}O_{10}$)	$3CL^{pro}$, Spike, and RdRp (Pandit[19])	Viral replication and attachment to host cell
Camellia sinensis (L.) Kuntze	Theaflavin ($C_{29}H_{24}O_{12}$)	Binding to RdRp (Lung[16])	Replication
Glycyrrhiza glabra L.	Glycyrrhizin($C_{42}H_{62}O_{16}$), glycyrrhetic acid ($C_{30}H_{46}O_4$), liquiritin ($C_{21}H_{22}O_9$), isoliquiritin ($C_{21}H_{22}O_9$)	ND (Chowdhury[7])	Counterbalance of COVID-19 activeness
Citrus sp.	Hispidin ($C_{13}H_{10}O_5$), lepidine E ($C_{20}H_{18}N_4O_2$), folic acid($C_{19}H_{19}N_7O_6$)	Mpro (Serseg[24])	Viral replication
Eucalyptus sp.	Jensenone ($C_{13}H_{14}O_6$)	M^{pro} (Sharma[25])	Replication
Solanum nigrum L.	Solvanol ($C_{12}H_{14}O_4$)	NSP16 (Parida[20])	Methyltransferase
Nigella sativa L.	Limonin ($C_{26}H_{30}O_8$)	NSP16 (Parida20)	Methyltransferase
Catharanthus roseus (L.) G. Don	Vindolinine ($C_{21}H_{26}C_{l2}N_2O_2$)	NSP15 (Parida20)	Endoribonuclease

Main protease- M^{pro} or chymotrypsin like protease- $3CL^{pro}$; Papain like protease- PL^{pro}; Non-structural proteins- NSPs; RNA-dependent RNA polymerase- RdRp; ND- No data.

Future prospects :

This review sheds light on the broad spectrum of information available for traditional medicinal plants against SARS-CoV-2. The traditional medicines are generally underrated, but the source of medicaments is inexhaustible. In addition, innovative formulation and processing technologies might improve the solubility optimization of bioactive antiviral compounds, their delivery, and therapeutic activity to accommodate them like antiviral functional drugs and foods[21]. The design of the phyto-pharmacophores structure, bioinformatic studies can help in novel antiviral drug discovery. So far, this study has contributed to a great deal of knowledge about the molecular features and mechanism of action of antiviral compounds. By far, finding a cure for viral infections seems challenging and troublesome exercise as active vaccines and protective drugs are not available to treat viral infections. The broad ranges of bioactive natural compounds found in the herbal extracts impart significant beneficial effects on our health (antimutagenic, antiviral, antioxidant, anti inflammation) but need deeply examined.

Amid this global pandemic, scientists and researchers around the world are racing against time to find a treatment against COVID-19. To date, no clinically trial tested medicine could be developed to fight against COVID-19. The natural compounds with possible anti SARS-CoV-2 activity have the potential to fight the COVID-19, and consequently, may aid the discovery of new classes of medicines. However, most of the currently available research results are not clinically trial tested; therefore, a long way is still to go in terms of bio-analysis and standardization of extraction and production of COVID-19 cure.

Conflicts of interest :

The authors declare no financial or other conflicts of interest.

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