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**Ankur Malik**  
Department of Chemistry, Pt.  
Jawaharlal Nehru College,  
Banda-210001, (Affiliated to  
Bundelkhand University, Jhansi)  
India

**Jainendra Pathak**  
Department of Botany, Feroze  
Gandhi College, Rae Bareilly-  
229001, (Affiliated to University  
of Lucknow, Lucknow) India

## Potentials of Medicinal Plants and Herbal Drugs in Management of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

**Ankur Malik and Jainendra Pathak**

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### Abstract

The Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) or novel coronavirus (COVID-19) infection has been declared world pandemic and has resulted in a number of deaths, especially among vulnerable citizens, in more than 216 countries worldwide. The disease appeared in late December 2019 in Wuhan (China) as a result of zoonotic transmission. SARS-CoV-2 was shown to share 96% of the genomic identity with the related bat coronavirus and was found to be 91.02% identical to that of the Pangolin-CoV, raising the possibility that the latter acted as an intermediate zoonotic host between bats and humans. Although several therapeutic molecules are being tested, no specific treatments have been developed. Different herbal products (extracts) and purified molecules may exert their anti-SARS-CoV-2 actions by direct inhibition of the virus replication or entry. Some may block the ACE-2 receptor or the serine protease TMPRSS2 required by SARS-CoV-2 to infect human cells. Additionally, natural products were shown to inhibit the SARS-CoV-2 life-cycle related proteins such as papain-like or chymotrypsin-like proteases. Since the COVID-19 outbreak, different traditional herbal medicines with promising results have been used alone or in combination with conventional drugs to treat infected patients and Ayurveda, the indigenous medical science of India, have played a crucial role in this regard. Here, we have discussed about the use of prominent plant based natural products to prevent or treat COVID-19 infection. We conducted literature review using PubMed, Google Scholar, Scopus, and WHO website and it was concluded that more studies are required for proper understanding of the mechanisms responsible for the preventive or therapeutic effects of the natural compounds derived from medicinal plants against this deadly virus.

**Keywords:** Ayurveda, Coronavirus, COVID-19, Herbal medicine, Pandemic

### Introduction

The recent emergence of a novel coronavirus has caused a pandemic and sickened more than 2.5 million people in the world (Lai *et al.* 2020; World Health Organization 2020a, b) [20, 45, 46]. This novel strain of coronavirus which caused corona-virus disease 2019 (COVID-19) also belonged to the same family of viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in the past (Ang *et al.* 2020a, b; Wu A *et al.* 2020) [3, 4, 47]. The infection of COVID-19 can result in acute respiratory illness and present common symptoms such as fever, cough, and fatigue (Wang *et al.* 2020). According to reports from World Health Organizations, evidence has shown that there are three routes for the transmission of COVID-19: symptomatic transmission, pre-symptomatic transmission, and asymptomatic transmission (World Health Organization 2020a, b) [45, 46]. Recently, it was also shown that the actual intervals of transmission are shorter than the incubation period which suggests that pre-symptomatic transmission is more substantial than expected (Tindale *et al.* 2020) [42]. Hence, it is hard to predict or estimate the potential spread of COVID-19. As the understanding of COVID-19 remains limited, active monitoring, surveillance, and control of the disease are crucial for public health (Lauer *et al.* 2020) [21]. SARS-CoV-2 infection associated respiratory disease COVID-19 has evolved into a pandemic but, being a new form of virus, pathogenesis of disease causation is not fully understood and drugs against this virus are still being tested so that no effective drugs have been advised by regulatory authority (Gautam *et al.* 2020) [16]. Ayurveda has enough potential and possibilities to be employed both for prevention and treatment of COVID-19. It is pertinent to reiterate that participation of

**Corresponding Author:**  
**Jainendra Pathak**  
Department of Botany, Feroze  
Gandhi College, Rae Bareilly-  
229001, (Affiliated to University  
of Lucknow, Lucknow) India

Ayurveda in addressing the COVID-19 challenge in India should not remain limited and seen as the extension of healthcare services and support to bio-medical system. In this review, we aimed to discuss about important medicinal plants used in Ayurveda and related studies which have been recommended for use during the medical observation period of COVID-19.

### Structure of Sars-Cov-2 and mechanism of action

SARS-CoV-2 belongs to the  $\beta$  genus, Nidovirales order of the Coronaviridae family. SARS-CoV-2 is an enveloped, single (+) stranded RNA, with symmetric helical nucleocapsid (Khan *et al.* 2020) [19]. The virus encodes twenty different proteins including four main structural proteins (S: spike; E: envelope; M: membrane; N: nucleocapsid), and several non-structural proteins such as RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) (Chen *et al.* 2020a) [11]. The angiotensin converting enzyme II (ACE2) was found to be a key functional receptor for the SARS-CoV-2 allowing its attachment to human and bat cells and therefore its replication (Walls *et al.* 2020; Zhou) [43]. SARS-CoV-2 binds the host cells through interaction between the receptor binding motif of the spike protein-receptor binding domain (RBD) and the ACE2 receptor. This interaction will trigger conformational changes of the C-terminal S2 subunit (responsible for virus-cell membrane fusion) of the spike protein. The complex S protein-ACE2 is then proteolytically processed by the host cell-type 2 II transmembrane serine protease TMPRSS2 leading to the ACE2 cleavage and therefore to viral entry into the host cell (Jiang *et al.* 2020; Rabi *et al.* 2020) [25, 29]. After entry and uncoating, the genomic RNA is translated into two polyproteins (pp1a and pp1ab) which undergo a proteolytic cleavage generating 15-16 non-structural proteins. The double-membrane vesicle is then formed from the rearrangement of cellular membrane induced by the non-structural proteins. On the other hand, the genomic RNA is transcribed into subgenomic RNA which in turn leads to the synthesis of structural (spike, envelope, membrane, and nucleocapsid) and accessory proteins. Finally, virions are assembled in the ERGolgolgi intermediate complex, and then released *via* the secretory pathway (Fung and Liu 2020) [15]. SARS-CoV-2 shares several genetic and clinical similarities with other coronaviruses of the  $\beta$  genus such as SARs-CoV and NL63 (Fani *et al.* 2020) [13]. Indeed, the entry of both viruses needs their interaction with the ACE2 receptor. However, some differences have been reported among these strains such as the length of the S protein and the structure of the receptor binding region (Ceccarelli *et al.* 2020) [8]. On the other hand, a high nucleotides homology has been found between SARS-CoV-2 and SARS-CoV in addition to a high homology (95-100%) that has been demonstrated between the proteins of the two strains. Actually, S2 and N proteins of SARS-CoV-2 and SARS-CoV share 99 and 90% similarities, respectively (Xu *et al.* 2020) [51].

### Role of Ayurveda and medicinal plants in management of COVID-19

Ayurveda, being an ancient science have both medicinal and cultural values and had stimulated our kitchen and influenced what we ate in different seasons and the remedies we used for common ailments (Gautam *et al.* 2020) [16]. Herbs such as Tulsi, Marich, Sunthi, Dalchini are the most commonly used and easily available drugs in home. In this context, the Ministry of AYUSH, Government of India has recommended

'Ayush Kwath' to improve the immunity and combat the infection (Gautam *et al.* 2020) [16]. We searched for available literature on COVID-19 and immunomodulatory effects of medicinal plants against SARS-CoV-2 and it was found that certain medicinal plants such as Tulsi/ Holy Basil/*Ocimum sanctum*, Dalchini/ Cinnamon/ *Cinnamomum zeylanicum*, Sunthi/ Ginger/ *Zingiber officinale* and Marich/ Black Pepper/ *Piper nigrum* which were already used in different forms in Ayurveda showed significant immunomodulatory effects against SARS-CoV-2 (Alston *et al.* 2025) [2]. *Ayush Kwath* showed significant immunomodulatory, antiviral, anti-oxidant, anti-inflammatory, anti-platelet, anti-atherosclerotic, hepato-protective, reno-protective properties; and seems to be effective in immunoregulation for controlling viral infections like COVID-19 (Gautam *et al.* 2020) [16]. Further pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of this polyherbal formulation (Gautam *et al.* 2020) [16]. Indeed, with adequate monitoring and data keeping during the implementation, important lessons and research directions are likely to emerge on the management of increasingly frequent and virulent communicable diseases. Implementation of proposed action is likely to provide evidence-based insights strengthening the scope of Ayurveda beyond preventive health care and care for non-communicable diseases (Rastogi *et al.* 2020) [34]. Medical observation period is defined as a period of 14 days after any exposure of COVID-19 occurred and is set based on the incubation time from virus exposure to illness onset (Lauer *et al.* 2020; Xie *et al.* 2020) [21, 50]. Individuals who are put under medical observation are usually those who required monitoring and restriction of movements (i.e., home quarantine and quarantine stations). They are required to complete the 14 days of medical observation before they are given medical clearance. To date, many guidelines related to herbal medicine have been issued for the prevention and treatment of COVID-19 (Ang *et al.* 2020a, b; Luo *et al.* 2019) [3, 4]. Recent clinical evidence also showed the therapeutic effectiveness of traditional medicine in treating different stages of COVID-19 (Chan *et al.* 2020; Wu YQ *et al.* 2020; Yang *et al.* 2020) [9, 47, 54]. For unexposed asymptomatic group which include persons who currently do not have any related symptom nor have any associated risk factor and co-morbidities, preventive interventions include both pharmacological as well as non-pharmacological strategies. These apparently healthy people may be the most suitable for building of immunity so that infection-related pathogenesis can be countered to keep them healthy (Hotchkiss and Opal 2020; Rastogi *et al.* 2020) [17, 34]. Fumigation of homes, shelters and living-place by Ayurvedic herbs such as garlic (*Allium sativum*) peel, turmeric (*Curcuma longa*) powder, Carom or Ajwain (*Trachyspermum ammi*) seeds and Loban (resin of *Styrax benzoin* and *Boswellia* species) may also be a useful strategy for disinfection (Bhatwalkar *et al.* 2019) [16]. In addition, community based *Swarna Prashana* (Patil *et al.* 2017) [28] and mass prophylaxis through *rasayana* having the predominant effects upon respiratory tract can be useful (Rastogi *et al.* 2019) [33]. *Rasayana* may include *Brahma Rasayana*, *Chyavanprasha* or *Amrit Bhallataka* (Rege *et al.* 1999; Sharma *et al.* 2019). *Rasayana* act as antioxidant, anti-stress, anti-inflammatory, anti-microbial, vaccine adjuvant, and confer immunity against diseases (Rastogi 2010; Rekha *et al.* 2001) [31, 38].

Exposed asymptomatic (quarantined) group comprises of people who are without apparent symptoms, but at risk due to

contact history. They need to be quarantined carefully. Specific prophylaxis for this group may include Sanjeevani vati (Rastogi) and Chitrakadi vati and combination of Guduchi (*Tinospora cordifolia*), Shunthi (*Zingiber officinale*) and Haridra (*Curcuma longa*). This group may also be provided with decoction of a combination of Ayurvedic herbs including *T. cordifolia*, *Z. officinale*, *C. longa*, *Ocimum sanctum*, *Glycyrrhiza glabra*, *Adhatoda vasica*, *Andrographis paniculata*, *Swertia chirata*, *Moringa oleifera*, Triphala and Trikatu. These herbs are proposed for the reason that these are known to be broad-spectrum antivirals and protease inhibitors (Rege and Sadashiv Chowdhary 2013, 2014; Panche *et al.* 2019) [36, 26]. People with mild COVID-19 symptoms are the ones which were found positive to SARS-CoV-2 and are having mild upper respiratory infection (URTI) symptoms (Rastogi *et al.* 2020) [34]. Formulations like *Lakshmi Vilas Rasa*, *Pippali rasayana*, *Sanjeevani vati*, *C. vati*, *Go jihvaadi Kashaya*, *Vyaghri haritaki*, *Kantakaari Avaleha*, *Dashamul kwath*, *Sitopaladi*, *Talishadi*, and *Yashtimadhu* may be the most suitable drugs to be used at this stage in an integrative model (Rastogi *et al.* 2020) [34]. Patients with moderate to severe COVID-19 symptoms, constitute the population where the moderate to severe symptoms are already present and the patients also belong to high risk groups. These patients require tertiary care from the beginning itself but can also be co-prescribed with Ayurveda medicines in order to reduce the impact of the pathology and to buy more time to have intensive management (Rastogi and Srivastav 2011) [32]. Recommended formulations here may include *P. rasayana* (Bisht *et al.* 2009) [7], *Laghu Vasant Malati*, *Sanjeevani vati*, *Tribhuvan keerti rasa* (Panigrahi 2006) [27], *Brihata Vata Chintamni rasa*, *Mrityunjaya rasa*, and *Siddha makardhvaja rasa*. *Rasaauashadi* are shown to have better bioavailability and absorption through sublingual and oral route accounting to the nano size of their particles (Sharma and Prajapati 2016) [39]. For example, *suvarna bhasma* has been found to get absorbed well through sublingual administration when mixed with black pepper powder and ghee (Patil-Bhole *et al.* 2018). Considering the medicinal plants with crucial role in management of COVID-19, *Pericarpium Citri Reticulatae* and *Glycyrrhizae Radix et Rhizoma* were found to have significant roles (Ang *et al.* 2020a, b) [3, 4]. Both herbs are often prescribed together in herbal formulae (Chen *et al.* 2020b) [11]. In the theory of traditional medicine, *Citri Reticulatae Pericarpium* regulates the Qi, nourishes the spleen, and dry dampness to resolve phlegm whereas *Glycyrrhizae Radix et Rhizoma* tonifies the Qi and enhances the function of *Citri Reticulatae Pericarpium* in resolving phlegm and reducing cough (Xi and Gong 2017) [49]. Additionally, previous study on the distribution patterns of herbs used for respiratory disease treatment using data mining methods also reported that *Glycyrrhizae Radix et Rhizomawas* often grouped with *Citri Reticulatae Pericarpium* (Fu *et al.* 2013) [14]. Studies also showed that the herb *Citri Reticulatae Pericarpium* has anti-inflammatory and anti-asthmatic properties which may relieve fever, soothe cough and dyspnea, stimulate appetite, as well as enhance the immune system (Shi *et al.* 2009; Yu *et al.* 2018) [41, 55]. Particularly, the recommended dosage range for the herb *Glycyrrhizae Radix et Rhizoma* ranged from 3 to 60 g, which may be related to the nature of the herb itself (Chen *et al.* 2020b) [11]. The herb *Glycyrrhizae Radix et Rhizoma* has been the most commonly used adjuvant in most herbal medicine formulae in assisting herbal interactions. Studies have

reported that the herb itself contains antiviral and anti-inflammatory qualities (Chen *et al.* 2004; Li and Peng 2013; Yang *et al.* 2013) [10, 22, 52]. *Glycyrrhizae Radix et Rhizoma* possesses beneficial effects in respiratory diseases by nourishing Qi, resolving phlegm, and reducing cough (Yang *et al.* 2015) [53]. Based on the currently available evidence, this herb has also been proposed as a novel immunomodulatory drug for COVID-19 (Luo *et al.* 2020) [24]. Hence, the recommended dosage of the *Glycyrrhizae Radix et Rhizoma* highly depends on the role of herbs play in each herbal formula. Natural products could be used alone or in combination as alternative medicines to treat/prevent COVID-19 infection Benarba and Pandiella (2020) [5]. Moreover, their structures may offer clues for the development of anti-SARS-CoV-2 drugs. Recently, few vaccines have been developed but no specific treatments for SARS-CoV-2 have been developed, although extraordinary efforts are being made (Amanat and Krammer 2020) [1]. Some therapeutic approaches have been suggested such as nucleoside analogs, Remdesivir, anti-inflammatory drugs or Lopinavir/Ritonavir to treat COVID-19. At present, more than 200 clinical trials, some of them analyzing these drugs or others, have been registered. Nevertheless, the clinical usefulness of these drugs against COVID-19 infection remains unclear (Li) and certainly Ayurveda and other treatment systems involving medicinal plants are going to play crucial role in the management and treatment of COVID-19.

## Conclusion

Medicinal plants and natural products are still considered promising alternatives to prevent or treat several diseases. Since the outbreak of the COVID-19 pandemic in December 2019, various traditional herbal medicines have been used and resulted in positive health effects among COVID-19 patients in India and other countries. Although the studies evaluating the anti-SARS-CoV-2 effects of medicinal plants are still insufficient and relatively immature, some natural products with IC<sub>50</sub> below 10 µM could be considered as promising anti-SARS-CoV-2 agents since they were able to block its life-cycle related proteins such as the cellular receptor ACE2, papain-like or chymotrypsin-like proteinases. Nevertheless, several limitations have been detected in relation to the specificity of the action exerted by such products, sustainable sourcing of the species, doses range used, or the use of appropriate controls. While available studies offer several indications that these plant derived products may help in fighting COVID-19, further studies should be carried out to evaluate the clinical usefulness of such products against COVID-19 infection. Furthermore, the bioavailability of natural products with possible anti-SARS-CoV-2 effects such as tannins should be considered besides the need for clinical validation of their usefulness and safety. The herbal mixtures, medicinal plants, or natural products with possible anti-SARS-CoV-2 effects must be evaluated through prospective and interventional studies. A combination of natural products or herbal mixtures with validated anti-COVID-19 drugs may constitute a promising preventive and therapeutic alternative to be assessed.

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