



POTENT MEDICINAL PLANTS FOR COVID-19: A REVIEW

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Abstract: SARS-CoV-2, a highly transmissible virus, became a great havoc to the existence of mankind. It shows normal symptoms like – fever, cold, throat soreness, headache, etc. which may lead to death if cause severe infection. There is no proper treatment available till now. COVID-19 has also resulted in a paradigm shift from illness-oriented healthcare system to wellness-oriented healthcare system which has opened up innumerable opportunities in field of traditional medicine. Medicinal herbs which contain active compounds, have antimicrobial or antiviral, anti-inflammatory, and immune-stimulatory activities, are assumed to have the capacity to modulate the immune response and, therefore, they are believed to have beneficial effects on preventing or treating COVID-19. This literature review contains list of some majorly useful medicinal herbs for their effective response against this dreadful virus.

Index Terms –Phytomedicine, immunity, COVID-19, Anti-viral, Medicinal Plants, ACE2

I. INTRODUCTION

COVID-19, a global pandemic declared by WHO, is a highly infectious and severe acute respiratory disorder caused by a pathogenic virus called SARS-CoV-2 which is transmitted to humans via contact and/or feeding on infected animals. Coronaviruses are non-segmented positive-sense single stranded RNA viruses with a large viral RNA genome of diameter 80–120 nm. They belong to the family of Coronaviridae, in the subfamily Orthocoronaviridae which consists of four genera namely: alpha, beta, gamma, and delta. Some of the proposed modes of actions of SARS-CoV-2 include – hyper-inflammation characterized by a sudden and fatal hyper-cytokinaemia with multi-organ failure, immunosuppression, reduction of Angiotensin-Converting Enzyme 2 (ACE2) to enhance pulmonary vascular permeability and damage the alveoli. [1, 2]

Propagation is mainly through close contact with infected individuals via respiratory droplets from either sneezing or coughing. Infected patients show symptoms like - fever (98%) is the most frequent manifestation, followed by cough (76%), myalgia or fatigue (44%), headache (8%) and progressive respiratory failure (in case of severe infection). Damage is initiated by receptor-binding domain (RBD) attachment of virus to receptor on the respiratory tract, known as the angiotensin-converting enzyme-2 (ACE2) receptor. Humans have many ACE2 receptors in their respiratory tracts, which increase their susceptibility to COVID-19 which can lead to the release of numerous proinflammatory cytokines - IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1a, and TNF- α , are highly elevated in the blood of severely ill COVID-19 patients [1] (Fig. 1).

Till now, there are no absolute therapies for COVID-19, but preventive and supportive therapies are employed to control further complications and organ damage. Researchers and scientists across the world are focusing on repurposing the existing drugs, passive immunity and looking for vaccines against the virus [3]. Based on the information available key regions of new drug targets are RNA-dependent RNA polymerase of virus, cell membrane receptors of SARS CoV- 2 (ACE-2), and spike proteins (S protein), the antiviral mechanism of plant extracts varies as per the structure and replication process. However, screening of new therapeutic products will take an extended period, and medicinal plants could be an alternative, which is already tested by various ethnic groups since the ancient period. Natural compounds from plant have been recognized in their antiviral properties with numerous mechanisms to prevent infection and strengthen host immunity. Most antivirals are used for specific viral infections, while a broad-spectrum antiviral is effective against a wide range of viruses. Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and anti-parasitic drugs, or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections. Natural antivirals are produced by some plants such as *Azadirachita indica*, *Eucalyptus globulus*, *Ocimum sanctum*, *Camellia sinensis*, *Allium sativum*, *Picrorhiza kurroa*, *Lycoris radiata*, *Andrographis paniculata*, *Curcuma longa*, *Embllica officinalis*, *Glycyrrhiza glabra*, *Ginkgo biloba* and many others. Plant extracts can be used for the preparation of peptides/proteins with the medicinal value, which can be a good source of vaccines and protein/peptides-based treatment. Herbal extracts have become an exceptional alternative for the formulation of antiviral drugs that can inhibit multiple steps of the virus replication cycle. In the context of the

global burden of COVID-19, where an absolute medicine is waiting for patients, promptly available plant-based medicines with studied safety and efficacy can be on the frontline to tackle the ongoing calamity caused by COVID-19 [2,4].

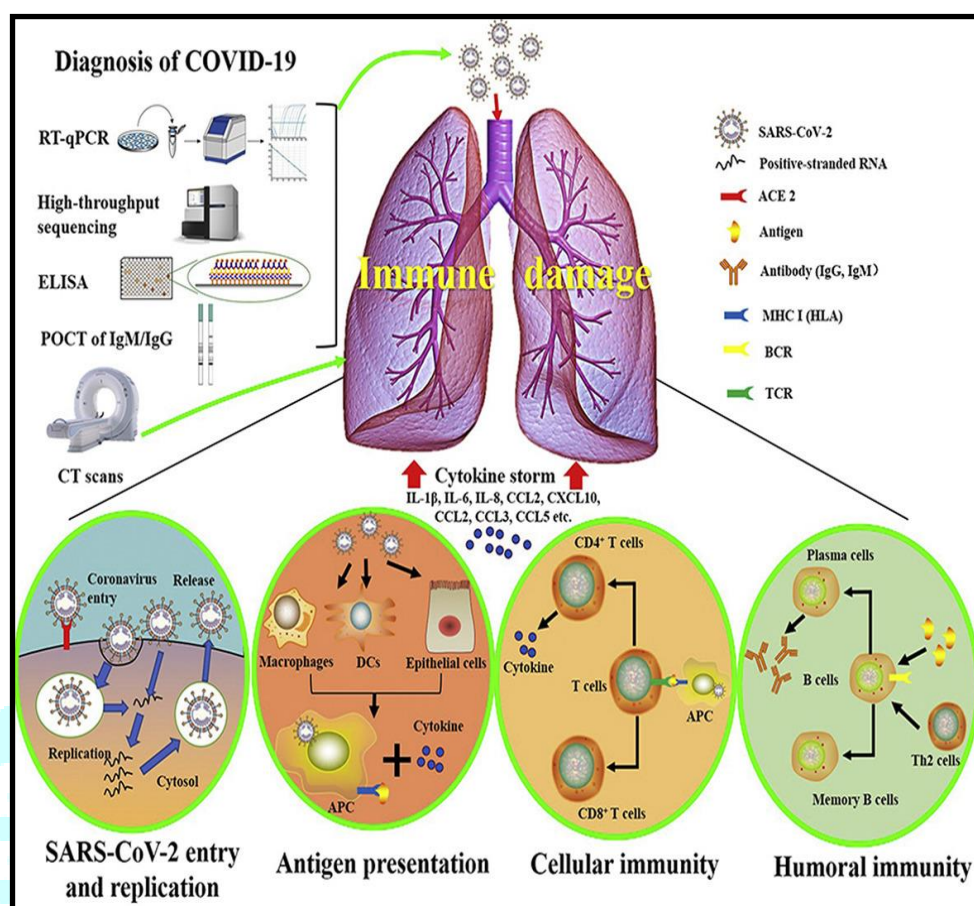


Figure 1: Schematic representation of immune response and associated tissues toxicity [20]

In the research of phytomedicine, it is common to observe multiple pharmacological properties from a single plant. At present, anti-inflammatory and immunomodulatory agents such as corticosteroids and IL-6 receptor antagonist are being utilized in the management of COVID-19 related cytokine storm associated with severe acute respiratory distress syndrome, in hopes to improve survival.

Medicinal plants such as *V. amygdalina* and *E. longifolia* [1] demonstrated suppression effects on specific pro-inflammatory cytokines correlated with worsened COVID-19 outcome such as the IL-6. Overall, these selected interventions of interest discussed here can be broadly categorized into those with 1) antiviral, 2) anti-inflammatory, 3) immunomodulatory effects also [5] **Fig. 2.**

1.1 Medicinal plants with anti-viral properties:

1.1.1 *Sida cordifolia*:

S. cordifolia has been reported to be a natural anti-human immunodeficiency virus (HIV) agent. One of the active compounds isolated from the plant is (10E, 12Z)-9-hydroxyoctadeca- 10,12-dienoic acid, a hydroxyl unsaturated fatty acid was found to be an exceptional NES (nuclear export signal) non-antagonistic inhibitor for nuclear export of Rev protein. The roots, leaves, and stems are utilized as traditional medicines in chronic dysentery, gonorrhea, and asthma. The root bark is exploited as stomachic, demulcent, tonic, astringent, bitter, diuretic, aromatic, and as antiviral agent. The seeds of *S. cordifolia* are traditionally used as aphrodisiac and also indicated in the treatment of gonorrhea, cystitis, piles, colic and tenesmus. It also acts as an immune booster serving as immune stimulants to strengthen and harmonize degenerative body systems and assists the immune system in its fight against invading antigens (bacteria and viruses). [1,6]

1.1.2 *Boerhavia diffusa*:

Another plant with potent antiviral activities is *Boerhavia diffusa* [7]. *B. diffusa* is commonly known as punarnava. It is mostly found in Asian countries and is basically used for the treatment of various diseases, such as abdominal pain, jaundice, dyspepsia, stress, spleen enlargement and liver diseases. *B. diffusa* bioactive components extracted from leaf, stem and root include flavonoids, triterpenoids, alkaloids, hypoxanthine, steroids, lipids, lignin, proteins, ursolic acid, boeravinone, punarnavoside, etc. Bose et al suggested that *B. diffusa* has a strong potential to inhibit the entry of hepatitis C virus and its major compound (boeravinone H component) were able to block the initial phase of HCV entry through acting directly on the viral particles. Moreover, Manu et al also showed that its second major bioactive compound (Punarnavine) was also able to enhance the immune response, especially IFN- γ and interleukin-2 cytokines. This categorizes *B. diffusa* as a therapeutically important plant to be considered under the current circumstances of the COVID-19 pandemic and worth further investigation. [8]

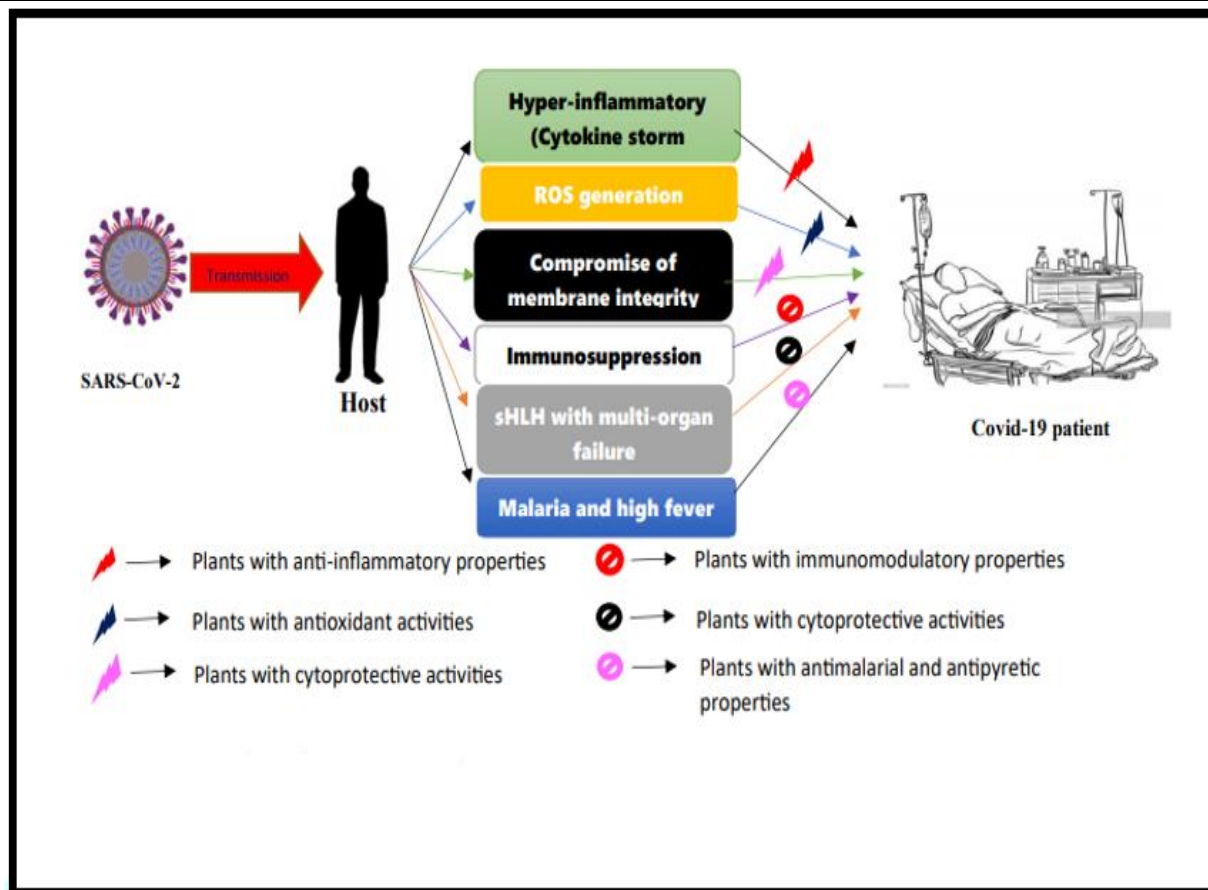


Figure 2: Pathological features of Covid-19 and possible clinical interventions by medicinal plants [1]

1.1.3 *Andrographis paniculata*:

A. paniculata, also known as “king of bitters,” is an herbaceous plant. Stem and leaves of this plant includes flavonoids, diterpenes, andrographolide, noriridoides, xanthones, etc. It has antimicrobial, antiprotozoan, antiangiogenic, antidiabetic, anti-inflammatory, antioxidant, immune stimulant, hepato-renal protective, liver enzymes modulation characteristics. The inhibitory role of Kalmegh against SARS-CoV-2 proteases was investigated using an in-silico methodology, focused on importance of andrographolide for the possible treatment of COVID-19 [9]. Andrographolide was investigated for antiviral activity against several viruses which showed effective results as an anti-viral agent. Lin et al. demonstrated that ethanolic extract of *A. paniculata* and andrographolide together, effectively inhibit the expression of proteins, during the viral lytic cycle. It has the most antiviral inhibitory effects among six medicinal plants tested during a study. [10].

1.1.4 *Glycyrrhiza glabra*:

In a comparative study of antiviral potential of 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients, glycyrrhizin was found to be the most active in inhibiting replication of the SARS-associated virus. It affects cellular signaling pathways such as protein kinase C; casein kinase II; and transcription factors such as activator protein 1 and nuclear factor. In addition to inhibition of virus replication, glycyrrhizin inhibits adsorption and penetration of the virus—early steps of the replicative cycle [11].

2.1 Medicinal plants with anti-inflammatory properties:

2.1.1 *Curcuma longa*:

C. longa, a rhizomatous herb containing curcumin, as an active ingredient which play crucial role in treating covid-19. Curcumin has several pharmacological effects such as antioxidant, anticancer, antibacterial, antiviral, antidiabetic effects as well as anti-inflammatory activity. It reduces IL-6 and TNF- α levels that both are the key inflammatory mediators, protects human genital mucosal epithelial cells against HIV-1 replication by inhibiting activation of pro-inflammatory chemokines such as IL-8 [1,12]. It is expected that curcumin may play an important role as a novel drug in the future against various virus oriented diseases. Besides these, support of the respiratory system is one of the main traditional uses of turmeric [13].

2.1.2 *Zingiber officinale*:

Z. officinale (ginger) has been shown to have potent anti-inflammatory effects. Shimoda et al. reported the anti-inflammatory potential of *Zingiber officinale* in acute and chronic inflammation models, showed that it possesses an effective inhibitory effect on acute and chronic inflammation, and suppressed activation of macrophage via anti-inflammatory pathway. It has been reported to decrease serum level of TNF- α and high-sensitivity protein in type 2 diabetic patients, indicating its value as an immune-modulatory agent [1]. Ginger is beneficial in to fight respiratory problems (relieve congestion associated with the common cold), strength immunity (due to high level of anti-oxidant), relieve stress (due to combination of the strong aroma and healing property. [14].

2.1.3 *Azadirachita indica*:

A. indica, a traditional ancient medicinal plant, have biologically active compounds, that act as an antiviral, anti-inflammatory, antiseptic, and antifungal agent. Neem bark and leaf extract has inhibitory effect on virus propagation and is thought to interfere at an early stage of the virus replication cycle. The proven antimicrobial property, and low toxicity of Neem extracts, makes this plant an excellent choice for harvesting and designing of potential antiviral components [15,16].

2.1.4 *Ocimum sanctum*:

O. sanctum have potential to block the activity of different pathogens and its parts e.g. leaves, flowers, stem, root, seeds etc. are known to possess therapeutic potentials and have been used as expectorant, analgesic, anticancer, anti-asthmatic, antiemetic, diaphoretic, antidiabetic, antifertility, hepato-protective, hypotensive, hypolipidmic and anti-stress agents Ghoke et al. showed that treatment with the crude extract derived from the leaves of *O. sanctum* lead to significant H9N2 virus reduction in all three—virucidal, therapeutic and prophylactic activities [8,17].

3.1 Medicinal plants with immuno-modulatory properties:

3.1.1 *Artemisia annua*:

A. annua possess artemisinin as the main active compound primarily used as an antimalarial drug acting by disrupting the function of parasite mitochondria and by modulating host immunity. Artemisinin and its derivatives increase immune reconstitution and promote T cell activity and are helpful in refurbishing immune function. Different phenolic compounds present in the extract have shown activity against HIV and autoimmune diseases and were found to be effective against the novel COVID-19 virus [18].

3.1.2 *Berberis vulgaris*:

B. vulgaris has medicinal importance due to its antioxidant, anticancer, anti-inflammatory, antidiabetic, antibacterial, and hepatoprotective properties. Studies about the chemical components show that alkaloids such as berberine, protoberberine, berberamine, etc. are among the important which increases immunity. It can be useful in the treatment of covid-19 by suppressing inflammatory factors produced due to the production of TNF- α and IL-1b in human pulmonary cells [18,19].

3.1.3 *Emblica officinalis*:

E. officinalis, commonly known as Indian gooseberry or Amla, is extremely rich in vitamin C and has been traditionally used as a tonic to recover vigor and lost energy. It also contains other bioactive constituents such as alkaloids, phenolic compounds, and tannins, exhibit a wide range of therapeutic actions, including antidiabetic, antioxidant, and anticancer [18]. The crude extract of fruit is reported to exhibit immune-suppression in adjuvant-induced arthritic rat model [22].

3.1.4 *Withania somnifera*:

W. somnifera (Ashwagandha) is commonly known as “Indian Winter cherry”. The pharmacologically active components are alkaloids, steroidal lactones, and saponins that are crucial for imparting these health benefits. Root extract of Ashwagandha possesses anti-viral, immunomodulatory, hepato-protective, anti-microbial, antiarthritic and anti-tumorigenic activity, etc. *W. somnifera* reported to suppress various pro-inflammatory cytokines viz. IL-2, IL-6, TNF- α , IFN- γ , this condition is interrelated with the improvement in the health condition associated with COVID-19 infection due to cytokine storm [20].

3.1.5 *Tinospora cordifolia*:

T. cordifolia commonly named as “Guduchi” has active phytochemical namely tinocordiside, which is capable of disrupting the interaction between ACE2 and RBD of viral S protein. The anti-inflammatory properties of *Tinospora cordifolia* extract (TCE) is mediated via suppression of proinflammatory cytokines such as IL-1 β , IL-6, IL-17 and TNF- α in rat model, which makes it potent to act as immuno-modulatory agent [20,21].

3.1.6 *Allium sativum*:

A. sativum is one of the good pharma-therapeutic immune-boosting herbs. The presence of sulfur-containing phytochemicals such as alliin, allicin, ajoenes, etc. provides substantial immunomodulatory, anti-inflammatory, anticancer, antitumor, antidiabetic, anti-atherosclerotic, and cardio protective features. These phytochemicals have the potential to decrease the expression of proinflammatory cytokines and to reverse the immunological abnormalities to more acceptable levels. Alliin is the main organosulfur compound in garlic and has been shown to induce a decrease in the expression of proinflammatory cytokines. Also, Ziai et al conducted in vitro study on *A. sativum* and its potential efficacy to inhibit the ACE-2 receptor, reported some effective results. [8, 15, 23, 24].

II. DISCUSSION

Till now, there are no absolute therapies for COVID-19, but preventive and supportive therapies are employed to control further complications and organ damage. Researchers and scientists across the world are focusing on repurposing the existing drugs, passive immunity and looking for vaccines against the virus. Natural compounds from plant have been recognized in their antiviral properties with numerous mechanisms to prevent infection and strengthen host immunity. Herbal extracts have become an exceptional alternative for the formulation of antiviral drugs that can inhibit multiple steps of the virus replication cycle. In the context of the global burden of COVID-19, where an absolute medicine is waiting for patients, promptly available plant-based medicines with studied safety and efficacy can be on the frontline to tackle the ongoing calamity caused by COVID-19.

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