

A Compendium of Global Traditional and Alternative Medicine: An Only Alternative to Thwart the Disease in the Current Scenario of the COVID Pandemic

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Abstract

Introduction: For centuries medicinal plants serve as a curative agent for many respiratory viruses. The emergence of another respiratory virus i.e. SARS-CoV-2 has already affected many lives worldwide. The unavailability of antiviral drugs and vaccines against COVID-19 has drawn attention to alternative therapy. This review article focused on the antiviral activity of medicinal plants as an alternative therapy to combat COVID-19.

Materials and Methods: Literature search was performed using scientific web portals including PubMed, Google Scholar, Scopus, and Science Direct. This covered articles published in English language from 1953-2020 for antiviral activity of medicinal plants against respiratory viruses. Data from Clinical Trials Registry- India was used to assess the current herbal trials used for the treatment of COVID-19.

Results: Studies showed that medicinal plants significantly inhibit the pathogenesis of respiratory viruses by acting as an immune booster, inhibiting viral attachment, entry, and replication into the host cell. Some of the proven ones for their antiviral efficiency are Ashwagandha (*Withania somnifera*), Tulsi (*Ocimum sanctum*), and Giloy (*Tinospora cardifolia*).

Conclusion: From the above finding, it can be anticipated that these medicinal plants may provide antiviral compounds in the future and can be used as an alternative therapy against COVID-19.

Keywords: Medicinal plants • COVID-19 • Antiviral activity • Respiratory viruses

Introduction

Respiratory viruses are the most frequent causative agents of disease in humans, and significantly affect morbidity and mortality worldwide [1]. Respiratory viruses that causes dreadful infection are Influenza Virus, Para Influenza Virus, Respiratory Syncytial Virus (RSV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Rhinovirus, and Adenovirus, that usually confined to the upper respiratory tract of the human body. These viruses are known to affect the population not only at endemic levels but now have become an emerging threat of causing potential pandemics [2]. Viruses reported with pandemic potential are H1N1, H5N1, and H5N7 influenza viruses, and the other viruses that have emerged in recent years. Omit this word belong to the family of coronavirus are severe acute respiratory syndrome SARS-CoV and Middle East respiratory syndrome MERS- CoV. Currently, COVID-19 has become the major pandemic after the outbreak of this virus in December 2019 where initially 41 patients with pneumonia-like symptoms were admitted to hospital that was later linked with the seafood market in Wuhan, China [3,4]. As of March 23, 2021, this deadly virus has affected 41 million individuals and 1 million deaths worldwide (WHO). These respiratory viruses can survive for longer periods and the factor that persuades the longevity of these viruses on the surfaces are their disparity in strain, titre, type of surface, suspending medium,

their mode of deposition, temperature, humidity, etc. [5]. These viruses are primarily transmitted through two ways i.e. inhalation of infectious droplets and contaminated fomites. The most common route of transmission of these viruses is through aerosol. Large aerosolized droplets approximately 10 to 100 μm can transmit virus particles to the new host at the proximity of $\leq 0.9\mu\text{m}$ whereas small aerosolized droplets of $<10\mu\text{m}$ in diameter can transmit virus particles to the new host through sneezing and coughing in the proximity of $\geq 1.8\text{ m}$ [6]. SARS-CoV and MERS-CoV cause unusual pneumonia with extra pulmonary presentations in both immunocompetent and immunocompromised patients. The typical clinical features of SARS-CoV-2 infection are close to severe acute respiratory syndrome (SARS) that include fever, myalgia, dry cough, dyspnea, fatigue, and radiological evidence of ground-glass lung opacities compatible with atypical pneumonia [7-9]. COVID-19 can be diagnosed through epidemiological history, clinical expressions nucleic acid detection, CT scan, immune identification technology (Point-of-care testing) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA) [10]. Taking into account the various spectrums of disease manifestations, various potential broad-spectrum antibiotics, antiviral, convalescent plasma therapy, and monoclonal antibodies have been used to treat this deadly virus (Table 1). Unfortunately, these drugs have shortcomings and limitations. Firstly, the clinical drug response results in severe adverse side effects. Secondly, though these drugs are being currently used to treat the ongoing pandemic, the treatment is not 100%. Treatment varies from patient to patient, in some these drugs Works in combination and in some not. The reason behind this is yet not clear. On the other hand, all the countries are putting their best to come up with a suitable vaccine, so that protection can be imparted. Some of the clinical trials are in their final phase [11]. In light of the above scenario, seeking out alternative protective therapy to combat these serious adverse side effects, medicinal plants play an important role for their protective effect against these respiratory viruses [12]. This review edifies the antiviral effects of Indian Medicinal plants for treating respiratory viruses specially targeting COVID-19 (Figure 1).

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Literature Review

Medicinal plants for treating respiratory viruses

For centuries, medicinal plants are used and explored for treating ailment and several population cultures still depend on medicinal plants as their chief healthcare needs [13,14]. Medicinal plants are now the basis of retrieving novel therapeutic compounds due to the presence of high secondary metabolite content such as flavonoid, phenolic, alkaloid, etc. [15]. Herbal medicine has been widely used in treating viral respiratory Infections (VRI). These herbs contribute to building immune stimulation and inflammation-modulating effect on viral respiratory infections [16]. In light of the developing personal medicine creating its niche, countries like China, Korea, South Africa, and India have been focusing on their traditional medicinal plants to treat respiratory viruses (Table 2). Nearly 70–95% of populations of rising countries are still relying on herbal medicine for basic health illness [17]. An *in-silico* study on *Clerodendrum spp.* was conducted where its natural compounds were studied for viral infections. *Clerodendrum spp.* is prevalent in various sections of Asia including India, Myanmar, Bangladesh, Thailand, Bhutan, Nepal, and in temperate regions of Tibet. They screened these natural compounds through molecular docking to evaluate their inhibitory potential. Results have shown that taraxerol was the most promising antiviral compound against the SARS-CoV-2 spike, Mpro and RdRp protein, followed by Friedelin and Stigmasterol [18-36].

Indian traditional medicinal plants for respiratory viruses

Ayurveda, the alternative medicine of the Indian sub-continent that used plants for treating almost every disease [37]. Ayurveda medicine now has become the substitute for treating various health ailments due to their easy accessibility, fewer side effect, and low cost. Due to the Agro-climatic zone, India is known to have rich biodiversity of medicinal plants [38-40]. In recent years, various antiviral agents like polyphenols, flavonoids, saponins, glucosides, and alkaloids have been extracted through chemical and pharmacological studies [41]. Indian herbs have been used for curing various diseases that comprise respiratory viral diseases [21]. The holistic approach of the Indian AYUSH system (The Ministry of Ayurveda, Yoga, Naturopathy, Unani, Siddha and Ho-

moeopathy) is purposed with developing education, research and propagation of indigenous alternative medicine systems in India. These medicines give focus on prevention through lifestyle alteration, dietary organization, and prophylactic involvements for building the protection, and basic medicines that depend on the presentation of the symptoms (AYUSH 2020).

Ministry of AYUSH recommended some precautionary and prophylactic herbal plants for boosting immunity and improving the respiratory symptoms (Table 3). Out of these some have undergone all phases of clinical trial and are available commercially Coronil® as an immune booster for prophylaxis of COVID-19. Apart from these medicinal plants, various common medicinal plants can be used against respiratory viral infections (Table 4). An *in-silico* study was conducted to check the antiviral efficacy of natural products from Ayurveda against SARS-CoV-2. They found Curcumin, Nimbin, Withaferin A, Piperine, Mangiferin, Thebaine, Berbine, and Andrographolide showed significant binding affinity towards spike glycoprotein of SARS-CoV-2 and ACE2 receptor that could be used as a prophylactic agent for inhibiting the entry of virus attachment to the host cell [42]. In a recent *in-silico* study, 70 compounds from Neem (*Azadirachta indica*) an Indian medicinal plant were virtually screen against two proteins i.e., Membrane and Enveloped proteins. The study revealed the inhibitory potential of the neem compounds that bind and interact with the critical region of M and E proteins which is responsible for virus association [43]. Another *in-silico* study examined the inhibitory potential of three natural compounds i.e. Wi-A, Wi-N,s, and CAPE derived from the plant Ashwagandha *in-silico* against Transmembrane Protein Serine 2 (TMPRSS2) which is a cell surface receptor required for the entrance of virus into the host cell. Molecular docking revealed that among the three natural compounds, Wi-N induces changes in allosteric sites and down regulation of TMPRSS2 that suggested the potential of the Wi-N component of Ashwagandha in blocking of SARS-CoV-2 to host cell attachment [44].

Discussion

March 23rd marked the crossing of 11.7 million Covid-19 cases in India. With this sudden hike in cases across the country, there emerges an intense

Table 1. Current treatment modalities.

| Drugs | H1N1 | SARS-CoV-1 | Mers CoV | COVID-19 |
|-----------------------------------|------|------------|----------|----------|
| Antivirals | | | | |
| Lopinavir/ ritonavir | - | - | + | - |
| Ribavirin | - | + | + | - |
| Favipiravir | + | + | + | + |
| Remdesivir | - | + | + | + |
| Anti-malarials | | | | |
| Hydroxy Chloroquine | + | + | + | + |
| Antibiotics combinations | | | | |
| Hydroxychloroquine - Azithromycin | - | + | + | + |
| Monoclonal antibodies | + | + | + | + |
| Convalescent plasma | + | + | + | + |

Table 2. List of traditional medicinal plants of various countries used for respiratory viral infections.

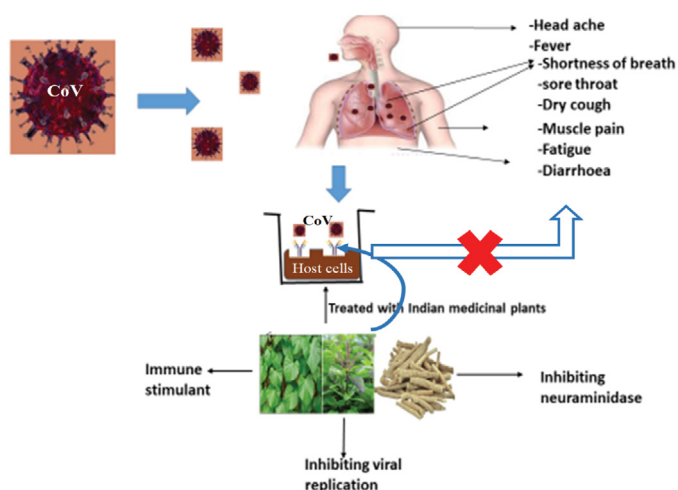
| Indian Medicinal Plants | South African Medicinal Plants | Chinese Medicinal Plants | Korean Medicinal Plants |
|----------------------------------|--|--|--------------------------------------|
| <i>Phyllanthus emblica</i> [19] | <i>Agathosma betulina</i> [30] | <i>Astragalus membranaceus</i> [32] | <i>Ephedra sinica</i> [35] |
| <i>Tinospora cordifolia</i> [20] | <i>Aloe ferox</i> [30] | <i>Glycyrrhizae uralensis</i> [32] | <i>Areca catechu</i> [35] |
| <i>Glycyrrhiza glabra</i> [21] | <i>Aspalathus linearis</i> [30] | <i>Saposhnikovia divaricate</i> [32] | <i>Paeonia lactiflora</i> [35] |
| <i>Curcuma longa</i> [22] | <i>Harpagophytum procumbens</i> [30] | <i>Rhizoma Atractylodis Macrocephalae</i> [32] | <i>Magnolia obovate</i> [35] |
| <i>Azadirachta indica</i> [23] | <i>Hypoxis hemerocallidea</i> [30] | <i>Sophora flavescens</i> [33] | <i>Portulaca oleracea</i> [36] |
| <i>Withania somnifera</i> [24] | <i>Tabernaemontana ventricosa</i> [31] | <i>Scutellaria baicalensis</i> [33] | <i>Pheretina aspergillum</i> [36] |
| <i>Zingiber officinale</i> [25] | <i>Cussonia spicata</i> [31] | <i>Radix patycodonis</i> [32] | <i>Angelica dahurica</i> [36] |
| <i>Allium cepa</i> [26] | <i>Rapanea melanophloeos</i> [31] | <i>Lycoris radiata</i> [34] | <i>Chaenomeles speciosa</i> [36] |
| <i>Ocimum sanctum</i> [27] | <i>Pittosporum Viridiflorum</i> [31] | <i>Artemisia annua</i> [34] | <i>Ledebouriella seseloides</i> [36] |
| <i>Barleria prionitis</i> [28] | <i>Clerodendrum glabrum</i> [31] | <i>Pyrosia lingua</i> [34] | <i>Notopterygium incisum</i> [36] |
| <i>Hottuyania cordata</i> [29] | <i>Sutherlandia frutescens</i> [30] | <i>Lindera aggregate</i> [34] | <i>Alisma oriental</i> [36] |

Table 3. AYUSH recommended medicinal plant extracts for treating COVID-19 Ref: AYUSH Ministry of Health Corona Advisory –D.O. No.S.16030/18/2019-NAM.

| Indian Medicinal Plants | Recommended usage | Effectiveness | Medicinal properties |
|--|-------------------|---------------|---|
| Preventive and prophylactic | | | |
| <i>Tinospora cordifolia</i> | 500 mg | Fever, Pain | Immunomodulatory, anti-inflammatory, anti-arthritic anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective [45] |
| Symptom management of COVID-19 like illnesses | | | |
| <i>Agasthya Hareetaki</i> | 5 gm | | Anti-viral, cough, intermittent fever [46] |

Table 4. List of Indian medicinal plants which may combat COVID-19.

| S. No | Indian Medicinal Plants | In-Vitro Activity/Mechanism Of Actions/Antiviral Effect |
|-------|--------------------------------|--|
| 1. | <i>Ocimum</i> | Antiviral activity was assessed on MDCK cells, Inhibiting viral replication and protein synthesis [47] |
| 2. | <i>Tinospora cordifolia</i> | potent immune stimulant [20] |
| 3. | <i>Curcuma longa</i> | Antiviral activity was assessed on MDCK cells, interrupts virus-cell attachment [48] |
| 4. | <i>Withania somnifera</i> | Stimulated the immune system [20] |
| 5. | <i>Zingiber officinale</i> | Inhibit virus-cell attachment [49] |
| 6. | <i>Strychnos minor</i> | Showed antiviral activity on MDCK cells [50] |
| 7. | <i>Chloroxylon swietenia</i> | Showed antiviral activity on MDCK cells [50] |
| 8. | <i>Pergularia daemia</i> | Anti -mouse coronavirus activity [51] |
| 9. | <i>Sphaeranthus indicus L.</i> | Anti-mouse coronavirus activity [51] |
| 10. | <i>Evolvulus alsinoides L.</i> | Anti-mouse coronavirus activity [51] |



1. The current COVID scenario is lacking the targeted treatment therapy thus the treatment modalities are very limited to none.
2. Alternative protective therapies are gaining importance as the sole alternative for prevention.
3. This review encapsulates the role of Indian medicinal plants in respiratory viral infections along with discussing the traditional therapies from other part of the world too which have been brought up in use for respiratory viral infections.

Figure 1. Graphical abstract and highlights

need for “Self-Preparedness”. Amidst the education and practice of social distancing, basic sanitation, and hand hygiene, supplementing one’s immunity to combat this viral infection is also the need of the hour. This COVID-19 pandemic has posed a global threat and is worsening the current situation due to the non -availability of effective treatment. Traditional Indian medicinal plants thus come to rescue by inculcating the AYUSH recommended herbal drugs for “Self-Preparedness”. This review has summarized the recommended plants with their prophylactic functions as they play an important role against respiratory viruses through several ways like inhibiting viral replication, blocking entry, and attachment of the virus to the cell surface. Many clinical trials are underway that are using medicinal plants and their products against COVID-19. A few have been able to prove their antiviral efficiency by going through the drug trials, Ashwagandha (*Withania somnifera*), Tulsi (*Ocimum sanctum*), and Giloy (*Tinospora cardifolia*) to name a few (www.ctri.nic.in). Thus, in this daunting scenario of morbidity and mortality by COVID-19, it is obvious to see the use of unproven drugs with certain permutations and combinations. This

should still be done in the light of evidence-based medicine. And the untiring exploratory efforts for testing traditional herbal drugs should not be given up as it is the only alternative way to protect our vulnerable patients.

Conclusion

This review article focusses on the antiviral potential of medicinal plants against respiratory viruses that may or may not be 100% effective against SARS-CoV-2. Though some of them have proven to be good immune-modulators and immune-boosters. However, to further prove them against specific antigenic targets of respiratory viruses like COVID-19, *in-vitro* and *in-vivo* studies needs to be performed.

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