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ETHNOPHARMACOLOGICAL SIGNIFICANCE OF SOME HERBS IN COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered Coronavirus disease 2019 (COVID-19). To treat COVID-19 any active antiviral medicine is not present. For the discovery of new drugs, natural products having known safety profiles are hopeful source. In our review, we are providing an overview of natural products and traditional medicine products, which were reported to prevent SARS-CoV-2 infection and to manage COVID-19. Knowledge about the mechanism of action of the SARS-CoV-2 infection in the human host cell, the availability of disease-specific drugs, ongoing clinical trials, recent diagnostics and the potential use of certain Indian medicinal herbs for the effective treatment of COVID-19 are mentioned. For the potential effective treatment to provide solid evidence, double-blind and placebo-controlled large systematic clinical trials are required.

At present, to find a quickly effective treatment for COVID-19 drug remodel is a satisfactory strategy.

Keywords: - COVID-19, Severe acute respiratory syndrome, antiviral herbs, transmembrane protease serine,

INTRODUCTION

In 1960s, human coronaviruses first characterized which affect both children and adults and cause respiratory infections. There are large number of viruses in the family of coronavirus which are found in birds and mammals which are present in nature [1]. Coronaviruses have 39 total species under the broad kingdom of Riboviria, belonging to the family-Coronaviridae, suborder-Cornidovirineae and order-Nidovirales [2]. Under electron microscope the surface glycoproteins of this virus are visible which creates a crown-like appearance. The important part of SARS-CoV-2 is crown like spike proteins. The spike protein of the SARS-CoV-2 virus mainly interact with the human proteins which coats inside of the nose and the cells of lungs [3]. SARS-CoV-2 is RNA-enveloped, single-stranded, positive-sense virus having 80 nm–160 nm diameter and 29.9 kb genome size. By binding to the angiotensin-converting enzyme II (ACE-II) receptor with glycosylated viral structural spike (S) protein it gains entry into host cells. S protein is activated by host transmembrane protease serine 2 (TMPRSS2) and SARS-CoV-2 then cell entry is facilitated. For the synthesis of the large replicase polyproteins such as RNA-dependent RNA polymerase (RdRp) SARS-CoV-2 disassemble intracellularly and release their RNA into the cytoplasm for the replication of viral genomic RNA [4]. The WHO stopped human-human contact, separate patients at initial stages to identify and reduce transmission from the animal source, and accelerate research, communicate information properly to the

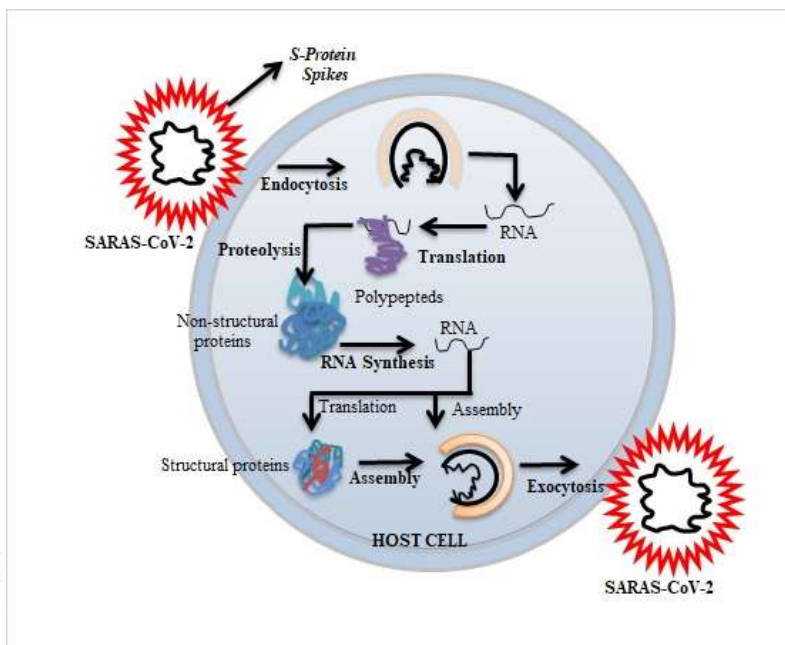
community and lessen the societal and commercial impact. It has been reported that SARS-CoV-2 shares sequence homology with the SARS-CoV and a bat corona virus. The SARS-CoV and MERS-CoV (Middle east respiratory syndrome) are the two major causes of severe pneumonia in human [2]. The new corona virus is most closely related with the batcov ratg13 detected in bats from Yunnan Province [1]. No logically valid evidence is available about this airborne transmission disease. The most common symptoms of COVID-19 are fever, dry cough, tiredness, headache, diarrhea, skin infection and less working of sensing organs like tasteless feeling of food, less sensing of smell etc. Some infected people have only mild symptoms or even become asymptomatic. Till now we don't have any specific therapies for COVID19 that is the main point of concern. The combinations of some clinically applied anti-malarial drugs (e.g. Chloroquine, hydroxychloroquine) and anti-HIV vaccines can be used to treat covid-19. Some conventional FDA approved drugs which are the potential drug against this cov-2 and found with certain curative effect in vitro are Remdesivir, Nelfinavir, Paritaprevir, Raltegravir, Praziquantel, etc. Toxicity of the currently applied drugs causing serious adverse effects to the patients are also an unavoidable issue. But till now nothing of the clinically applied drug or vaccine response is effectively active [3]. For the treatment of respiratory infections caused by the coronavirus Meliaecortex, Coptidis rhizoma, Phellodendron cortex and Sephorasubstrata radix extracts are used as antiviral [5].

Mechanism of action of corona virus: -

Virus infection is initiated by interaction between spike (S) protein and host cell surface receptors. Virus has a lipid envelope including the membrane (M) glycoprotein, the envelope (E) protein, and the S glycoprotein and covered with structural protein. The cellular serine proteases TMPRSS2 would cleave S protein into S1 and S2 subunits, which are responsible for receptor recognition and membrane fusion. Conformational change of S2 is triggered by binding the C-terminal domain (CTD) of S1 specifically to host cell receptors angiotensin-converting enzyme 2 (ACE2). For the mixing of viral and cellular membranes, two heptad repeats join in S2 forming an anti-parallel six-helix bundle, due to which viral genome release into the cytoplasm. The viral genomic RNA begins to express after release [6]. After the entry of viral genome in the cytoplasm of the target cell, it translates into two polyproteins 1a, 1b (pp1a, pp1b) to form a replication-transcription complex (RTC). These polyproteins are processed into 16 non-structural proteins (NSPs) and that RTC is involved in genome transcription and replication [7].

The S, E and M viral structural proteins are translated and inserted into the endoplasmic reticulum (ER), after replication and sub genome RNA synthesis moved into endoplasmic reticulum-Golgi intermediate compartment (ERGIC). To form mature viruses N protein encapsulates viral genome buds into a membrane containing ERGIC, which are transported

to the cell surface in vesicles and released by exocytosis. Pathogenic T cells are rapidly stimulated after SARS-CoV-2 infection to produce granulocyte macrophage colony exciting factors, like GM-CSF and IL-6. To produce a large amount of IL-6 and other inflammatory factors, GM-CSF will additional trigger CD14+/CD16+ inflammatory monocytes by a positive response. Furthermore, cytokine release and contribute to high levels of neutrophil extracellular traps. In the end, shock and tissue damage in the heart, liver, kidney and respiratory failure or multiple organ failure result due to uncontrolled inflammatory responses which cause death of severe COVID-19 patients. Spike protein, ACE2, TMPRSS2, 3CLpro, RdRp and PLpro are the main targets according to previous studies for antiviral drugs against SARS and other coronavirus infections. Virus and cell fusion can be prevented by a virus-host cell fusion inhibitor to treat COVID-19. The initial stage of SARS-CoV-2 invasion into the host is done due to ACE2 which is the crucial step of entry into host cell surface receptor. Thus, to treat COVID19 excess soluble forms of ACE2 or ACE2 inhibitors can be used. An effective treatment for COVID-19 can be the present TMPRSS2 inhibitor. Two viral proteases such as 3C-like protease (3clpro) and Papain-like protease (plpro) are responsible for cleaving viral peptides into functional units for virus replication and packaging in host cells, their inhibitors exhibit strong antiviral activity in cell-based systems [6].

Fig. Representation of mechanism of action of coronavirus:**Herbs used to treat COVID-19 are:**

1. Indian Traditional Ayurvedic Herbs: An ancient system of medicine created on the holistic attitude of life, health, and healing system. Ayurveda knows as 'The Science of Life'. It imparts biological nourishment to the body tissues and group of rejuvenative methods that was described in Ayurvedic text [10]. There are variety of herbs for immunomodulatory effects in Ayurveda like Ocimum sanctum, *Tinospora cordifolia*, *Curcuma longa* L., *Piper longum*, *Mangifera indica*, *Withania somnifera*, *Shilajatu*, *Emblica officinalis* and *Boerhaavia diffusa* [9]. It describes many medicinal plants in treating respiratory system having wide range of therapeutic potentiality like: -

(a) *Tinospora cordifolia* (Guduchi or Giloy)

extracts have alkaloids, glycosides, steroids and polysaccharides. It is used as immunomodulatory, antidiabetic, antioxidant, antihepatotoxic and cytotoxic. The active phytoconstituents, Tinocordioside, Cordifolioside A, Magnoflorine, and Syringin which are immunomodulators and strengthen the body against infections.

(b) *Ocimum sanctum* (Tulsi)

is adaptogenic, immunomodulatory, antimicrobial, cardioprotective, and anti-inflammatory effects, anti-viral, anti-fungal and anti-bacterial activity, anti-diabetic, analgesic, antifertility, anticancer, antispasmodic, antiemetic, diaphoretic and hepatoprotective. For the treatment

of rheumatism, bronchitis, and pyrexia its leaves are used and it is considered as 'Elixir of life' due to its medicinal properties. Its main phytoconstituents are Eugenol and Ursolic acid. It strengthens the immune response by the enhancement of both cellular and humoral immunity.

(c) *Withania somnifera* known as Ashwagandha, it enriches physical and mental state, rejuvenate the body in weakened situations and upturns longevity and categorized as a rasayana (rejuvenator). 'Withanolides' is its active ingredient holds steroidal saponin, alkaloids, and steroidal lactones. Withaferin-A and Withanolide D, along with Withanoside I-VII, new Withanolide Glycosides extracted from its roots, shows most of biological action. It has anti-inflammatory, anti-diabetic, antimicrobial, analgesic, anti-tumor, anti-stress, neuroprotective, cardioprotective, rejuvenating and immunomodulatory effects.

Mechanism of inhibition of coronavirus growth by ayurvedic treatment

According to previous studies SARS CoV- 2 M^{PRO}, and other target proteins (S, E, N) of COVID-19 when shows interaction with phytoconstituents of medicinal plants (*Giloy, Tulsi and Ashwagandha*), such as Withaferin A, Withanolide B, Tinocordioside, Somniferine A, Tinosporide, Withanolide, Orientin, Flavonol glucoside, Apigenin, Kaempferol, Withanone, Dihydrodieuginol B and Tulsinol A, B, C, D, E, F, G of *O. sanctum* they potentially inhibit Papain-like Protease and SARS Coronavirus main Protease, and Viral S-Protein RBD (receptor binding domain) and ACE2(host receptor of COVID-19) interconnections could be disrupted by Withanone. Thus, by hindering the viral translation into functional polyproteins and replication of virus these phytoconstituents disrupt physiological/ biological functions of host which helps to treat COVID-19 [10]. The phytochemicals such as Withanoside X, Ashwagandanolide, Dihydrowithaferin A and Withanolide N inhibit the SARS-CoV-2 which is principal viral proteins [11].

Table 1. Ayurvedic medicinal plants which are presented in table 1 can support the body against infections and shows antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

S.no.	Condition of patient	Name of Herbal dru	Name of herbs it contains	Working Mechanism of herbs	Use of Herbal medicine
1	Moderate Patients	Yupingfeng San	(a)Astragal	It reduce phlegm by improving lung Qi.	Body's immune function can be regulated by the Yupingfeng San.
			(b)Fangfeng	It relieve pain and remove dampness by relieving the pathogenic Qi.	
			(c)Atractylodes	It affect our digestion and absorption by enhancing the spleen Qi.	
2	Mild Patients	Sangju yin	(a)Mulberry leaf 15g+ Mint 6g C	These herbs are used to clear lung heat, expel phlegm, relieve cough.	Severe coughing patients can use this medicine.
			(b)Chrysanthemum 10g+ Chinese bellflower 6g		
			(c)Forsythia 10g+ Reed root 15g		
			(d)Almond 9g + Licorice 3g		
3	Mild Patients	Yinqiao san	(a)Forsythia 15g +Bamboo leaves 6g +Burdock 6g	These herbs can restore normal lung function and regulate the patient's lungs.	Patients having high fever can use this. It enhance the upper respiratory tract immune function, and have antibacterial and antiviral functions.
			(b)Chinese bellflower 6g+Licorice 3g		
			(c)Honeysuckle 15g +Nepeta 6g		
			(d)Mint 6g+Light tempen 5g		
4	Severe Patients	Maxinshigan Tang	(a)Ephedra 15g	These herbs are mainly used to reduce phlegm and to clear lung fever.	It help the lung to expel sputum and pathogenic Qi and get air.
			(b)Almond 10g		
			(c)Plaster 20g		
			(d)Licorice 9g		
5	Severe Patients	Baibegujin Tang	(a)Shudhuang 15g+Xuanshen 10g +Beimu 6g	All these can invigorate the lung Qi.	It help the lung to expel sputum and expel pathogenic Qi and and get air.
			(b)Dihuang 15g+Chinese bellflower 6g +Licorice 3g		
			(c)Angelica 15g+Ophiopogon 6g		
			(d)White peony 6g+Lily 6g		

2. Unani medicines-These are plant-based nontoxic medicines without any side effects. Some important plants are *Glycyrrhiza glabra*, *Allium cepa*, *Allium sativum*, *Ocimum sanctum*, *Ocimum tenuiflorum*, *Piper nigrum*, *Cinnamomum verum*, *Daucus maritimus*, *Curcuma longa*, etc. Aqueous extract along with lemon juice and honey was effective against virus

infections. The root of *Licorice (Glycyrrhiza glabra)* showed antiviral activities against several viruses including SARS-associated coronavirus, HIV-1, and respiratory syncytial virus. More than 300 flavonoids and 20 triterpenoids are present in this plant. Persons can use after proper consultation with the Unani medical practitioners.

3. Homeopathy- Homeopathy has no specific mechanism of action. Arsenic Album-30 is highly diluted arsenic trioxide, taking 4 pills of Arsenic Album-30 medicine once daily in empty stomach for 3 days can treat COVID-19 and work as homeopathic prophylaxis. There is no clinical evidence for Arsenic Album-30 medication as an effective treatment. Fever, runny nose, headache, sore throat in the patients with swine flu symptoms are treated by Arsenical album medicine. Many studies indicated that homeopathy does not work. Scientific studies are required to support the working of Homeopathic medicine for COVID-19 [16].

4.Chinese Traditional Herbs: Qi is the basic substance according to traditional Chinese medicine; they believe that it

constitutes the human body and maintains basic functions. Qi is divided into two, the healthy Qi (Substances that maintain the normal operation of our body is the healthy Qi) and the pathogenic Qi (Substances that can harm the health of our body is the pathogenic Qi) [17]. By inhibiting the viral replication, blocking the infection, regulating the immune response and decreasing the inflammation, Chinese herb exhibit therapeutic effects. Traditional Chinese medicine treatment were performed only in China on COVID-19, where the is the most common type is B type of SARS-Cov-2 [4].

Table 2. Chinese herbal drug.

S.no.	Name of Herbal Drugs	Biological Source	Part of herb used	Bioactive Chemical Constituents
1	Cinchona	Cinchona officinalis L.	Bark	Chloroquine (quinine analog)
2	Guduchi or Giloy	Tinospora cordifolia	Stem	Tinocordioside, Cordifolioside A, Magnoflorine, Syringin and Berberine
3	Tulsi	Ocimum sanctum	Leaves	Eugenol, Ursolic acid, Dihydrodieuginol B, Tulsinol A, B, C, D, E, F, G of O.
4	Turmeric	Curcuma longa	Rhizome	Demethoxy curcumin
5	Spinach	Spinacia oleracea	Leaves	Kaempferol
6	Cabbage	Brassica oleracea	Leaves	Kaempferol
7	Green tea	Camellia sinesis	Leaves	Catechin, Epicatechin gallate
8	Kalmegha	Andrographis panicula	Leaves	Andrographolide
9	Ginger, Sunthi dried ginger	Zingiber officiale	Rhizome	6-Gingerol
10	Garlic	Allium sativum	Bulb	Allicin
11	Onion	Allium cepa	Bulb	Quercetin
12	Chilli pepper	Capsicum annum	Bulb	Quercetin
13	Shankupushpam	Clitoria ternatea	Flower	Delphinidin-3-O-glucoside
14	Kuntze	Strobilanthes cusia	Leaves	Lupeol
15	Madhunashini	Gymnema sylvestre	Leaves	Tartaric acid
16	Dadima	Punica granatum	Fruit	Punicalagin
17	Neem	Azadirachta indica	Leaves	Azadirachtin
18	Ashwagandha or Indian Ginseng	Withania somnifera	roots	withanolide N, Withanoside X, Ashwagandhanolide, Withanoside IV and Withanoside III

Foods and herbs Immunomodulatory effects

By motivating phagocytosis rice bran, wheat bran, Lawsonia alba (hina), Echinacea purpurea (eastern purple coneflower), Plumbago zeylanica (Ceylon leadwort), and Cissampelos pareira Linn (velvetleaf) exhibit immunomodulatory properties. Eucalyptus essential oil enhance the immune system and protect the body against COVID19. In Vero cells Chinese mahogany, Chinese liquorice, red spider lily, the rhizome of Scythian lamb, and its extract, shows anti-SARS-CoV-1 activity. Even some natural products such as baicalein and baicalin were inhibitors of SARS-CoV-2. But these explanations should be verified by scientific or clinical studies [8].

Ministry of AYUSH issued guidelines for boosting immunity among the common people [18].

- Yoga practice for physical fitness and drinking luke-warm water for cleaning of body.
- To encourage the health, nutrient rich cumin, garlic and turmeric are useful.
- Body rejuvenation effects by Ayurvedic Rasayana.
- For cough herbal tea (Ocimum sanctum leaves 4 parts, Cinnamomum zeylanicum stem bark 2 parts, Zingiber officinale Rhizome 2 parts and Piper nigrum fruits 1 parts) should be taken.
- Turmeric in milk (Golden milk) is healthy.
- For healing agent, use of sesame oil or coconut oil or ghee is preferred. In throat infections gargling with oil and Trachyspermum ammi extract is helpful.

- In respiratory disease inhalation of mint is favored.

Plenty of citrus fruits having various vitamins and some dry fruits (almonds, walnuts, and dates) are useful to improve the immune system. Vitamin A, C, D and E are vital vitamins. Zinc and iodine intakes are advisable to take. Do not smoke and don't take any narcotic product. Sleep is important for the improvement of immune system, avoid any stress and do proper and regular exercises. Though, patients when take vitamins and zinc supplements should consult medical practitioners [16]. Thus, nutritional therapy and herbal medication might be a corresponding preventive therapy for COVID-19. Though, these hypotheses require experimental validation in COVID-19 patients [8].

Conclusion

At present, there is no specific allopathic medicines present for COVID-19. A great study on mechanism of SARS-CoV-2 is mandatory for design and development of drugs and vaccines of COVID-19. This review provides the ethnopharmacological significance of herbal products and dietary therapy which are effective antivirals against SARS-CoV-2 and as protect against COVID-19. The entire world is in a urgency to discover drug and treatments for COVID-19. For this review, we summarized the effect of natural herbs and traditional medication products on COVID-19. There are no clinical reports or registered clinical trials of herbal product that can claim to cure COVID-19. It is suggested that some herb may exhibit beneficial antiviral effect on COVID-19.

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