



Review Article

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Review on preclinical and clinical trials of Indian herbal formulation against SARC COV-2

Neha Mishra¹, Shraddha Tripathi², Pragya Mishra³, Neetu Mishra⁴

¹ Department of Food Nutrition and Public Health, ECHS, SHUATS-211007, Prayagraj U.P, India
ORCID ID: <https://orcid.org/0000-0001-6931-9544>

² Department of Home Science, University of Allahabad-211002, Prayagraj U.P, India
ORCID ID: <https://orcid.org/0000-0003-4559-5944>

³ Food Processing and Management, DDU KAUSHAL Kendra, RGSC, BHU, Varanasi-221005, U.P, India
ORCID ID: <https://orcid.org/0000-0003-1612-1424>

⁴ Department of Home Science, University of Allahabad-211002, Prayagraj U.P, India
ORCID ID: <https://orcid.org/0000-0002-3146-2465>

ABSTRACT

Mutation of the SARS-CoV-2 spikes protein leads to the appearance of novel variants with modified form that appear to be more transmissible and can escape immunity generated by the vaccine. Continuous mutation in SARC COV and the emergence of more competent variants have sparked alarm for the alternative way to strengthen the immunity and fight corona sustainably. Natural products have been investigated in the last decades to develop novel candidates for drug research. Medicinal plants are considered helpful for preventing and treating several diseases and COVID-19 patients. Thus, this review presents the Indian medicinal plant and its promising active ingredients that exhibit *inhibitory* activity against SARS-CoV-2. The present paper also reviewed the AYUSH recommended formulations and their ingredients routinely used by the Indian population and covid positive patients.

Keywords: AYUSH, COVID-19, Indian Herbs, Medicinal Plants.

INTRODUCTION

The severe acute respiratory syndrome (SARS) coronavirus-2 has emerged as a novel coronavirus from Wuhan, China, and in a short time, spread across the world [1]. It belongs to the family Coronaviridae, designed as COVID-19. On March 11, 2020 it was declared as pandemic by world Health Organization (WHO). Coronavirus is primarily a respiratory illness affecting the lungs and causes a rapid inflammatory response in the body. The clinical symptoms comprise cough, cold, high temperatures, shortness of breath, chest pain, myalgia, diarrhea, altered taste, and confusion which lasts for a few days [2]. However, the release of pro-inflammatory cytokines storm caused by systemic inflammatory reactions made it more lethal in some cases due to occurrence acute respiratory distress syndrome (ARDS). Previous studies have reported that 80% of patients are asymptotically or with minor symptoms, although more critical cases were up to 20% [3]. The high mortality in COVID-19 was seen in patients with compromised immune systems and/or existing underlying conditions such as renal disease, diabetes, obesity, and CVD³. The symptoms and severity of the disease vary with the status of the host's immune system. Furthermore, mutation of the SARS-CoV-2 spikes protein leads to the appearance of novel variants which are more communicable or deadlier. It was found that new variants can escape immunity generated by the vaccine. Continuous mutation in SARC COV and the emergence of more competent variants have sparked alarm for the alternative way to strengthen immunity and sustainably fight corona.

A robust immune system helps the body fight the new virus and subside the severity of the disease. Therefore, developing a strong immune system is vital to reducing the death rate. Till date, there is no proper medicinal remedy accessible for this disease. As a defense mechanism the immune system produces immune cells and molecules that may able to differentiate and work to abolish foreign and undesirable micro agents. The modulation of the immune system will modify the immune response, which includes stimulus evoking, expression of response, magnification, or inhibition of any portion or phase of the immuno-modulatory response, which might help reduce the severity of the disease. Therefore, there is an urgent need for potential immune modulators to strengthen the host immune system to fight different new variants of covid. Even in the second wave, medicinal decoction has been used to manage the effect of SARS Cov-2. People around the world were restricted to stay at homes and were advised to include easily accessible medicinal plants decoction in various proportion as part of daily diet with an

***Corresponding author:
Dr. Neetu Mishra**

Department of Home Science,
University of Allahabad-211002,
Prayagraj U.P, India
Email: neha.alladuniv@gmail.com

intension to strengthen the immune system and to reduce the risk of SARS-CoV-2 infection. This might lessen the cases of COVID-19 infection and also initiate a rapid recovery in such cases.

Since the century, India has been an abundant reservoir of medicinal plants used for various infectious diseases. Since prehistoric time medicinal plants have widely been distributed for potential treatment of innumerable infectious and non-infectious diseases. According to an estimate, most commonly used medicine developed, constitutes around 25% of plants derived bioactive compounds. The potential of the plant extracts is to boost the inherent antiviral defense of the human body. Therefore, the present study was conducted to discover potent anti-COVID-19 natural compounds.

Herbal Bioactive Compounds for the Management of COVID-19

Since the dawn of medicine, the ancient herbal phytomedicine has been used to treat infections. Indian traditional health care system includes Ayurveda, Unani, Siddhi, and Homeopathy, which are among the oldest systems of medical practice in the world. Since immemorial time, it has been well accepted and utilized by the people; they are ignored in health care systems for the last few decades. The global pandemic crisis leads to a paradigm shift toward traditional medicine and improving lifestyles as they are safe and sustainable ways to enhance efficacy for the prophylaxis and treatment of coronavirus infection.

Currently, plant-derived medicinal products have been exploited to check the Effectiveness of this virus and strengthen the world's immunity [4,5]. Undeniably, they have the potential to manage a wide array of infections without causing any side effects. Indian medicinal

plants are a reservoir of biologically active compounds that might help defeat viral infections and their transmission. Isolation, identification, and characterization provide a new approach to combating such deadly infections.

Novel antiviral compounds are developed through utilizing medicinal plants and purified natural components. Saikosaponins, triterpene glycosides which is a naturally occurring bioactive compounds isolated from various medicinal plants like *Bupleurum spp.*, *Heteromorpha spp.*, and *Scrophularia* revealed excessive antiviral activity against human coronaviruses [6]. These compounds of natural origin efficiently help to prevent the initial phases of coronavirus infection by affecting viral attachment to the host cell and its penetration. Furthermore, numerous naturally occurring bioactive compounds from plant sources (*Isatisindigotica* and *Torreya Nucifera*) such as myricetin, scutellarein and phenolic compounds have been recognized to have inhibition action against coronavirus enzymes (nsP13 helicase and 3CL protease) [7]. The aqueous extract from *Houttuynia cordata* has also been known as anti-coronavirus medicine. It has been detected to inhibit the viral 3CL protease and block the viral RNA-dependent RNA polymerase activity, as a consequence exhibiting various antiviral mechanisms against SARS-CoV1 infection [8].

Further 25,000 herbal formulations have been used as folk medication therapies in Ayurveda alone to treat numerous acute and chronic ailments [9]. A single AYUSH formulation combines many herbal phytoconstituents that generate a pharmacological effect with minimal side effects [10].

Table 1: Promising active ingredients of Indian Medicinal plant that exhibit *in vitro* activity against SARS-Cov-2

Medicinal plant	Compounds	Biological activity	Reference
<i>Aloe vera</i>	Aloin	H1N1 in MDCK cells and in mice	Huang <i>et al</i> [11].
<i>Camellia sinensis</i>	Epigallocatechin gallate	High affinity for proteases and NSP 15 endoribonuclease	Khan <i>et al</i> [12].
<i>Withaniasomnifera (L.) Dunal (Ashwagandha)</i>	Withaferin, Withanolide M	Antiviral activity against spike protein of SARS-CoV-2	Straughn and Kakar [13] Khanal <i>et al</i> [14].
	Withaferin A	binding affinity to ACE2 protein and main protease (MPro)	Cai <i>et al</i> [15]. Straughn and Kakar [13].
	Withanolide I, Withanolide G	3 CL protease	Khanal <i>et al</i> [14].
	Withanone Withanolide A	ACE2-RBD interface	Balkrishna <i>et al</i> [16]. Muhseen <i>et al</i> [17].
<i>Silybum marianum</i>	Silybin	Act on Spike glycoproteins, main protease (M ^o par) and RNA depended RNA polymerase (RdR _p)	Pandit [18].
<i>Ginkgo biloba</i>	Ginkgolic acids	anti-influenza virus activity	Borenstein <i>et al</i> [19].
	Ginkgolide A, Terpenoids	High affinity with proteases	Shaghghi [20].
<i>Tinospora cordifolia (Guduchi)</i>	Berberine	Act on 3 CL protease	Chowdhury [21]. Shree <i>et al</i> [22].
	Cordioside and other constituents	High binding affinity to ACE2 protein and main protease (MPro)	Jena <i>et al</i> [23].
	Tinocordiside	High binding affinity to main protease (MPro)	Shree <i>et al</i> [24].
<i>Phyllanthus Emblica (Amalaki)</i>	Phyllaemblicin B Phyllaemblinol	Antiviral via Helicase inhibitors against hepatitis virus	Ott <i>et al</i> [24].
	Phyllaemblicin G7	Antiviral via Inhibiting the enzyme activity of TMPRSS2	Ilona <i>et al</i> [25].
	Phyllaemblicin G7	High binding affinity to ACE2 protein and main protease (MPro)	Kothandan <i>et al</i> [26].
<i>Ocimum sanctum (Tulsi)</i>	Vicenin, Isorientin 4'-O-glucoside 2''-O-p-hydroxybenzoate, Ursolic	High binding affinity to ACE2 protein and main protease (MPro)	Shree <i>et al</i> [22].

	acid		
	Tulsinol, dihydroeugenol	Anti	Ghoke <i>et al</i> [27].
<i>Citrus sp.</i>	Essential oils, pectins, naringin and hesperidin (flavonoids)	Binds with high affinity to cellular receptors of SARS-CoV-2 that restrain the pro-inflammatory overreaction of the immune system.	Meneguzzo <i>et al</i> [28].
	Hispidin, lepidine E, and folic acid	Inhibition of 3CL hydrolase enzyme responsible to counteract the host innate immune response and elucidate the main interactions in inhibitor-enzyme complex	Serseg <i>et al</i> [29].
	Hesperidin, Rutin, Diosmin	Inhibitory action against SARS-CoV-2 main protease (M ^{OPAR}).	Adem <i>et al</i> [30].
<i>Curcuma longa</i> (Turmeric)	Curcumin	3 CL protease	Vajragupta <i>et al</i> [31].
	Curcumin	Antivirus activity against H1N1 in silico study;	Richart <i>et al</i> [32].
	Curcumin; 50 mg/kg body weight	Acute Respiratory Distress syndrome; in vivo study	Avasarala <i>et al</i> [33].
<i>Glycyrrhiza glabra L.</i> (Yashtimadhu)	Glycyrrhizin	Inhibit SARS-CoV replication	Hoever <i>et al</i> [34].
<i>Piper longum L.</i> (Pippali)	Piperolactam A	binding affinity to ACE2 protein and main protease (MPro)	Kothandan <i>et al</i> [26].
<i>Embeliaribes</i> (Vidang)	Embelin	High binding affinity to ACE2 protein and main protease (MPro)	Caruso <i>et al</i> [35].
<i>Ocimum tenuiflorum</i> (Tulsi)	Apigenin	Antiviral activity against H1N1 in silico study;	Alhazmi [36].
<i>Zingiber officinale</i> (Ginger)	6-Gingerol	HRSV strain in HEP-2 and A549 cell lines;	Chang, <i>et al</i> [37].
	6-Gingerol	Binding potential with active residues of ACE2 that mediate host viral interface.	Dhanasekaran and Pradeep [38].
	Gingerol	SARS-CoV-2 papain-like protease (PLpro) inhibitors.	Goswami <i>et al</i> [39].
	Gingerol	Potential inhibitors of COVID-19 proteases.	Srivastava <i>et al</i> [40].
<i>Nigella sativa</i>	Nigelledine, α -Hederin	Inhibitory action of 3CL ^{PRO} /M ^{OPAR} proteases,	Bouchentouf and Missoum [41].
<i>Psoralea corylifolia</i> (Bawchan seed)	Bakuchiol,	H1N1 and H3N2 strains in MDCK cell	Shoji <i>et al</i> [42].
<i>Betula pubescens</i>	Herbacetin, Isobavachalcone, Quercetin, 3- β -d-glucoside, Helichrysetin and Betulinic acid	Inhibitory bioactive compounds against MERS-CoV 3C-like proteases (3CLpro).	Jo <i>et al</i> [43].
<i>Eucalyptus sp.</i>	Jensenone	COVID-19 M ^{OPAR} inhibitor	Sharma and Kaur [44].
<i>Andrographis paniculata</i> (Kariyat)	Andrographolide	SARS-CoV-2 in silico study;	Enmozhi <i>et al</i> [45].

Table 2: Promising crude extracts from Indian Medicinal plant for the treatment of SARS-CoV-2 infection

Medicinal plant	Part used	Dose	Mechanism	Reference
<i>Adhatodavastica Nees.</i> (Vasa)	Aqueous and methanolic extract of leaves	10 mg/ml each	Significant inhibition of plaques in Vero cells infected with 100 pfu of HSV1 and 2 by 100% in methanolic extract while in aqueous extract by 100% and 86%, respectively	Chavan <i>et al</i> [46].
<i>Withaniasomnifera</i> (L.) Dunal	Aqueous root extract	25 μ g/ml	Antiviral activity against IBD virus by cytopathic effect reduction assay	Ghoke <i>et al</i> [27].
<i>Acacia arabica</i>	leaves extract		Antiviral activity against Influenza A virus subtype H9N2 (H9N2)	Ghoke <i>et al</i> [27].
<i>Aloe vera</i>	Ethanol extract of leaves;	25 or 250 μ g/ml	H1N1 in MDCK cells;	Choi <i>et al</i> [47].
<i>Andrographis paniculata</i> (Kariyat,)	Ethanol and aqueous extract of leaves	8.2 μ g/ml (ethanol extract), 380.3 μ g/ml (water extract)	H5N1 strain in MDCK cells	Sornpet, <i>et al</i> [48].
<i>Bergenia ciliata</i> fringed elephant's ears, Pasanabheda (Sanskrit)	Methanolic extract of rhizome	8 to 10 μ g/ml	H1N1 strain in MDCK and Vero cell	Rajbhandari <i>et al</i> [49].
<i>Cinnamomum cassia</i> (Cinnamon, Dalchini)	Nanoparticles of bark	50, 100, and 200 μ g/ml	H7N3 strain in Vero cells	Fatima <i>et al</i> [50].
<i>Curcuma longa</i> (Turmeric, haldi)	Ethanol and water extracts	69.3 μ g/ml (ethanol extract), 142.3 μ g/ml	H5N1 virus infection	Sornpet <i>et al</i> [51].

		(water extracts)		
	AgNPs from rhizomes;	0.12 nM and 0.24 nM	RSV strain in Hep-2 cells	Yang <i>et al</i> [52].
<i>Embeliaribes Burm</i> (False black pepper)	Ethyl acetate extract of Fruit	0.2 µg/ml	H1N1, H3N2, H5N2 in MDCK cells	Hossan <i>et al</i> [53].
<i>Glycyrrhiza glabra</i>	Ethanol extract	1.70 µg/ml	H1N1 strain in MDCK cells;	Hossan <i>et al</i> [53].
<i>Syzygiumcumini</i>	Aqueous crude extract of leaves and bark;	1.28 µg/ml and 8.69 µg/ml	Antiviral activity against H5N1 in MDCK cells	Sood <i>et al</i> [55].
<i>Zingiber officinale</i> (Ginger)	Aqueous extract of Fresh ginger rhizomes	300 µg/ml	HRSV strain in HEp-2 and A549 cell lines;	Chang <i>et al</i> [37].
	Aqueous extract	10% concentration	H9N2 strain in embryonated chick eggs	Rasool <i>et al</i> [56].
<i>Viscum album</i> (Mistletoe)	Aqueous extract of leaves;	1 µg/ml	HPV2 strain in Varo cells	Karagöz <i>et al</i> [57].

Table 3: Clinical trial of Indian Herbal formulation against SARC CoV-2 by AYUSH [58].

Trial registration	Title of the study	Study design	Sample	Herbal formulation	Dose
CTRI/2020/05/0251 66	Study of Ashwagandha tablet on healthy individuals to prevent Covid 19	Randomized, Parallel-Group Trial	18-68 yrs n=1200	250 mg Tablet	2/d for 1 month
CTRI/2020/05/0253 41	A study to know the effect of Ayurvedic Kwath (KiratiktadiKwath) & Ashwagandha Churna along with yoga exercises in the treatment of COVID-19 Positive patients.	Randomized, Parallel-Group Trial	20-60 yrs n = 30	Kirati ktadi Kwath, Ashwagandha churna (5 gm), Yoga exercises (45 min, 2/d), AyushKwath	Kirati ktadi Kwath-30 ml twice/d for 14 days AyushKwath 40 ml/d
CTRI/2020/12/0294 76	A clinical trial to study the effect of herbal medicine on enhancing immune function in COVID recovery patients	Randomized, Parallel-Group, Placebo-Controlled Trial,	18-60 yrs n=120	Capsule containing standardized extract of Aswagandha, Amla & Shilajeet,	125 mg, twice daily for 12 weeks
CTRI/2021/08/0357 55	Comparative study of Ashwagandha for its effect on quality of life in patients during post-COVID19 period	Randomized, Parallel-Group, Placebo-Controlled Trial	18 to 50 years n=120	Ashwagandha Standardized Extract (KSM66)	300 mg KSM 66 Ashwagandha twice a day for 12 weeks
CTRI/2020/04/0248 83	Clinical research on safety and efficacy of Zingi Vir-Has an add on therapy in COVID-19 patients.	Randomized controlled Single blinded prospective multicentre clinical trial	18-60 yrs, n-112	Polyherbal tablet (500 mg)	Every 3 hours between 6 AM and 9 PM, 10-15days
CTRI/2020/05/0254 34	A clinical trial to evaluate the Medicinal effects of Zing iVir-H as Antiviral therapy in COVID-19 patients.	Randomized, double-blind, placebo-controlled prospective multicenter trial	18-60 yrs, n=135	Tablet (500 mg)	Every 3 hours between 6 AM and 9 PM in a given day
CTRI/2020/05/0251 61	To study the Effectiveness of herbal formulation - Aayudh Advance as a supplementary treatment for the Corona Virus 2019 (Covid-19) infected patients	Randomized, Parallel-Group, Active Controlled Trial	18-99 yr, n-120	Mixtures of herbal extracts and essential oils in water medium with sweetener.	Thrice in a day
CTRI/2020/05/0253 97	A study to evaluate the effect and safety of a phytopharmaceutical drug in treatment of Coronavirus infection	Randomized, Parallel-Group Trial	18-75 yrs, n=210	Purified aqueous extract of <i>Cocculus hirsutus</i> (AQCH) tablets	400 mg thrice daily (every 8±1 hours), 10 days; 30 mins before meal
CTRI/2020/08/0272 24	To observe the effect of Ayurvedic medicine (Ashwagandha and Shunti) for the treatment of COVID-19	Randomized, Parallel-Group, Active Controlled Trial	18-75 yrs, n=60	Ashwagandha tablet and Shunti capsule (dried rhizome of <i>Zingiberofficinale</i>)	2 Tablets 250 mg each (twice daily)
CTRI/2020/09/0280 07	Prophylactic study of Ashwagandha and HCQ in health care providers	Randomized, Parallel-Group, Active Controlled Trial	20-69 yrs, n=400	Ashwagandha tablet (250 mg) & HCQ tablet (400 mg)	Ashwagandha, 2 tablets 2/d for 12 weeks; HCQ-1. tablet 2/d on Day 1, 400 mg once a week for 7 weeks
CTRI/2021/06/0344 96	Enhancing protective action of COVID-19 vaccine by using Ashwagandha	Randomized, Parallel-Group, Placebo-Controlled Trial	18-45 yrs, n=	Ashwagandha Tablet 500 mg	once daily For 24 Weeks
CTRI/2021/09/0368 26	A study on the efficacy of Tulasi-Ashwagandhadi Herbal Drops on Oxygen Saturation (SPO2) in the management of COVID-19 affected cases.	Randomized, Parallel-Group, Placebo-Controlled Trial	18-65 yrs, n=110	Tulasi-Ashwagandhadi Herbal Drops	

CTRI/2020/05/025275	Role of Chyawanprash in the prevention of COVID-19 in health care workers	Randomized, Parallel-Group Trial	25-0 yrs, n=200	Poly Herbal paste	12 g twice daily.
CTRI/2020/05/025425	Ayurvedic intervention (Chyawanprash) in the prevention of COVID-19 pandemic among Health Care Personnel	Randomized, Parallel-Group Trial	20-60 yrs, n=50	Poly Herbal paste	12 g twice daily.
CTRI/2020/09/027914	Evaluation of efficacy of Fixed Ayurvedic Regimen of Giloy Ki GhanVati, Tulsi Tablets, Kalmegh Tablets and Dabur Chyawanprash in COVID-19	Randomized, Parallel-Group Trial	18-60 yrs, n=72	Dabur chyawanprash, Giloy ki Ghanvati, Tulsi	1 tsp/d for 2 days
CTRI/2020/09/027974	Clinical Evaluation of Chyawanprash for the prevention of COVID-19 among Health Care Personnel	Randomized, Parallel-Group Trial	18-60 yrs, n=200	Poly Herbal paste	12 gm twice daily
CTRI/2021/10/037479	Effect of chyawanprash on immune system when administered after covid-19 vaccination in health care personnel	Randomized, Parallel-Group, Active Controlled Trial	25-60 yrs, n=100	Poly Herbal paste	12 gm with warm water for 3 months
CTRI/2020/05/025069	Ayurvedic Interventions in prevention of COVID-19 infection-A survey study	Single Arm Study	18-70 yrs, n=9200	ShanshamaniVati (500 mg) or Sudarshana Ghanavati (250 mg) or Ashwagandha (250 mg)	2/d for 15 days
CTRI/2020/05/025088	Study of GUDUCHI TABLET on healthy individuals to prevent covid 19.	Randomized, Parallel-Group Trial	18-68 yrs, n=1200	Guduchi tablet (500mg)	2/d for one month
CTRI/2020/05/025213	Ayurveda formulation for COVID-19 prevention	Single Arm Study	18-70 yrs, n=1500	Guduchighanvati (500 mg)	2/d for 30 days
CTRI/2020/06/025769	A prophylactic interventional study to determine the possible protective effect of Siddha Polyherbal formulation Kabasura Kudineer against the COVID 19 on intermittent, month-long consumption by public with close contacts to COVID patients and frontline workers in Tamil Nadu, India	Non-randomized, Multiple Arm Trial	18-80 yrs, n=40,000	Polyherbal formulation- KabasuraKudineer	Kabasurakudineer (5- 10g) boiled with 240ml of water will be reduced to 60 ml, filtered
CTRI/2020/06/025779	Study of Ayush Kwath in quarantine persons	Single Arm Study	20-60 yrs,	AyushKwath (Tulasi+Dalchini+ginger+ Piper nigrum)	3 gmwith 150 ml warm water twice a day
CTRI/2020/07/026579	Role of Herbal Immunomodulators in Boosting the Immunity among healthcare workers assigned to COVID-19 wards	Randomized, Parallel-Group, Active Controlled Trial	18-60 yrs, n=100	Herbal Formulations (Tab. Immusante and Tab. Guduchi)	1 tablet twice daily orally (BD) for 30 days
CTRI/2020/07/026674	Effect of Ayurveda Spice Mix Tablet for the Prevention of COVID-19 infection in people exposed to Covid 19 and in high risk patients	Randomized, Parallel-Group, Active Controlled Trial	18-75 years, n=130	Ayurveda Spice mix tablet (500 mg)	Thrice a day
CTRI/2020/07/026820	Curcumin for COVID-19 Pre Exposure Prophylaxis	Randomized, Parallel-Group, Placebo-Controlled Trial	18-70 yrs	Oral Curcumin capsule (500 mg)	twice daily for 12 weeks

CONCLUSION

The use of herbal medicine is a potential platform for management of COVID-19 virus. Herbal medicine and its bioactive fractions are found to have potential preventive candidate and as supportive measures through boosting the immune system. The Clinical evidence of the potential traditional AYUSH medicines and recommendations for treatment of SARS coronavirus (SARS-CoV) infections has shown significant results, and reinforced the awareness regarding use of herbal medicine as potential agent with beneficial effect in the treatment and management of Covid 19 disease.

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Conflict of Interest

None declared.

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