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PHYTOMEDICINES FOR COVID-19: OPPORTUNITIES AND OBSTACLES

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ABSTRACT: COVID-19 is a disease caused by SARS-CoV-2 that can trigger respiratory tract infection. Due to its tendency to affect the upper respiratory tract (sinuses, nose and throat) or lower respiratory tract (windpipe and lungs), this disease is life-threatening and affects a large number of populations. This virus's unique and complex nature enhances the scope to look into the direction of herbal plants and their constituents for its prevention and treatment. The herbal remedies can have preventive as well as therapeutic actions. This review focuses on various aspects of using herbal medicines for COVID-19, as herbal constituents may also have adverse effects. Various studies revealed that some medicinal plants show life-threatening adverse effects, so selecting plants, and their related studies should be appropriate and strategic. This article includes various factors that should be considered before herbal drug use in COVID-19 patients. These are clinical trials, safety, molecular mechanism, and self-medication, which have been elaborated. This article also discusses the targets of covid-19 and different coronavirus strains. As before, treatment diagnosis of the disease is very important. Various patents have been filed and granted for its proper diagnosis so that its treatment can be easy.

INTRODUCTION: Coronavirus Disease-2019 (COVID-19), a dreadful disease's first case was reported in December 2019 in Wuhan city of China and is caused by a novel coronavirus which was temporarily named as 2019-nCoV. As of August 2021, the WHO reported more than 209396015 positive cases of COVID-19 all over the world. Around 4,394,971 deaths were reported due to various tragic health conditions after being infected with coronavirus¹. A study in 2012 revealed that the traditional herbal medicine in combination with western medicine can prove helpful in eliminating

various symptoms of certain diseases as like decrease use of corticosteroids in SARS patients². The government of China started its campaign for the treatment of COVID-19 patients with the use of Traditional Herbal Medicine (TCM). A number of clinical trials were performed by china to understand the safety and efficacy of various TCM. Baicalin and Glycyrrhizin compounds extracted from *Scutellaria baicalensis* and *Glycyrrhiza glabra* herbs evenced certain *in-vitro* anticoronaviral activity³.

Plants like *Lonicerae japonicae*, *Saposhnikovia divaricate*, *Forsythia Vahl*, and *Atractylodis macrocephalae* recognize a new framework for future research in anti-anti corona TCM medicines⁴.

Doctrine of Signatures: In older times, a human suffering from various disorders and diseases evaluated plants for their medicinal use, but the

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question arises which plant to select to treat a particular disease. The belief that God has created plants for human well-being and to fulfill this objective, the whole plant or its part created by god resembles human tissue, organ, or disease. The word 'doctrine' means belief and the word 'signature' is said to be a duplet, which has been derived from two words, sign and nature, meaning signs of nature. In simple terms 'doctrine of signature' is a belief on various signs of nature or clues given by nature. On the basis of the structure of the coronavirus (SARS-CoV-2), *Momordica charantia* (bitter gourd), *Lagenaria breviflorus* (wild colocynth), *Citrullus colocynthis* (bitter apple), *Annona muricata* (soursop) and *Citrus aurantium bergamia* (bergamot orange) might be useful in combating COVID-19⁵.

Targets in COVID-19: There are three major targets in COVID-19:

Inhibition of Coronavirus at Structural Level:

Phyllanthus emblica is a herbal plant that acts as an immunomodulator for boosting immunity and health of the population fighting against dreadful COVID-19. Phyllaemblicin G7 from *Phyllanthus emblica* exhibited a high binding affinity to the Spike Protein of COVID-19.

Inhibit Coronavirus RNA Synthesis and Replication:

Tribulus terrestris is one of the herbal plants whose extract acts on coronavirus by inhibiting of its RNA synthesis and replication. The methanol extract of *T. terrestris* fruits showed potent inhibition against papain-like protease (PLpro), an essential proteolytic enzyme for protection to pathogenic viruses and bacteria.

Inhibit Virulence Factor of Coronavirus:

Inhibition of virulence factor of coronavirus is also a major target of COVID-19⁶.

Corona Virus Strains: Different strains of coronavirus for which different medicinal plants or isolated pure compounds of herbal drugs can be used are given in the elaborated form.

The isolated compound can be beneficial for the prevention as well as treatment of various coronavirus strains⁷. In search of beneficial phytotherapeutic compounds for curing coronavirus

infections, two types of research approaches were followed:

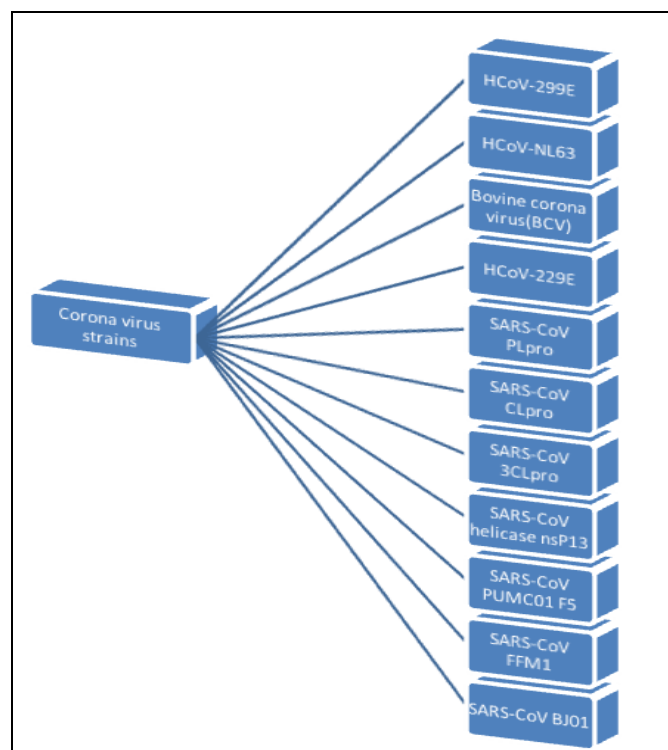


FIG. 1: VARIOUS STRAINS OF CORONAVIRUS⁷

Herbal Remedies with Preventive Effects:

Prevention is better than cure” is the theory used in this option. Boosting up the immunity can reduce the risk of COVID-19. This approach involves searching for herbal medicines with immunomodulatory effects that can help prevent this disease, *Echinacea purpurea* and *Astragalus membranaceus*⁸. Immuno-modulatory properties of polysaccharides and *Uncaria tomentosa* (from medicinal mushrooms) are also such examples.

Herbal Remedies with Therapeutic Effects:

When an active compound derived from a medicinal plant carries antiviral activity, various clinical studies can be proposed for the treatment of COVID-19. The plant extract shows various antiviral mechanisms such as viral penetration, replication inhibition, or inhibiting the SARS-3CLpro activity⁹. Extracts from plants such as *Pelargonium sidoides* and *Sambucus nigra* have undergone various clinical trials and are proposed to treat respiratory system infection regardless of the etiology¹⁰. Various studies for the anticoronaviral activities of polyphenols and pelargonium have also been performed⁹.

On the basis of various studies, it is concluded that quercetin, kaempferol and cryptotanshinone is a set of compounds which carries anti-SARS-CoV action (Zhang, Wu, Zhang, Deng and Peng, 2020). Research in the field of plant-based products offers a vast area for future investigation. Similarly, phytotherapy can be useful in managing or preventing the adverse effects of conventional drugs¹¹. As the covid-19 virus (2019-nCoV) is so novel and unique that its characteristic behavior is quite uncertain, any conclusion regarding its prevention and cure with the herbal medicinal plants, spices, or isolated compounds would be an early conclusion.

As novel coronavirus has so many structural and functional similarities with SARS-CoV-2, MERS-CoV, and SARS-CoV, various research has been performed on the antiviral activity of many phytochemical extracts to be a suitable guide for further demonstration in the field of treatment and prevention of COVID-19¹²⁻¹⁵.

Herbal Approaches: COVID-19 occurrence as a life-threatening pandemic open many gates for research related to the treatment and prevention of

this disease. Chinese, Indian, and Iranian herbal medicine with 1000 years' experience in preventing pandemic and endemic infectious diseases are worth learning and providing alternative candidates for controlling patients with COVID-19 infection. The medicines' scantiness for eradicating the disease provides numerous chances for testing herbal plants and their parts for effectively controlling the disease. Successful compliance with the clinical trial parameters, explicate the herbal drug as a positive approach with herbal medicines alone or in combination with herbal medicines for recovery of the COVID-19 disease¹⁶. The active drugs from chemical sources and the natural plants and their products can be potent anti-covid-19 drugs. Using herbal drugs and their derivatives may be the biggest support for reducing the morbidity and mortality associated with the COVID-19 pandemic. The research also needs support and complete resources from the government and related agencies. There is an urgent need to look after certain aspects of research for herbal drugs in COVID-19 treatment¹⁷. Many herbal constituents from various plants are traditionally being used for various pharmacological actions for years.

TABLE 1: HERBAL CONSTITUENTS OF PLANTS WITH PHARMACOLOGICAL ACTION¹⁸

S. no.	Plant constituent	Plant	Pharmacological action
1	taxol, docetaxel	<i>Taxus brevifolia</i>	anticancer
2	Lovastatin	<i>Aspergillus terreus</i>	hyperlipidemia
3	Ternatolide	<i>Ranunculus ternatus</i>	antituberculosis
4	Artemisinin	<i>Artemisia annua</i>	antimalarial
5	Colchicines	<i>Colchicum autumnale</i>	antigout
6	Deserpidine	<i>Rauwolfia canescens</i>	antihypertensive
7	Thymol	<i>Thymus vulgaris</i>	topical antifungal
8	Colchicines	<i>Colchicum autumnale</i>	antigout
9	Deserpidine	<i>Rauwolfia canescens</i>	antihypertensive
10	Thymol	<i>Thymus vulgaris</i>	topical antifungal
11	Tubocurarine	<i>Chondodendron tomentosum</i>	skeletal muscle relaxant
12	Emetine	<i>Cephaelis ipecacuanha</i>	amoebicide, emetic

Loop Holes in using Herbal Medicines as Treatment: After prolonged investigation and research, many patent herbal drugs were approved to relieve mild to severe symptoms of COVID-19, such as fever, cough and fatigue, and also minimize the risk of severity of the disease. On April 14, 2020, China claimed that Lianhuaqingwen capsules and Jinhuaqinggan granules for mild conditions and Xuebijing (injectable) for severe conditions were the three patent herbal drugs discovered for COVID-19. However, due to insufficient clinical

trial studies and relative data, one herbal drug and Xuebijing (injectable) was withdrawn from the market after severe adverse effects. Various internationally accepted peer-reviewed journals gives incomplete and insufficient information about the clinical trial studies for herbal drugs. However, despite the profound therapeutic benefits of these medicinal plants, some constituents of these agents have been shown to be potentially toxic, mutagenic, carcinogenic, and teratogenic¹⁹.

TABLE 2: HERBAL PLANTS AND THEIR ADVERSE EFFECTS¹⁹

S. no.	Herbal plant	Adverse effects
1	<i>Echinacea Engustifolia</i>	Liver toxicity
2	<i>Allium sativum</i>	Allergic reactions, skin inflammation
3	<i>Panax ginseng</i>	Nose bleeding, Elevated blood pressure
4	<i>Azadirachta indica, Morinda lucida, Enantia chlorantha</i>	Mutagenic potential
5	<i>Alstonia boonei</i>	induce testicular and kidney damage

Some points which should be taken under consideration for using herbal drugs are as follow:

1. Safety: The studies on herbal drugs are based on various *in-vitro* testing and unreliable clinical trials, which is alarming for its usage and related effects. Although these patent herbal drugs have been used clinically for several years, their safety should be cautiously evaluated when applying them to a novel disease like COVID-19, especially in combination with other antivirals, antibiotics, and immune suppressants.

2. Clinical Trials: The efficacy of the herbal drug should be supported by various clinical trial studies. The patent herbal drug of the fixed composition should be tested for efficacy against the endpoint parameters like mortality, time to clinical improvement, and number of days in an intensive care unit.

Even after being time-consuming and requiring lots of human efforts, the study should be done effectively as it can affect a herbal drug response in human beings. Certain adverse effects cannot be adequately evidenced due to insufficient clinical studies.

Patents:

TABLE 3: PATENTS FILED FOR DIAGNOSIS OF COVID-19²¹⁻²⁷

S. no.	Patent no.	Description
1	CN111363860A	The invention belongs to the technical field of molecular biology and particularly relates to a nucleic acid composition for detecting a novel coronavirus COVID-19 and application thereof ²¹
2	CN111239400A	A colloidal gold immunochromatographic device is invented to detect novel coronavirus, and it also explains the method of using it ²²
3	CN111551713A	The invention is related to a kit for biological detection of novel coronavirus, which involves an antibody detection microsphere and also its preparation method ²³
4	CN111060691A	The invention relates to the technical field of biological detection, in particular to an immunochromatographic fluorescence device for detecting a novel coronavirus COVID-19 and a using method thereof ²⁴
5	CN111239392A	The invention belongs to the technical field of biology and particularly relates to a novel serological diagnosis kit for coronavirus pneumonia (COVID-19) ²⁵
6	CN111118225A	A novel micro-drop digital PCR kit is invented that involves the detection of coronavirus nucleic acid. In the kit, there is a reaction solution which is containing a primer and a fluorescent group labeled probe for detecting a COVID-19ORF1ab gene and a COVID-19N gene, and a primer and a probe for detecting a human RNA reference gene ²⁶
7	CN111426840A	This patent involves in-vitro diagnosis with the help of a test strip for the detection of novel coronavirus. It also involves the preparation method of the test strip and also its application ²⁷

3. Molecular Mechanism: The study of basic molecular mechanisms is not clear for herbal drugs. Herbal drugs may contain more than one active ingredient, and it is quite obscure to identify which active ingredient is functional and which one is non-functional.

The mechanism of action of the functional, active ingredient is also not known. So, to guarantee safety and efficacy, it is important to do as many as experiment possible.

4. Self-medication: During the COVID-19 pandemic, a huge population took many herbal drugs as just in case medicines based on symptoms developing in them.

The main reason behind the frequent and inappropriate use of herbal drugs is that they need no prescription by a health professional. So, to avoid severe side effects due to self-medication, proper testing should be done²⁰.

Before giving treatment, diagnosis of COVID-19 is very important. For diagnosis of COVID-19 certain patents have been filed and granted are enlisted below:

TABLE 4: PATENTS GRANTS FOR DIAGNOSIS OF COVID-19²⁸⁻³¹

S. no.	Inventors	Date	Patent no.	Description
1	Kinilova MS, Stepanova, AY	06-08-2020	RU2729368C1 RUSSIA GRANT	This method provides a simple and affordable ultrasonic diagnostic technique for assessment of the severity of pulmonary involvement in patients with pneumonia in COVID-19 pandemics ²⁸
2	Zadorozhny AA	07-04-2021	RU203478U1 RUSSIA GRANT	This model helps to examine COVID-19 infected patients in the initial stage by checking the functioning of the olfactory analyzer ²⁹
3	Peixuan C, Yan Z, Xiofang P, Donglin, C, Liangbin H, Huiqin L, Xuating C	13-11-2020	CN111560478B CHINA GRANT	This patent invented a kit that can detect novel corona virus by combining reverse transcription PCR with Sanger sequencing in a one-step method ³⁰
4	Ten X, Wenjirao Y, Shumei X, Fusheng H,	26-02-2021	CN111378788B CHINA GRANT	In this invention, a microorganism strain marker is used, which can be used for COVID-19 diagnosis and belongs to the technical field of pathogenic microorganism infection detection ³¹

CONCLUSION: Coronavirus Disease-2019 (Covid-19) is a life-threatening disease. It affected the whole world to the extremes in the last two years. Many studies have already been done, and millions are going on in search of effective medicament. The study provided a deep insight into herbal medicines, including their beneficial effects and adverse effects. We always need to study the bad side of the medicament and the beneficial effects in the case of herbal medicines. There is a misconception in society that herbal medicines do not possess any side effects. This review highlights that important points about herbal medicine used in the treatment and prevention of COVID-19 which are to be followed before launching any herbal drug on the market. Following proper guidelines eliminates the risks to human beings and drug withdrawal from the market. This review also includes various patents filed and granted for diagnosis of COVID-19.

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