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## Potential Roles of Medicinal Plants for the Treatment of Covid-19

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**ABSTRACT:** The whole world is entangled by the coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), people are dying in thousands each day, and without an actual medication, it seems not possible for the bringing this global health crisis to a stop. Natural products have been in constant use since ancient times and are proven by time to be effective. Crude extract or pure compounds isolated from medicinal plants and/or herbs such as *Artemisia annua*, *Agastache rugosa*, *Astragalus membranaceus*, *Cassia alata*, *Ecklonia cava*, *Gymnema sylvestre*, *Glycyrrhizae uralensis*, *Houttuynia cordata*, *Lindera aggregata*, *Lycoris radiata*, *Mollugo cerviana*, *Polygonum multiflorum*, *Pyrrosia lingua*, *Saposhnikoviae divaricate*, *Tinospora cordifolia* etc. have shown promising inhibitory effect against coronavirus. Several molecules, including acacetin, amentoflavone, allicin, blancoxanthone, curcumin, daidzein, diosmin, epigallocatechin-gallate, emodin, hesperidin, herbacetin, hirsutenone, iguesterin, jubanine G, kaempferol, lycorine, pectolinarin, phloroeckol, silvestrol, tanshinone I, taxifolin, rhoifolin, xanthoangelol E, zingerol etc. isolated from plants could also be potential drug candidates against COVID-19.

#### I. INTRODUCTION

Extracts from medicinal plants such as *Dioscorea batatas*, *Glycyrrhiza radix*, *Mollugo cerviana*, *Polygonum multiflorum* Thunb., *Psoralea corylifolia*, *Rheum officinale* Baill., *Salvia miltiorrhiza*, and *Trichosanthes cucumerina* L. were shown active against coronavirus. Herbal extracts obtained from four different plants *Artemisia annua*, *Lindera aggregata*, *Pyrrosia lingua*, and *Lycoris radiata* have shown remarkable antiviral activity. Polyphenols, flavonoids, proanthocyanidins, saponins, monoterpenoids, triterpenoids, glucosides, sesquiterpenes, and alkaloids isolated from various medicinal plants have diverse antiviral activities . Neuraminidase inhibitors (NAIs) can block the viral enzyme neuraminidase, which prevents the release of viruses from host cells . *Garcinia celebica* L. leaves extract areneuraminidase inhibitors, which bind to active amino acid residues of neuraminidase by hydrogen bonds and van der Waals force and interfere virus release from host cells .[1]

Antiviral drugs undergo action by (a) acting as blocking agent during adsorption and penetration of virus on receptors; (b) inactivation of virus particles; (c) altering properties of virus membrane; (d) inhibition of viral enzymes (DNA polymerase, RNA polymerase, deoxypyrimidine nucleoside kinase, and thymidine kinase, viral neuraminidase, mRNA guanylyltransferase, and mRNA Methyltransferase); (e) inhibiting reverse transcriptase; (f) inhibiting translational process; (g) decrease in expression level; (h) inhibiting viral assembly; (i) reduced endocytic activity.

There are various methods available for in vivo and in vitro screening of extracts of medicinal plants. Notably, this review focused on a little known method in the area of medicinal chemistry, which is mostly known as emulsion-based in vitro compartmentalization (IVC) technique . Usually, IVC uses aqueous droplets that contain DNA and machinery for protein production within water-in-oil emulsions . Herbal medicines have become a promising option to tackle the ongoing pandemic caused by COVID-19. A large number of Chinese herbal-based medicines were used in China for the treatment of patients infected by COVID-19. The National Health Commission (NHC) of China has recommended a couple of plants originated medicines for the treatment of viral disease patients. China used a similar treatment strategy even in 2003 . Chinese experts claim that herbal drugs such as *Radix isatidis* granula, and Huoxiang Zhengqi soft capsules have an excellent function to improve problems like weakness, coughs, anxiety, and digestive disorder. Many secondary metabolites with antiviral properties have been isolated from medicinal plants. Various researches have been carried out throughout the world to develop antiviral drugs effective against SARS-CoV-2 responsible for COVID-19. The best way of preventing COVID-19 infections could be finding the compounds responsible for altering or disturbing any steps of the virus replication cycle. Natural products capable of inhibiting or



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altering the configuration of structural proteins (spike glycoprotein), non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RdRP) [2]

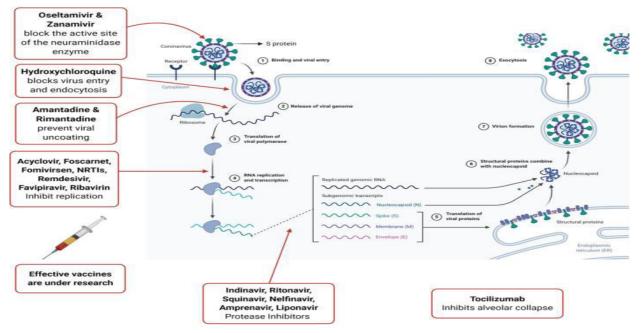


Figure contributed by Sagar Aryal; created with biorender.com

#### Fig. Multliplication stages of virus in a living cell and major antiviral drugs with their mode of action

#### **II. DISCUSSION**

Prescription of typical herbs at the time of viral infections is in practice in India for the optimum immunity and better physiological status of the patients. Herbal drugs such as Radix isatidis granula, and Huoxiang Zhengqi soft capsules have an excellent function to improve problems like weakness, coughs, anxiety, and digestive disorder. Ayurveda means 'Science of life'. It provides a complete system to have a long and healthy life. It is derived from the concepts of "Dinacharya" - daily regimes and "Ritucharya" - seasonal regimes to maintain a healthy life. Uplifting and maintaining the immunity is duly emphasized across the Ayurveda's classical scriptures. The Unani system of medicine, known as Greco-Arab Medicine, is built on the four conditions of living (hot, sodden, frosty, and dry) and four humors of Hippocratic hypothesis namely, blood, yellow bile, dark bile, and mucus. The formulation is made of four herbs Ocimum sanctum L. leaves, Cinnamomum verum J. Presl. stem barks, Zingiber officinale Roscoe rhizomes and Piper nigrum L. fruits. It is available in powder and tablet forms in the market. These herbs are reported to boost immunity. Samshamani vati is made of aqueous extract of Tinospora cordifolia, and reported to be an immunomodulator due to the synergistic effect of the various compounds present. It is also effective in various viral diseases. Alstonia scholaris (L.) R. Br. bark, Picrorhiza kurroa Royle ex Benth. rhizomes, Swertia chirayita (Roxb.) H. Karst. whole plant, and Caesalpinia crista L. seed pulp is effectively antiviral, anti-asthmatic, and immunoboosting. Agastya Haritaki Rasayana is a popular 'Avaleha kalpana', used in the management of various respiratory infection and comprises more than 15 herbal ingredients.[3]

Most of its ingredients showed antiviral, anti-asthmatic, anti-inflammatory, and immunomodulatory activities. Anuthaila consists of about twenty ingredients and out of them *Leptadenia reticulate* (Retz.) Wight and Arn. has been reported in allergic response, treatment of asthma, bronchitis, and throat trouble . Similarly, *Ocimum sanctum* L. is recommended for a wide range of conditions including, cough, asthma, fever, and malaria and *Sesamum indicum* L. oil for dry cough, asthma, migraine, and respiratory infections . There are reports on *S. indicum* seeds with *Tachyspermum ammi* (L.) Sprague seeds for dry cough, asthma, lung diseases, and common cold . On the basis of above literature, Anuthaila justifies its use in corona virus pandemic condition . Triyaq-e-Araba is an important Unani formulation used as a detoxifying agent. It contains *Laurus nobilis* L. berries, *Bergenia ciliate* (Haw.) Sternb. stem, *Aristolochia* 



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indica L. roots and Commiphora myrrha (Nees) Engl. It has been reported by several authors as a potent antiviral agent. Roghan-e-Baboona is an Unani remedy utilized as an anti-asthmatic and for the treatment of inflammatory complaints. Flowers of Matricaria chamomilla L. are the main ingredient of Roghan-e-Baboona.[4] It is composed of the flowers of *M. chamomilla*, which is found effective for acute viral nasopharyngitis . Khamira-e-Banafsha is a semisolid Unani formulation prepared by adding decoction of flowers of Viola odorata L. to a base of sugar or sugar with honey and used for cold-cough as expectorant and for the treatment of ailments of respiratory system and chest diseases, bronchitis, whooping cough, fever, expectorant, antipyretic etc. Further, V. odorata has been reported to suppress the viral load and increase antiretroviral drug efficacy. Laooq-e-Sapistan is a semisolid sugar-based polyherbal Unani formulation extensively used by the masses in India for the treatment of cold and cough, whooping cough, and phlegm. It reduces inflammation of the pharvnx, tonsils, and irritation or infection. The jelly like sticky mass of ripe fruit of Cordia myxa L. is the main ingredient, which has been reported as antiviral and antitussive. Sharbat-e- Sadar is an Unani polyherbal syrup formulation and is widely used for common cold, cough and respiratory diseases. Trachyspermum ammi (L.) Sprague, an important ingredient, reported to neutralize antibodies . Khameera marwareed is a compound, sugar-based, semisolid Unani formulation used as an immunomodulator. It has been reported to stimulate the immune system through T helper 1 (Th1) type cytokine response and maintains the body in a healthier position to fight against viral infections. Asgand (Withania somnifera (L.) Dunal) is a very popular Indian medicinal plant. The root powder is used in the Unani system of medicine as an immunomodulator.[5]

Habb-e-Bukhar is a polyherbal tablet formulation of Unani system of medicine, prescribed in elephantiasis and malarial fever. The main ingredient of Habb-e-Bukhar is cinchona bark. Its active constituent quinine is being used by some countries as either experimental treatment or suggested as a drug with a promising profile against COVID-19. Sharbat-e-Toot Siyah is composed of the juice of Morus nigra L. in a sugar base and is used to treat tonsillitis and sore throat. It has been reported as anti-inflammatory and analgesic and inhibits the pro-inflammatory cytokines.[6] Laooke-Katan is a sugar-based semisolid Unani formulation composed of Linum usitatissimum L. seed, which contains alpha linolenic acid and has been reported to have antiviral, anti-inflammatory, and immunomodulatory activities. Nilavembu Kudineer is a polyherbal Siddha formulation prescribed for the prevention and management of viral infections and fevers. It acts as an immunomodulator and plays a defending role against dengue fever and chikungunya. Recent studies showed that formulation has antiviral and antimicrobial actions, which makes it suitable for viral fevers, malaria, and typhoid fever. Ahatodai Manapagu is composed of Adathoda vasica Nees leaves, which contains alkaloids like vasicine, the active ingredient in various cough syrups. A. vasica has been used in the Indian medicinal system for thousands of years, to treat various types of respiratory disorders. Kabasura Kudineer is a traditional formulation used in the Siddha system of medicine for managing common respiratory complaints such as flu and cold. Siddha practitioners also recommended this formulation for severe phlegm, dry cough, and fever. It is made up of more than ten herbal ingredients, and each ingredient has a unique pharmacological activity in respiratory disorders. [7]

#### **III. RESULTS**

Ashwagandha, giloe, ginger, cinnamon, tulsi, black pepper, black cumin, amla, turmeric, garlic, and flax seeds have been traditionally used as herbal remedies for multiple diseases since ancient times. These herbs have been utilized in food preparations and traditional medicines in several countries. However, in India, their culinary use is very common and they are a part of kitchen in every house. Similarly, there are some traditional Indian formulations such as Chyawanprash, Triphala, and Rooh Afza etc. that are very common and at least one of them is being used daily used nutritional supplements. These plants and formulations are very common and at least one of them is being used daily by every Indian, irrespective of religion/community/financial status. The above-mentioned herbs and formulations have been proved potent scientifically for their immunomodulatory, antioxidant, and anti-infective properties, which might be one of the reasons behind the lower death rate of Indians per million of population due to COVID-19 even with minimum health infrastructure.

It has been found that fresh raw garlic extract showed anti-inflammatory effects by decreasing production of prostaglandin E2 (PGE<sub>2</sub>), IL-6, IL-1 $\beta$ , nitric oxide (NO), and leukotrienes (LT D<sub>4</sub> and E<sub>4</sub>) in lipopolysaccharide activated RAW264.7 cells. *C. verum* essential oil and powder exhibited anti-oxidant, immunostimulant, and antiviral activity in Newcastle disease virus in chickens mainly by modulating total protein, globulin, total antioxidant capacity, and lysozyme activity, and significantly increased phagocytic activity. Aqueous extract of *C. longa* decreased relative spleen weight and modulation in hematological changes indicating the potential of *C. longa* as an immunomodulator in cyclophosphamide-immunosuppressed *in vivo* model.[8] The study observed promising effects of turmeric as an



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immunomodulator. *Nigella sativa* L.'s bioactive compounds have been observed as potential inhibitors of COVID-19 in molecular docking studies. Nigellidine gave energy complex at active site (6LU7) with energy scores closest to chloroquine and better than hydroxychloroquine and favipiravir whereas  $\alpha$ -hederin gave energy complex at the active site (2GTB) with energy scores better than chloroquine, hydroxychloroquine, and favipiravir. Hydro-alcoholic extract of *Ocimum sanctum* inhibited intracellular multiplication of virus. It also inhibits non-specific interference with viruscell interactions in H9N2 viruses. Amla has been reported to significantly relieve chromium-induced immunosuppressive effect on lymphocyte proliferation and led to restoration in production of IL-2 and INF $\gamma$ .Phenolics from emblica has been found to increase splenocytes proliferation. Geraniin and isocorilagin showed significant immunostimulatory effects.[9]

#### **IV. CONCLUSION**

The whole world is entangled by the coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), people are dying in thousands each day, and without an actual medication, it seems not possible for the bringing this global health crisis to a stop. Natural products have been in constant use since ancient times and are proven by time to be effective. Crude extract or pure compounds isolated from medicinal plants and/or herbs such as *Artemisia annua*, *Agastache rugosa*, *Astragalus membranaceus*, *Cassia alata*, *Ecklonia cava*, *Gymnema sylvestre*, *Glycyrrhizae uralensis*, *Houttuynia cordata*, *Lindera aggregata*, *Lycoris radiata*, *Mollugo cerviana*, *Polygonum multiflorum*, *Pyrrosia lingua*, *Saposhnikoviae divaricate*, *Tinospora cordifolia* etc. have shown promising inhibitory effect against coronavirus. Several molecules, including acacetin, amentoflavone, allicin, blancoxanthone, curcumin, daidzein, diosmin, epigallocatechin-gallate, emodin, hesperidin, herbacetin, hirsutenone, iguesterin, jubanine G, kaempferol, lycorine, pectolinarin, phloroeckol, silvestrol, tanshinone I, taxifolin, rhoifolin, xanthoangelol E, zingerol etc. isolated from plants could also be potential drug candidates against COVID-19.[10]

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