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Herbal medicine is the way of potential therapeutic option for the treatment of COVID-19: Recent updates

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ABSTRACT

COVID-19 is an acute and progressive respiratory illness, which is highly contagious. In 2020, COVID-19 has become a major health issue; its prevalence has been increasing at an alarming rate across the world. Less availability of COVID-19 drugs, high treatment cost, and side effects affect the quality of life of a person infected with COVID-19 in countries with poorly developed health systems. Through infection, patients can die due to acute respiratory distress syndrome (ARDS) initiated by systemic inflammatory reactions due to the undue emancipation of chemokines and pro-inflammatory cytokines by the immune effector cells. The aim of this review is to summarize and evaluate the evidence of traditional medicine, which can facilitate the treatment options according to the clinical manifestations of COVID-19 patients and has proven effectiveness in prevention and control of disease. The systemic search for medicinal plants for the therapeutics of COVID-19 was performed considering the articles published through the different scientific databases. The results suggested that some important medicinal plants reported for antiviral and anti-allergic/anti-inflammatory activities are *Withania somnifera* "Ashwagandha", *Asparagus racemosus* "Shatavari", *Ocimum sanctum* "Basil", *Foeniculum vulgare* "Fennel", *Allium Sativum* "Garlic", *Tinospora cordifolia* "Giloy", *Glycyrrhiza glabra* "licorice", *Organum vulgare* "Oregano", *Rosmarinus Officinalis* "Rosemary", *Salvia* "Sage", *Zinger officinale* "Ginger", *Torreya nucifera* "Japenese torreya", *Isatis indigotica* "Ban-Lan-Gen" *Echinacea*, *Panax ginseng*, *Houttuynia cordata*, Cannabinoid (CBD). The traditional medicines against COVID-19, currently under clinical trials (NCT04494204, NCT04387643, NCT04395976, NCT04621903, NCT04621903, NCT04544605) and clinical application of traditional Indian and Chinese medicine for the treatment of COVID-19 are also found. This review highlights the major goal of herbal remedies and their significant role to cure antiviral diseases like COVID-19. It is suggested that promising polyherbal formulations and traditional plants must be investigated on the priority basis to solve current crisis.

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INTRODUCTION

Present decade witnesses the outbreak of life-threatening viral disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has issued a caution that, although the COVID-19 is a pandemic disease, it should be contained to prevent the global spread. It spread rapidly and to date has 3 million deaths with more than 140 million cases of infection all over the world (wordometers.info/coronavirus). SARS-CoV-2, a novel and pathogenic coronavirus causes respiratory illness. Many variants of SARS-CoV-2 are found they are up to 70% more transmissible than the previously circulating form of virus, which is why every country is worried, and needs urgent follow-up and investigation (1, 2). Extensive treatment to reduce the infection of COVID-19 is a use of allopathic medicine (3, 4) but we should also implement the herbal medicine to control the current outbreak because prescribe drugs used for the treatment of COVID-19, has too much cost along with their side effects due to their toxicity. These antiviral drugs show allergic reactions or hypersensitivity, with symptoms such as fever, nausea, bleeding, bone loss, heart disease, high blood sugar and kidney, liver, or pancreas damage (5-7).

KEYWORDS:
COVID-19, Medicinal plants, Traditional medicine, Phytotherapy.

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For public health assessment, there is an urgently required to develop antiviral therapy. Additionally, social, and economic problems generated by the COVID-19 pandemic also called for rapid intrusions. Therefore, at this moment, herbal medicine needs special attention and efforts to protect or reduce the infection. The herbal (traditional) medicines get hold of a significant proportion of >83 billion dollars annual production growing exponentially (8, 9). In developing countries like 70-95% of inhabitants rely on herbal medicines for primary care since they are cost-effective and unavailability of conventional drugs. WHO estimated that about 80% of the world population still uses herbs and traditional medicines for fulfilling their primary health care needs (10). In India, more than 80% of the population relay upon herbal drugs and it shares about 2.5 % of the global market. More than 60% of market share is being controlled by North America and European Union (WHO, 2002) (11). At present herbal formulations are used more as therapeutic agents for arthritis, liver disease, diabetes, cough remedies, adaptogens and memory enhancers (12). Despite such extensive acceptability, the number of standardized herbal drugs is less due to being short of regulatory standards and implementation protocols. Standardization requires a natural plant product to be certified at the origin itself by a good agricultural practices (13). There is a need to improve techniques for good manufacturing practices for extraction procedures (14).

There are so many herbal formulations and scientifically validated herbal plants but to date, no single approved herbal drug is available for mass usage. It is due to a lack of standard methodologies adopted before the development of drugs. However, some in-silico/docking studies have shown potential to treat the patient infected with COVID-19 (15-17). Herbal medicinal therapy is a unique alternative for this pandemic disease COVID-19 (Figure 1). This review focuses on a new perspective regarding COVID-19 prevention. We summarized the most recent advances in COVID-19 prophylactics and vaccine development in brief and deeper insight on medicinal plants and herbal drugs used in the treatment and management of viral and respiratory diseases all over the world.

RECENT PROPHYLACTICS DEVELOPMENT OF COVID-19

The present scenario has emphasized the requirement for therapeutic opportunities to relive and overcome this latest pandemic. Despite the fact, the deteriorating developments of COVID-19, there is no drug certified to have considerable effects in the medical treatment for COVID-19 patients. The COVID-19 pandemic requests for the rapid testing of new treatment approaches. Based on the evidence, hydroxychloroquine is the first medicine opted for the treatment of disease. Umifenovir, remdesivir, and favipiravir are deemed the most hopeful antiviral agent; by improving the health of infected patients (3, 4). Tocilizumab has emerged as an alternative treatment for patients with high risk of cytokine storms (18). The anti-inflammatory dexamethasone is known steroid medicine that can save the lives of seriously ill patients, and it is shown in a randomized clinical trial by the United Kingdom that it reduced the death rate in COVID-19 patients. Antiviral drugs currently used to treat COVID-19 were initially developed for Ebola, influenza, or SARS (See table 1 for mechanism of action of potential drugs used for COVID-19 treatment). Convalescent plasma might be a potential therapy for critically ill COVID-19 patients. But the latest study revealed that remdesivir, hydroxychloroquine, lopinavir and interferon regimen had little or no effect on hospitalized patients (19). Vaccine is a very urgent need to prevent COVID-19 super spreading. A COVID-19 vaccine is a vaccine intended to provide acquired immunity against COVID-19. Several companies are developing DNA, RNA, protein, and vectored vaccines (3, 20). Nucleic acid-based vaccines can be produced quickly based on viral sequences, which permits a rapid path to the Clinic. Vaccines authorized for emergency use or approved for full use in USA, UK, India and other countries are Tozinameran from Pfizer, mRNA-1273 from Moderna, AZD1222 from AstraZeneca, and BBV152 from Bharat Biotech (https://covid.cdc.gov; https://www.timesnownews.com/health/article/oxfords-azd1222-and-bharat-biotechs-covaxin -a- timeline-of-development/624966). However, medication options and standard treatment for Covid19 are restricted (see table 2 for vaccines certified by WHO for treatment of COVID-19).

APPLICATION OF TRADITIONAL MEDICINE (TM) TO PREVENT AND TREAT COVID-19

Traditional medicine has therapeutic effects on all clinical stages of COVID-19 (Xiang et al., 2020). Traditional medicines are effective in preventing COVID-19, In China and India medical staff avert an iatrogenic infection by using a decoction made on the principal of clinical trial (CT; NCT04387643). As of March 2020, latest cases of COVID-19 in China have reduced in figure to single digits. Traditional Chinese Medicines (TCM) therapeutic outcomes was outstanding, with a national participation rate of over 90% (21). For primary stages, traditional medicines can relive fever, cough, shortness of breath and can improve the cure rate by preventing the infection from becoming severe. For severe and critical cases, traditional medicines combined with supportive therapy such as modern medicine and oxygen therapy, can enhance pulmonary ventilation function and an excessive immune response (CT; NCT04621903, NCT04544605). Taking traditional medicine compound decoctions can help to reduce pulmonary interstitial fibrosis and pulmonary inflammation, as well as restore physical strength (22, 23).

The development of new agents against COVID-19 is not realistic to pass toxicity tests and safety measures. Consequently,

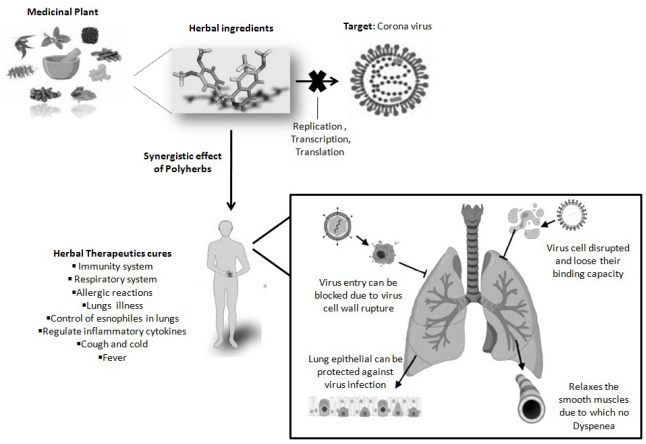

Fig.1: Effect of herbal therapeutics in COVID-19 associated lung injury

Table1: Site of action of potential agents used for COVID-19 treatment

Drug	Mechanism of Action
Chloroquine, Hydroxychloroquine	Inhibition of Endosomal Acidification
Remdesivir, Favipiravir, Ribavirin	Inhibition of the RNA dependent RNA Polymerase
Lopinavir/ritonavir	Inhibition of Protease Enzyme
Umifenovir	Inhibition to Critical Membrane Fusion
Interferons	Inhibition of Viral Exocytosis
Dexamethasone	Regulate Cytokines Formation
Tetracyclines	Inhibition of Bacterial Translation
Tocilizumab	Regulate Cytokines Formation
Meplazumab	Inhibition of CD147
Itolizumab	CD6 Inhibitor
Teicoplanin	Inhibition of cathepsin L
Nitazoxanide	Inhibition of Neuraminidase Enzyme
Ivermectin	Inhibition of Replication
AMY101	Inhibition of C3 Complement Protein
Eculizumab	Inhibition of C5 Complement Protein
SDRV-003	Regulate Cytokines Formation
LCB1	Neutralizing Protein
Nafamostat	Serine Protease Inhibitor
Famotidine	Histamine H2 Receptor Antagonist
Dipyridamole	Nucleoside Transport Inhibitor
Chlorpromazine	Antagonist of D2 Dopamine receptor

Table 2: List of vaccination trail done for COVID-19

Name	Developmental Status	Properties	Developer
BNT162	Completed	mRNA vaccine	BioNTech and Pfizer
mRNA-1273	Completed	mRNA vaccine	Moderna and NIAID
INO-4800	Phase 2/3	DNA vaccine	Inovio Pharmaceutical
Unnamed	Phase 1/2	Inactivated virus	Wuhan Institute of Biological Products and Sinopharm
Unnamed	Phase 1/2	Inactivated virus	Beijing Institute of Biological Products and Sinopharm
Unnamed	Phase 1	Inactivated virus	Institute of Medical Biology and Chinese Academy of Medical Sciences
AZD1222	Phase 2b/3	Adenovirus vaccine	University of Oxford and AstraZeneca
Ad5-nCoV	Phase 2	Adenovirus vaccine	CanSino Biologics
Covaxin	Completed	Inactivated vaccine with alum as adjuvant	Bharat Biotech and ICMR
CDX-005	Phase 1	Live-attenuated	UK's Oxford University, a manufacturing partner of which is India's Serum Institute
ChAdOx1 nCoV-19	phase 1/2	adenovirus	Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford; NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton; Clinical Research Facility, Imperial College London; St Georges University of London and University Hospital NHS Foundation Trust; and University Hospitals Bristol and Weston NHS Foundation Trust)
NVX-CoV2373	Phase 3	Protein subunit	Novavax
Sputnik V	Completed	adenovirus vaccine	Gamaleya Research Institute of Epidemiology and Microbiology
PiCoVacc	Phase 1/2	Inactivated virus, plus adjuvant	Sinovac
ZyCoV-D	Phase 2	DNA vaccine	Zydus Cadila
Johnson &Johnson COVID-19 vaccine	Completed	adenovirus vaccine	Janseen Pharmaceutica

active compounds affecting viruses or host targets in existing herbal medicines were screened by many scientists. Currently, various natural products have been found to potentially possess anti-SARS-CoV-2 activity (24). There are some compounds with anti-coronavirus activity shown in table 3. Clinical findings have revealed that integrated medicine tends to reduce the mortality rate of SARS and help in improving the clinical symptoms of COVID-19 patients (24, 25). The effective experience of fighting COVID-19 has shown that traditional medicine has a distinctive advantage in infectious diseases.

Table 3: Natural compounds with anti-coronavirus action

Compounds	Pharmacological action	References
Baicalin	Anti-inflammatory, antioxidant, neuro-protective	(126, 127)
Hesperetin	Antioxidation, anti-inflammation	(128, 129)
Glycyrrhizic acid	Antiviral, antioxidant, immunomodulatory, cell membrane stabilization	(127, 130)
Curcumin	Antioxidant, anti-inflammatory, anti-virus, anti-cancer	(131, 132)
Luteolin	Antioxidation, anti-inflammation, anti-tumor	(133, 134)
Rutin	Anti-inflammation, anti-virus, anti-oxidation, neuroprotective effects	(135, 136)

MEDICINAL PLANT WITH ANTIVIRAL EFFECT

There are many herbal remedies suggested for viral and respiratory disease complications. To cure these diseases, there has been many plants reported during the last 20 years.

Withania somnifera

Withania somnifera belongs to Solanaceae family, is commonly known as "Ashwagandha" in Indian tradition, has been studied to some point as an antioxidant (26), but it has powers to boost the immune system. The application of the biologically active new compounds derived from the *Withania somnifera* makes it potential to treat various immunological diseases (27, 28). Ayurveda uses the root of this plant as a general health tonic, adaptogenic, nootropic, immunomodulatory. With its extensive and expanding use, it becomes judicious to systematically evaluate and document both the efficacy and safety of this plant in humans (29). It is also used for the treatment of arthritis, tuberculosis, cancer (30). A recent study highlights the significance of natural origin phytochemicals in controlling COVID-19 entry into host cells and presents a desirable and eccentric means for managing COVID-19 infection (16). Withaferin A, an active constituent of *Withania somnifera*, has been revealed to have a broad range of medicinal properties, including its antiviral activity (31). This study provides shreds of evidence for the reasonable inhibitory potential of Withaferin A. The results demonstrate a strong binding affinity of Withaferin A toward neuraminidase, the key enzyme in the life cycle of the influenza virus (31). Another active constituent of *Withania somnifera* is Wethanone revealed to interact with the main protease of SARS-CoV-2 and inhibit its activity (32). *W. somnifera* could well be the first choice of medicinal herbs in these directions, to control the COVID-19 infectivity.

Asparagus racemosus

Asparagus racemosus is a well-known medicinal plant, grown in the tropical and subtropical regions of India.Its therapeutic importance is well recognized in the Indian and British Pharmacopoeia along with several traditional systems of medicines such as Ayurveda, Siddha and Unani (33). Traditionally, this plant is popularly known as 'Shatavari', and designated in Ayurveda as a potential rasayana which prevents aging, provides immunity, increases longevity, improves mental function and also helps in the treatment of diseases related to the female reproductive system, inflammation, dysentery, biliousness, tumor and diseases of the blood and eyes (33, 34). The pharmacological studies carried out on this plant has revealed the potential adaptogenic, immunostimulant, anti-inflammatory, anti-microbial, antioxidant, anti-ulcer, galactagogue, phytoestrogenic, neuroprotective, aphrodisiac, anti-dyspepsia, anti-tussive and anti-cancerous activities (33-35). Shatavari has been reported for its anti-bacterial, anti-candidal, anti-viral activities (17, 36). There is a study in 2020 shows that in-silico investigation of phytochemicals from *A. racemosus* as the credible antiviral agent to treat COVID-19 (17).

Ocimum Sanctum

Holy basil is a culinary herb belonging to the family Lamiaceae that has several health benefits (37). Essential oils obtained from basil have been reported to have strong inhibitory activity against a wide range of pathogenic microorganisms (38, 39). Basil extracts, thus, provide an attractive mode of treatment strategy against many emerging pathogens that demand viable therapeutic options. The application of extracts and purified components of basil as possible antiviral agents has already been reported. The extracts and specific purified compounds have shown broad-spectrum activity against both DNA and RNA viruses. However, basil leaves have been tested directly on the Zika virus (40) and it showed that basil leaves extract inhibits the entry of Zika virus. Basil seed oil revealed to modulate both humoral and cell-mediated immune responsiveness (41). Based on the molecular simulation study, *Ocimum sanctum* extract can be incorporated as a preventative measure against COVID-19 due to its potential to prevent replication of Covid-19. *Ocimum sanctum* and different species of *Ocimum* have been shown to target the reverse transcriptional activity of HIV and can be studied for activity against SARS-CoV-2 as well (42, 43). These findings give a clue to investigate and find the structure-based drug designing in the development of newer drug moieties against the COVID-19.

Echinacea

Echinacea is a plant genus belong to the family Asteraceae and is comprised of 11 taxa of herbaceous and flowering plants (44). *Echinacea* preparations (which are mainly based on three commercially important species; *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*) are generally used for preventing and alleviating the symptoms of bacterial and viral infections (45). Furthermore, some *Echinacea* preparations are known to exert antioxidant and anti-inflammatory and potential immunomodulatory activities (46). *Echinacea*, a native plant of North America, is widely used to prevent or to provide early treatment for the common cold (47). Studies with *Echinacea* lend plausibility to the idea that herbs somehow stimulate the immune system and numerous clinical trials have documented the beneficial effects of *Echinacea* preparations (48). Yamada et al showed that *Echinacea*, can enhance immune function by increasing immunoglobulin production. Furthermore, this herb might regulate antibody production by enhancing both Th1 and Th2 cytokine production (49). One pharmacodynamic study showed significant broncho-dilatory and anti-inflammatory effects of *Echinacea* complex that was like the effects of classic synthetic drugs. Thus, this herb in traditional medicine used as a treatment for allergic

disorders of the airways, such as asthma and may improve the broncho-pulmonary illness.

Foeniculum vulgare

Foeniculum vulgare, universally known as Fennel is a medicinal plant belonging to the Umbelliferae (Apiaceae) family, used by humans since ancient times, due to its flavor. It was cultivated nearly in every country (50). A series of studies revealed that *F. vulgare* effectively controls numerous infectious ailments of bacterial, fungal, viral, mycobacterium, and protozoal origin. It has antioxidant, antitumor, chemopreventive, cytoprotective, hepatoprotective, hypoglycemic, and oestrogenic activities (51). Study done in 2014 showed that *F. vulgare* has a special kind of memory-enhancing impact and can reduce stress. Limited clinical trials as well as in -vivo studies showed that chronic use of *F. vulgare* is not harmful (51, 52). Ethanol extract and essential oil from *F. vulgare* exhibited broncho-dilatory activity on contracted tracheal chains of guinea pig and contributed to its relaxant effect on guinea pig tracheal chains (53).

Allium sativum

Allium Sativum (Garlic) has been traditionally used for both gastronomic and medicinal purposes (54). Garlic is alleged to have antimicrobial, antifungal, antidiabetic (55-57) and antiviral properties (58). It has properties to lower the cholesterol and triglyceride levels, reduce blood pressure, and slow down the development of atherosclerosis and act as an anticoagulant (59). Garlic extract alone or as an adjunct to classical antibiotics retains the great potential for the treatment of drug-sensitive as well as drug-resistant tuberculosis (60). Kyo et al study has shown anti-carcinogenic and immunomodulatory effects (59). The exact usage of garlic for the common cold most likely varies countrywide. A cross-sectional population study conducted in Australia in 2007 found that 10.7% of participants used garlic, 29.8% for cold, flu or fever (61). According to Barnes et al, in USA in 2004, 3.76% of the population used garlic supplements (62). Since many manufacturers of garlic supplements claim their products enhance the immune system and support for the prevention and cure of the common cold. The pervasiveness of herbal medicine use seems to be relatively reliable between Western countries (62, 63).

Tinospora cordifolia

Tinospora cordifolia (Giloy), is a member of Menispermaceae family, and a large, deciduous shrub found all over India, particularly in the tropical parts soaring to an altitude of 300 m. and also in some particular parts of China (64). Studies on the effects of natural immunomodulators to heal various diseases associated with the immune system have been increasing interest in recent years (65). *Tinospora* species have been one of the widely investigated plants for their effects on the immune system to treat various diseases related to immune health. However, their ethnopharmacological uses are mainly very limited (66). A range of active constituents derived from the plant like alkaloids, steroids, diterpenoid, lactones and glycosides have been isolated from the different parts of the plant like root, stem, leaves, and whole plant (67, 68). Nowadays these plants have more importance of research to prepare several dosage forms because of medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, antiarthritic, antioxidant, antiallergic, anti-stress, anti-leprotic, anti-malarial, hepato- protective, immune-modulatory and anti-neoplastic activities (69). *T. cordifolia* encompasses several components that might affect the body. Some of these constituents have antioxidant effects while others might boost the body's immune system (70). It aids to eliminate toxins and purifies blood, fights against bacteria, and helps to recover fevers. It is an anti-pyretic herb; it can reduce signs and symptoms of several life-threatening conditions like Dengue, Swine Flu and Malaria as well. It helps to improve blood platelets in fever (71). It has been shown to decrease in the recurrent resistance of HIV virus thus improving the therapeutic outcome , revealing its promising role of application in management of the disease (69). Study published in 2012, confirmed that an immunomodulatory protein in *T. cardiofolia* stem showed lymphoproliferative and macrophage-activating properties strengthen the rationale of the use of its preparations in several ayurvedic medicines for immunomodulation (72).

Panax ginseng

Panax ginseng has been described as one of the most common herbal medicines used in humans. Ginseng extracts have been reported to elevate the production of inflammatory IL-6 and IL-8 cytokines and to increase antiviral cytokine interferon (IFN) upon influenza virus infection in mice model (73). Active component of *ginseng* ginsenoside metabolite protopanaxatriol demonstrated significant inhibition effect on IP-10 production upon H9N2/G1 infection and it could protect endothelial cells from H9N2/G1-induced apoptosis and DNA damage (74). Ginseng ginsenoside compounds (Rg1, Rb1, Rb2, Rg3) are transformed into pharmaceutically active components (PPD, Rh2, Compound K, PPT) by the intestinal microbes during digestion (75). Fermented products of ginseng exhibited antimicrobial activity (76). Most clinical trials disclosed that ginseng, at various dosages, is a safe and effective method of prophylaxis, reducing the symptoms and lowering the risk and duration of colds and flu. So, these findings suggest ginseng as a possible therapeutic agent for respiratory infections (77). Nevertheless, it has been well documented whether fermented ginseng extracts have antiviral activity, conferring *in-vivo* safeguard against influenza virus (73, 78).

Houttuynia cordata

Houttuynia cordata belongs to the family Saururaceae, is a traditional Chinese medicine used for hundreds of years to relieve lung-related symptoms such as lung abscess, phlegm, cough and dyspnea (State Pharmacopoeia Commission of People's Republic of China, 2005) and is effective in treating pneumonia, infectious disease, refractory hemoptysis as well as malignant pleural effusion. Recently, several studies also provided scientific data to support and unveil its anti-inflammatory (79), anti-allergic (80), virucidal (81), anti-oxidative (82) and anti-cancer activities (83). *H. cordata* extract may decrease the process of viral replication by inhibiting the key enzymes and activate negative feedback control in the immune system (84). Recent study published in 2018, indicated that *H. cordata* improved lung and intestine injury generated by Influenza virus infection (85). Site of action of H. *cordata*

is associated with inhibition of inflammation, protection of intestinal barrier and regulation of mucosal immunity. *H. cordata* may have clinical potential to treat viral infection and may use as an alternative medicine for human beings (86).

Glycyrrhiza glabra

Glycyrrhiza glabra (licorice), also known as Mulethi and sweet wood, is native to the Mediterranean and certain areas of Asia. Licorice is a perennial herb, which has extensive pharmacological effects for human beings. The most common medical use is for treating upper respiratory diseases including coughs, hoarseness, sore throat (86). Licorice is effective against human respiratory syncytial virus (HRSV) infection on airway epithelial cells. It inhibited HRSV mainly by preventing viral attachment, internalization, and by stimulating IFN secretion (87). Licorice extracts have been used for more than 60 years in Japan to cure chronic hepatitis, and have therapeutic benefits against other viruses, including human immunodeficiency virus (HIV), cytomegalovirus (CMV), and Herpes simplex. Deglycyrrhizinated licorice formulations are useful in treating various types of ulcers, while topical licorice formulations have been used to smooth and heal skin eruptions, such as psoriasis and herpetic lesions (88).

Organum vulgare

Organum vulgare (Oregano) is a flowering plant belongs to family Lamiaceae, sometimes called wild marjoram known as sweet marjoram. It is native in Western and Southwestern Eurasia and the Mediterranean region. A wide range of pharmacological functions has been reported from this plant like antioxidant, antiplatelet, antifungal, antibacterial, antiprotozoal, anti-inflammatory, antiatherosclerosis, antitumor and antiulcer (89). Oregano oil and its active components, like carvacrol, have antimicrobial efficacy against numerous pathogenic bacterial species (90-92). Based on the studies, their antimicrobial efficacy is also broad-spectrum, as they are effective against MNV, a nonenveloped virus. These derived compounds appear to cause the viral capsid to lose its integrity by binding to the capsid or by preventing adsorption of the virus to host cells, thus true virus inactivation occurs. The antibacterial activity is slightly different due to the complexity of bacterial cell wall components and its structures; even so, there are some evidences that carvacrol acts directly upon bacterial membranes/cell wall components as well (90, 93).

Rosmarinus Officinalis

Rosmarinus Officinalis (Rosemary), is a member of the mint family Lamiaceae that widely native in the Mediterranean region. This aromatic plant is used as a natural food preservative due to its antiseptic properties, besides its medicinal uses (94). Polyphenols derived from this aromatic plant have been used as natural antiviral agents, especially the flavonoids including quercetin, galangin, procyanidin and pelargonidin (95, 96). The antiviral effects of these substances are higher when used before virus adsorption (95, 97). While the antioxidant and antibacterial activities of this medicinal plant are variously described (98), its antiviral properties have been little investigated (99). Thus, we can presume that Rosemary could be a rich source for bioactive components that can act as antibiofilm and antiviral agents against human pathogens (100).

Salvia

Salvia (Sage) is an important genus belongs to the family Lamiaceae, consisting of about 900 species. It is distributed throughout the Central and South America (approx 600 species), Central Asia and Mediterranean (250 species), Eastern Asia (approx 90 species) (101). Many species of *Salvia*, including *Salvia officinalis L.*, have been used as medicinal herbs worldwide. In traditional medicine, Sage is used for different diseases, including inflammation of the mouth and throat (102, 103). Extract of different species of *salvia* has been checked for their biological activities like antimicrobial, antioxidant, anti-inflammatory, antimutagenic, antiviral, spasmolytic, cancer preventive and cholinergic binding properties. These mechanisms are partially described in some scientific studies (104, 105). Antiviral action of the ubiquitous human pathogens was assessed against fourteen salvia species extracts, (105, 106). It is also published that it works against viral disease like HSV-1 (herpes simplex virus type 1), it has been also reported that extract of *S. coccinia* shows anti-HSV-1 activity (107). Salvia species have pharmacological activities especially targeting cardiovascular, renal, hepatic and immune systems diseases (108).

Zinger officinale

Zinger officinale (Ginger) belongs to family Zingiberales, is originated in Islands of Southeast Asia but now it is transported all over the world from Asia. This is one of the classic examples holding unique therapeutic significance and its bioactive molecules used as an immune booster and can control the extent of gastric, colorectal, liver, ovarian and skin cancers (109, 110). Concealed humoral and cellular immune reactions through direct inhibition of sensitized T and B lymphocytes (111, 112). An Intraperitoneal injection of ginger extract diminishes exotoxin, and IL-4, IL-5 levels along with a decrease in eosinophils to the lung (113). The ginger and its bioactive molecules provide protection against hepatotoxicity induced through ethanol, bromobenzene, and acetaminophen via modulation of enzymes (114). The anti-inflammatory potential of ginger will be helpful for the management of disorders like respiratory infections (115). It can also protect our body from hazardous effects of chemicals; it has been highlighted in several scientific investigations (116).

Torreya nucifera

The Japenese torreya (*Torreya nucifera*) belongs to a family Taxaceae. It is a coniferous evergreen tree native to southern Japan and to South Korea's Jeju Island. Lipid metabolism studies have been done on the composition of the essential oils of the coniferous trees; some have been done on the medicinal values of *Torreya nucifera* (117). It has been used traditionally as a remedy for various diseases in Asian country. More than ten phytochemicals isolated from the leaves of *Torreya nucifera* were shown the anti SARS-CoV activity by inhibiting 3CLpro activity from the ethanol extracts of the leaves of *T. nucifera* (118). It could well be the choice of medicinal herbs in these directions, to control the COVID-19 infection.

Isatis indigotica

The root of *Isatis indigotica* belonging to the family Cruciferae, popularly as Ban-Lan-Gen is used as a traditional Chinese medicine for influenza, epidemic hepatitis, inflammatory disease with redness of skin, sore throat, etc (119). As one of the popular herbal medicines, the root of *I. indigotica* has been documented in Chinese Pharmacopoeia since 1985 and its purified extracts have been formulated for clinical use (Ministry of Public Health, Chinese Pharmacopoeia (English Version), Part I, Chemical Industry Press, Beijing, 2000). *I. indigotica* root and phenolic Chinese herbs were frequently used for the prevention of SARS in China, HongKong, and Taiwan. Some studies are there which shows antiviral activity of *I. indigotica* (13, 120, 121), so this medicinal plant can be used as antiviral treatment of COVID-19.

Cannabis

Cannabinoid (CBD) is also a possible treatment for severe COVID-19 patients. Studies published in 2020 showed that cannabinoids were also used as a treatment to control the inflammatory response of Covid-19 virus (3, 122, 123). It is designed in an injectable drug form to help a serious syndrome occurs in severe cases of coronavirus "acute respiratory distress syndrome (ARDS)". This syndrome can be triggered during a cytokine storm, a dangerous over-elevation of cytokines, which signal the body to produce more inflammation. It will have the advantage of impacting several pro-inflammatory signaling pathways, by enhancing the effectiveness of the drug to rapidly dampen the cytokines release and prevent the acute outcomes like ARDS. Which can be linked to drowning as the lungs fill with fluid. Now, cannabinoid is designed as synthetic injectable drug named, ARDS-003, has been approved for the phase I clinical trial by FDA, it will proceed by Tetra Biopharma. Initially, FDA asserted that was appropriate to support for starting study in COVID-19 infected patients.

A literature search was done to investigate medicinal plants, which can be used in treating COVID-19. These medicinal plants with antiviral and other important properties are present in the available literature with a high level of studies; but there have been very limited randomized clinical trials (RTCs). Though, it can be observed that comprehensive chemical and pharmacological review of numerous bioactive constitutes have anti-viral, ant-inflammatory, immune boosters, and hold other unique therapeutic significance activities. Cohort studies and controlled trials should be done to warrant their pharmacological applications.

MULTIFUNCTIONAL, CONJUGATED THERAPY BY POLYHERBAL FORMULATION FOR COVID-19

Most of the studies in traditional medicine, executed are based on the single herbal active constituent. But polyherbal formulations more important and interesting than mono-therapeutic herbal preparation that are commonly used because of the synergistic effect. Herb-herb combinations have been used in Chinese medicine practice for thousands of years (124). The pharmacological principles of polyherbal work together in a dynamic way to generate maximum therapeutic efficacy with minimum side effects. The increasing interest in the use of plant-based formulations is leading to a fast-growing market for Ayurvedic medicines (125). In the Ayurvedic system of medicine mainly polyherbal compounds are used for the treatment of various infections. Many of them under clinical trials in COVID-19 patients (see table 4). The Ministry of AYUSH (Government of India) and TCM has listed out some formulations and recommended their use as prophylactic measure (see table 5). The future goal in the successful treatment of COVID-19 must be given herbs to make polyherbal preparations that must maintain a normal respiratory function with minimal risk of severing hypoxemic respiratory episodes. Drugs prescribed for the treatment of COVID-19 reduces fever, cough, and fatigue either by increasing immunity, reducing toxins in the body, or preventing the virus from fusing to the cell by blocking a receptor to facilitate the binding of virus to the cell. In ayurvedic polyherbal formulation, through in the study of various phytoconstituents and finding of useful herbal combinations, that may work synergistically to treat COVID-19.

CONCLUSION

The COVID-19 pandemic has led to the high-priority search for herbal therapies that work effectively. Herbal medicine is

Table 4: List of traditional medicine clinical trials done for COVID-19

A. Source: www.clinicaltrials.gov

Trail identifier	Status	Study Title	Interventions	Locations
NCT04494204	Completed	Effect of a Combination of Treatment of Reginmune Capsule and Immunofree Tablets in the Treatment of Mild to Moderate COVID-19 Patients	Combination Product: Immunofree tablets and Reginmune capsule	Govt Medical College and Govt General Hospital (Old RIMSGGH) Srikakulam, Andhra Pradesh, India Parul Institute of Ayurveda and Research Parul University Vadodara, Gujrat, India Lokmanya Hospital Pune, Maharashtra, India
NCT04387643	Completed	Protecting Health Care Workers During the COVID-19 Outbreak	Dietary Supplement: Ayurvedic Kadha	Samta Ayurveda Prakoshtha Jaipur, Rajasthan, India
NCT04395976	Withdrawn	Ayurveda as Prophylaxis for Suspected COVID-19 Patients	Other: Ayurveda	British Ayurvedic Medical Council London, United Kingdom
NCT04621903	Completed	A Pilot Study on Efficacy and Safety of Ayurveda Combination in Patients with Mild-to-Moderate COVID-19	Other: Shanshamani Vati Plus	Aarogyam (UK) CIC Leicester, United Kingdom
NCT04544605	Recruiting	Special Chinese Medicine Out-patient Programme for Discharged COVID-19 Patients	Other: Individualized-Chinese herbal medicine	School of Chinese Medicine, Hong Kong Baptist University Hong Kong, Hong Kong, China

B. Source: www.ctri.nic.in

Trail identifier	Status	Study Title	Interventions	Locations
CTRI/2020/05/025215/ Kabasura kudineer	Completed	Effectiveness of siddha medicine, kabasura kudineer and vitamin c-zinc supplementation in the management of mild COVID-19 patients	Interventional (randomized, parallel group Trial)	The role of vitamin C with zinc supplementation in the management of COVID 19 is still not clear. Therefore, study will compare the effect of kabasura kudineer and vitamin C with zinc supplementation in terms of negative conversion of SARS CoV2 infection
CTRI/2020/05/025161/ Herbal formulation-aayudh advance	Completed	To study the effectiveness of herbal formulation - aayudh advance as a supplementary treatment for the corona virus 2019 (COVID-19) infected patients	Interventional (randomized, parallel group, active controlled Trial)	"Aayudh advance", when given concomitantly with standard of care, was found to be 100% safe, devoid of any drugdrug interaction, effective as virucidal to reduce viral load, and increased the recovery rate when compared to standard of care alone when tested in mild symptomatic COVID-19 patients
CTRI/2020/04/024883 ZINGIVIR-H	Completed	Clinical research on safety and efficacy of ZingiVir-H as an add on therapy in COVID-19 patients	Interventional (Other)	Zingivir H consumption with standard of care in COVID 19 confirmed patients showed a remarkable recovery compared to that of placebo
CTRI/2020/05/025275/ Ayurveda rasayana along with conventional guidelines for health care workers	Completed	Role of chyawanprash in the prevention of COVID-19 in health care workers	Interventional (randomized, parallel group Trial)	No adverse effect was found in the study
CTRI/2020/06/025592/ Immunity kit	Completed	Use of herbal medicine like tulsi, amruth (giloy), turmeric, ashwagandha as add on treatment in COVID-19 patients	Interventional (single arm Trial)	Upon using the ayurvedic formulation as add on treatment, the recovery was better in terms of signs and symptoms of COVID-19 patients
CTRI/2020/06/025590/ Astha 15 capsule	Completed	A clinical trial to evaluate safety and efficacy of polyherbal capsule Astha-15 used as an add on therapy with standard care of therapy as an immunity booster in the suspected and COVID-19 diagnosed patients	Interventional (randomized, parallel group, placebo-controlled Trial)	A better recovery rate was observed
CTRI/2020/06/025556/ Virulina® along with standard treatment protocol	Completed	A clinical trial to know the effect of Virulina® along with standard treatment in COVID-19 positive patients	Interventional (randomized, parallel group, placebo controlled Trial)	The formulation was found to boost the immunity of the patients and help ease the symptoms
CTRI/2020/07/026371/1. Kabasura kudineer 2. Shakti drops 3.Turmeric plus tablets	Completed	Kabasura kudineer, shakti drops and turmeric plus in the management of COVID-19	Interventional (Others)	Better recovery rate was observed in terms of signs and symptoms of stage 1 and 2 of COVID-19 cases on addition of ayurvedic medicines, thereby improving the quality life of stage 1 and 2 of COVID-19 patients
CTRI/2020/07/026570/ Cap. IP	Completed	Safety and efficacy of ayurvedic capsule in mild to moderate COVID-19 infection	Interventional (randomized, parallel group Trial)	Improvement was observed in respiratory symptoms of covid patients
CTRI/2020/05/025425/ Chayapanprash (an ayurvedic herbal preparation)	Completed	Ayurvedic intervention (chyawanprash) in the prevention of COVID-19 pandemic among health care personnel	Interventional (single arm Tria)	This remedy was found to be a possible safe prophylactic remedy for COVID-19
CTRI/2020/07/026433/1. Dashamula kwatha and pathyadi kwatha with trikatu churna 2. Sansamani vati 3. AYUSH 64 4. Yastimadhu Ghanavati	Completed	Effect of ayurveda medicine in COVID-19 mild symptoms	Interventional (randomized, parallel group, active controlled Trial)	No adverse reaction was observed and improvement in signs and symptoms
CTRI/2020/05/025397/ Purified aqueous extract of cocculus hirsutus (AQCH)	Completed	A study to evaluate the effect and safety of a phytopharmaceutical drug in treatment of coronavirus infection	Interventional (randomized, parallel group Trial)	Clinical improvement was observed in covid patients in terms of disease severity
CTRI/2020/05/025276/ Ayurveda protocol	Completed	Effect of ayurvedic intervention in COVID-19 positive cases	Interventional (single arm Trial)	Ayurveda treatment protocol includes sanshamani, nagaradi kwath, amalaki churna and golden milk improved the strength of the patient

Table 5: Clinical application of traditional Indian and Chinese medicine for the treatment of COVID-19

AYUSH recommended traditional Indian medicines			
Traditional herbal formulas	**Constituent**	**Therapeutic effect**	**References**
AYUSH kwath	Ocimum sanctum L. (leaves), Cinnamomum verum J.Presl. (stem bark), Zingiber officinale Roscoe (rhizome), Piper nigrum L. (fruit)	Immunomodulator, antiviral, anti-allergic and anti-inflammatory	(137-144)
AYUSH-64	Alstonia scholaris (L.) R.Br. (bark), Picrorhiza kurroa Royle ex Benth. (rhizome), Swertia chirayita (Roxb.) H.Karst. (whole plant), Caesalpinia crista L. (seed pulp)	Immunomodulator, antiviral, anti-allergic and anti-inflammatory	(145-152)
Anuthaila	Leptadenia reticulate (Retz.) Wight and Arn. (root/ stem bark), Cedrus deodara (Roxb. ex D.Don) G.Don (stem), Vetiveria zizanioides (L.) Nash (root), Ocimum sanctum L. (leaves), Berberis aristata DC. (bark), Glycyrrhiza glabra L. (root rhizome), Cyperus rotundus L. (rhizome), Asparagus racemosus Willd (root), Aegle marmelos (L.) Correa (stem bark), Solanum indicum L. (leaves), Solanum xanthocarpum Schrad. and Wendl (fruit), Uraria picta (jacq.) DC. (whole plant), Embelia ribes Burm.f. (fruit), Cinnamomum verum J.Presl. (bark), Elettaria cardamomum (L.) Maton (fruit), Vitex negundo L. (leaves), Sesamum indicum L. (seed oil)	Immunomodulator, antiviral, anti-allergic and anti-inflammatory	(143, 144, 153-166)
Samshamani vati	Tinospora cardifolia (Willd.) Miers (stem)	Immunomodulator, antiviral, anti-allergic and anti-inflammatory	(167-169)
Agasthaya hareetaki	Aegle marmelos (L.) Correa (root/stem bark), Oroxylum indicum (L.) Kurz (root/stem bark), Gmelina arborea Roxb. (root/stem bark), Stereospermum suaveolens (Roxb.) DC. (root/stem bark), Premna mucronta Roxb. (root/stem bark), Desmodium gangeticum (L.) DC. (whole plant), Uraria picta (jacq.) DC. (whole plant), Solanum indicum L. (whole plant), Solanum surattense Burm.f. (whole plant), Tribulus terrestis L. (whole plant), Mucuna pruriens (L.) DC. (seed), Convolvulus pluricaulis Choisy (whole plant), Hedychium spicatum Sm. (rhizome), Sida cordifolia L. (root), Piper chaba Hunter (fruit), Achyranthes aspera L. (root)	Immunomodulator, antiviral, anti-allergic and anti-inflammatory	(155, 165, 170-187)
Coronil	*Withania somnifera*, *Tinospora cordifolia*, and *Ocimum sanctum*	Immunomodulator, antiviral, and anti-inflammatory	(16, 188)
Traditional Chinese medicine			
Huo Xiang Zheng Qi powder	Perilla frutescens (L.) Britton, Thespesia populnea (L.) Sol. ex Correa, ^ Pinellia ternata (Thunb.) Makino, Atractylodes macrocephala Koidz., Citrus × aurantium L., Areca catechu L., Angelica dahurica (Hoffm.) Benth. and Hook.f. ex Franch. and Sav., Magnolia officinalis Rehder and E.H.Wilson, Platycodon grandiflorus (Jacq.) A.DC., Pogostemon cablin (Blanco) Benth., Glycyrrhiza glabra L	Anti-inflammation, immune protection and gastrointestinal motility regulation effects	(85)
Hua Shi Bai Du recipe	Ephedra sinica Stapf, Pogostemon cablin (Blanco) Benth., Gypsum Fibrosum, Prunus amygdalus Batsch, Pinellia ternata (Thunb.) Makino, Magnolia officinalis Rehder and E.H.Wilson, Atractylodes lancea (Thunb.) DC., Lanxangia tsao-ko (Crevost and Lemarié) M.F.Newman and Skornick., Thespesia populnea (L.) Sol. ex Correa, ^ Astragalus mongholicus Bunge, Paeonia lactiflora Pall., Descurainia sophia (L.) Webb ex Prantl, Rheum officinale Baill., Glycyrrhiza glabra L	Cough symptom relief effect	(189) (190)
Jin Hua Qing Gan granule	Lonicera japonica Thunb., Gypsum Fibrosum, Ephedra sinica Stapf, Prunus amygdalus Batsch, Scutellaria baicalensis Georgi, Forsythia suspensa (Thunb.) Vahl, Fritillaria thunbergii Miq., Anemarrhena asphodeloides Bunge, Arctium lappa L., artemisia annua L., Mentha × piperita L., Glycyrrhiza glabra L	Antiviral and immune regulation effects	(191)
Qing Fei pai Du decoction	Ephedra sinica Stapf, Glycyrrhiza glabra L., Prunus amygdalus Batsch, Gypsum Fibrosum, Cinnamomum cassia (L.) J.Presl, Alisma plantago-aquatica subsp. orientale (Sam.) Sam., Polyporus umbellatus (Pers) Fr., Atractylodes macrocephala Koidz., Thespesia populnea (L.) Sol. ex Correa, ^ Bupleurum falcatum L., Scutellaria baicalensis Georgi, Zingiber officinale Roscoe, Aster tataricus L.f., Tussilago farfara L., Iris domestica (L.) Goldblatt and Mabb., Asarum sieboldii Miq., Dioscorea alata L., Citrus × aurantium L., Pogostemon cablin (Blanco) Benth	Anti-inflammatory and lung injury reduction effects	(192)
Lian Hua Qing Wen capsule	Forsythia suspensa (Thunb.) Vahl, Lonicera japonica Thunb., Ephedra sinica Stapf, Isatis tinctoria L., Gypsum Fibrosum, Mentha × piperita L., Pogostemon cablin (Blanco) Benth., Houttuynia cordata Thunb., Rheum officinale Baill., Prunus amygdalus Batsch, Glycyrrhiza glabra L	Antiviral, anti-inflammatory and immune regulation effects	(193)

AYUSH recommended traditional Indian medicines			
Traditional herbal formulas	**Constituent**	**Therapeutic effect**	**References**
Xuan Fei Bai Du granule	Ephedra sinica Stapf, Prunus amygdalus Batsch, Coix lacryma-jobi L., Atractylodes macrocephala Koidz., Pogostemon cablin (Blanco) Benth., artemisia annua L., Gypsum Fibrosum, Reynoutria japonica Houtt., Verbena officinalis L., Phragmites australis subsp. australis, Citrus maxima (Burm.) Merr., Descurainia sophia (L.) Webb ex Prantl, Glycyrrhiza uralensis Fisch. ex DC.	Detoxify and remove blood stasis, diffuse the lung, removing dampness, clear heat.	(189)- (190)

intended to exhibit therapeutic outcomes by attacking multiple diseases causing a module simultaneously. However, it is still a challenge for researchers to untangle the complex biological mechanisms and underlying material basis of herbal medicine. Along with this, there is no magic bullet available among herbs that can decrease the high level of COVID-19 infection in a short period of time, so there is a need for awareness regarding the use of raw material, crude extract, or isolated compounds to prevent infection. In nutshell, this review highlights the major goal of herbal remedies and their significant role to cure viral diseases is exploring to build a systems-biology platform to investigate the molecular active compounds, with a typical example applied to an herbal formulation in the treatment of COVID-19.

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