

## Review Article

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## Role of Traditional Medicine, Nutraceuticals & Botanicals in COVID-19

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### Abstract

Currently, there is no curative medicine available for the current pandemic caused by Coronavirus disease 2019 (COVID-19). With the rising death toll across the globe, considering effective prevention measures and a healthy immune system is paramount for the management of COVID-19. Nutrition based interventions may play an essential role in the prevention and management of viral infections, particularly in respiratory infections. While researchers are still discovering the impact of nutrition-based interventions in COVID-19 infection, several publications have discussed the possible benefits of traditional medicines (Ayurveda and Chinese medicine), nutraceuticals, and botanicals, in viral infections, including COVID-19. Different sources are touting the next best cure and prevention, making a lot more information available to the public that may or may not be supported by research-based data. Here we discuss the role of traditional medicine, nutraceuticals, and botanicals in the prevention and therapeutic uses of COVID-19. Further clinical trials, warranted to determine the effectiveness of using and capitalize on the substantial potential against viral infections, including COVID-19.

**Keywords:** COVID-19, Coronavirus, Nutraceuticals, Botanicals, Ayurveda, Traditional Chinese Medicine

### Introduction

Currently, there is no curative medicine available for the current Coronavirus 2019 (COVID-19) pandemic. With the rising death toll across the globe, considering effective prevention measures and a healthy immune system is paramount for the management of COVID-19. Nutrition based interventions may play an essential role in the prevention and management of viral infections, particularly in respiratory infections [1]. While researchers

are still discovering the impact of nutrition-based interventions in COVID-19 infection, several publications have discussed the possible benefits of nutraceuticals, botanicals, and traditional medicine in other viral infections. Jayawardena et al. [1] conducted a review of 22 studies (13 vitamins, 8 minerals, 18 nutraceuticals, and 4 probiotics), and the study suggested suppression of immunity was seen in individuals with micronutrient deficiency, which is mainly affected by T-cell-mediated immune response and adaptive antibody response. The

enhanced immunity supports beneficial effects in the host's ability to fight against respiratory viral infections [1].

During the pandemic, as the researchers are strained to find a cure or vaccine for the COVID-19, the general public is overwhelmed with the overload of information available through different mediums. Different sources are touting the next best cure and prevention daily making a lot more information available to the public that may or may not be research-based and data-driven. Puthiyedath et al. [2] reported a significant increase in the sale of zinc and elderberry during the single week period ending March 8, 2020, as much as by 415% and 255% respectively. In this dire situation, the US Food and Drug Administration (FDA) has an important job in monitoring any false marketing claims. Multiple companies have been known to have issued warnings for falsely claiming prevention and treatment for COVID-19. Here we discuss traditional ancient medicine of India and China, nutraceutical, and botanicals for practical recommendations in both prevention and adjuvant therapeutic uses in viral infections including COVID-19.

## **Ayurveda**

Almost every country across the globe bearing the weight of COVID-19 devastations on healthcare and economic system, many have turned to ancient and alternative medicine like Ayurveda as an option for prophylaxis, primary or adjuvant treatments. Kerala, the southern Indian state, home of Ayurveda, has successfully flattened the COVID19 curve and has started the use of Ayurveda in mitigating the spread of COVID-19. The government categorized the population into seven categories based on the possible spread of the virus and advised Ayurvedic treatment accordingly. The Sanskrit word Ayurveda means Ayur (life) and Veda (science knowledge) teaches about immunity and prevention and various stressors such as viral and bacterial infections [3]. While contemporary medicine focuses to attack foreign agents like viruses or boosting immunity against them, Ayurveda considers more focus on the host, encouraging a holistic approach to a healthy lifestyle than just curing the illness with prescriptions [3].

Ayurveda encourages certain lifestyle interventions and natural therapies to regain a balance between the body, mind, spirit, and the environment. It starts with an internal purification process, followed by a special diet, herbal remedies, massage therapy, yoga, and meditation. According to Ayurveda, just as everyone has a unique fingerprint, each person has a distinct pattern

of energy; categorized into three doshas: Vata, Pitta, Kapha; a combination of physical, mental, emotional characteristics. The Ayurveda practitioner focuses on the personalized balancing of doshas and recommends herbal medicine, as well as a non-pharmacological approach like yoga and meditations accordingly [2,3]. In India, the Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy) have suggested the use of a homeopathic approach to Ayurvedic preparations, including Kadha (ginger, curcumin, cloves, honey, fennel seeds, cumin seeds) and lukewarm water throughout the day as immunity booster [4]. Other non-pharmacological interventions including a healthy lifestyle of adequate physical activity, sleep, and contact precautions from infected individuals are also recommended [5].

In Gujarat, India, a prospective trial was conducted where a total of 3,173 people were given Ayurvedic preparation and a total of 2,000 people were given homeopathic medicine as means of immunity booster [5].

For a 14-day observation period, none of the people developed COVID-19 symptoms and negative COVID-19 tests were reported. As of August 2020, a total of 8 million people has received Kadha and more than 5 million people have received homeopathic medicine Arsenicum album 30 in the state of Gujarat alone [5]. Based on these preliminary results, the government of the state of Kerala in India has also started joining hands with public health officials and expanding care for COVID-19 affected patients with traditional medicine frameworks to help improve quality of life and shorten the duration of recovery [5].

A single case study report [6] is published from an Ayurveda Vaidya (doctor) in the state of Tamil Nadu, India of a first known case of a 43 years old male residing in New York, USA, who was COVID-19 positive and treated entirely with Ayurveda. The patient opted for a phone consultation and presented with symptoms of fever, body pain, cough loss of taste and smell, and abdominal pain. The patient experienced a fever for the past 7 days. On day 1, March 29, 2020, the patient was given Ayurvedic treatment of Sudarsana Churna 4 tables (2 gms) with room temperature water, Tid; Talisadi churna 1tsp with honey, Tid; Dhanwantara gutika, 2 tablets, Tid, and regulated diet. The same treatment continued for a total of 7 days. On Day 2 of the treatment, the patient experienced relief from abdominal pain, mild aches, and temperature of 101 F, loss of taste and smell, and mild

coughing persisted. On Day 5, body aches were relieved and the home nasopharynx COVID-19 test was negative. By day 6, the patient had no fever and most symptoms other than loss of taste and smell had disappeared and the patient was told no more COVID19 tests or follow up with a physician were needed.

Even though millions of people across the globe are receiving Ayurveda help as prophylaxis or treatment, not enough data is available or published. However, the Ayurveda Vaidya points out several lessons to learn from this case report [6]: 1) Patient's health did not deteriorate; 2) median time to symptom recovery of 7 days was much shorter than the 3 to 6 weeks of mild to severe cases reported by CDC; 3) The regulated diet played a significant supportive role in maintaining the dosha balance; which helped with slower digestion allowing time for stimulation of digestive fires and maintain nourishment. Since the patient resided in the United State, limited Ayurvedic formulations were available to them; however, the tremendous potential of available formulations cannot be ignored [6].

There is now enough evidence of pulmonary fibrosis in patients recovered from COVID19 [7]. AYUSH claims that Ayurveda and Yoga have lots to offer for patients requiring pulmonary rehabilitation, which will not only focus on symptom relief but improve lung function and therefore improve quality of life [3]. The concept of immunity building to cope with stressors in Ayurveda is what is known as innate and acquired immunity in modern medicine [4]. Before entering the lungs, the eyes, nose, and mouth are considered the main portal of entry for SARS-CoV-2 droplets. It is thought that the fatty acid outer layer of the SARS-CoV-2 virus adheres to these moist mucosal layers and gain entry through binding to ACE-receptors and stays in the throat for several hours [3]. Ayurveda offers several measures barricading the viral entry and invasion early on [4]: hot water, hot food, herbal decoction, gargling with medicated water, and steam inhalation.

As per Ayurveda, drinking hot water and eating hot food play a major role in improving digestion and removing waste. The proper waste removal (urine and stool) is imperative as waste is linked to increased susceptibility to bacterial and viral infections [4]. In addition to medications, this technique is also used in treatment for other medical conditions causing fever, inflammation, allergy, asthma, and metabolism issues. Several popular spices used in the kitchen may be added to boiling water

and consumed throughout the day, including but not limited to dry ginger, yashtimadhu, nut-grass rhizomes, khus, Indian sarsaparilla roots, coriander, fennel seeds, cinnamon, and catechu barks [4]. Mouth rinse and gargle and nasal oil applications are also routinely recommended for prophylaxis measures.

Many Ayurvedic herbs like curcumin and nimbin have exhibited interaction with spike glycoprotein and ACE2 receptors and have illustrated pharmacological properties towards SARS-CoV-2 and may be used as prophylactic agents [8]. Based on a preliminary analysis of the literature review, the WHO has also confirmed the benefit of alternative medicine as adjuvant therapy for SARS-CoV-2 [2], based on which COVID19 patients can be classified as mild, moderate, and severe and be provided personalized treatment. As more and more countries and their healthcare system are on the verge of crashing during the pandemic, a more affordable and data-driven approach using Ayurveda will be important [2].

## **Traditional Chinese Medicine**

Traditional Chinese Medicine (TCM) is a system of medicine that has been around for several thousands of years [9]; it is founded on a combination of philosophies, including Confucianism, Taoism, and Buddhism [10]. TCM focuses on re-establishing and maintaining balance in the body holistically, and combining natural medicines (made from plants, minerals, and animals) with physical maneuvers (such as acupuncture, massage therapy, etc) for successful treatment [11,12]. TCM addresses illness through multiple pathways, stemming from an understanding of the body's disease processes that have been accumulated over centuries of clinical practice and observation [11]. One of its fundamental beliefs is prevention: prevention before a disease arises, prevention of transmission after the occurrence of disease, and prevention of recurrence after treatment [11]. To promote prevention, Chinese medicine is based on the core principle of the relationship between healthy qi (life force) and pathogens [11,12] and strengthening healthy qi by regulating homeostasis and boosting the body's defense capabilities [11]. After utilizing diagnostic tools that include a mix of modernized techniques as well as TCM methods such as visual inspection, listening, and touching to determine the pathogens underlying an illness [10], the focus is placed on removing the pathogenic qi, such as poison, blood stasis, heat, and phlegm [12]. Ancient Chinese medicine instituted the theory of the body having a system comprised of four stages: wei (defense), qi (vital energy), ying (nutrient),

and xue (blood) [13], and combinations of these stages can be used to describe illnesses and guide treatment. In addition to physical techniques, TCM employs a range of established decoctions (concentration of a medicinal preparation made from plants and herbs and usually boiled) that have particular components and ingredients that are active towards specific pathogens [11,12].

TCM has been used to treat infectious viral and bacterial diseases for many centuries, and in general, it has been shown to have a significant effect on fevers (bringing the fever down rapidly), protects organs from damage in severe infections, and helps treat refractory pneumonia [12]. It was shown to help reduce disease progression and associated complications in the severe acute respiratory syndrome (SARS) outbreak in 2003 [14,15]. COVID-19 disease falls under the classification of pestilence within the Chinese medicine framework [9]. In addressing the rapid spread of this global pandemic, the Chinese government and the National Health Commission of the People's Republic of China released a multidisciplinary manual of measures and protocols to adopt, titled, "Diagnosis and Treatment Program of Coronavirus Disease 2019" [14]. Since there has been continually evolving research into the novel coronavirus, revisions and updates were presented in further editions that were released, resulting in seven total, and beginning in the third edition and through the seventh, TCM was included as a treatment for tackling COVID-19 [9,14]. Using TCM for diagnosis and treatment was well formulated in the later editions, and TCM is recommended throughout the disease process [14], with the pathogenesis of COVID-19 thought to be related to toxin, heat, stasis, and dampness [14,16]. Treatment methods are directed at eliminating or reducing various combinations of these pathogenic substances, depending on the specific patient and their needs [14]. In later editions, a primary protocol called QingFei PaiduTang was introduced; it was one that could be applied to all COVID-19 patients by all practitioners, not only TCM doctors [14]. The primary focus of QingFei PaiduTang is clearing the lungs and detoxification [17]. Official data showed that 1,183 patients on this treatment protocol in February 2020 were exhibiting positive effects, with 640 discharged and 457 with improved conditions [14]. The same treatment protocol has also been found to cause improvement in lymphocyte percentages, C-reactive protein levels, and erythrocyte sedimentation rates as well as symptomatic improvement. The treatment regimen includes decoctions formulated from four classic TCM preparations of herbs including multiple rhizoma types, radix glycyrrhizae, jujube, poria, raw gypsum, and

schisandra chinensis, among others [14,17]. These are to be taken twice a day after meals for three days with a second course recommended if symptoms persist [14]. Other methods like Chinese patent medicines (oral and injectable preparations) can address gastrointestinal distress, fatigue, and fever [16], but there are limited studies in COVID-19 and further research is necessary.

In classifying the treatments that have been used in China to battle COVID-19, 32% have involved TCM, while 15% have involved TCM in combination with Western medicine [10]. Evidence from multiple studies shows that TCM plays a role in decreasing days of hospitalization as well as causes symptomatic improvement, particularly with fever, cough, fatigue, headaches, and nasal congestion [10,14,16,17], particularly in non-critical patients. In more severe cases, it can decrease lung exudation, reduce inflammation, and prevent disease progression [15]. Most of the evidence for TCM is observational, and as such it would be very beneficial to encourage further study, especially randomized controlled trials to determine full efficacy. In the current absence of a vaccine or definitive therapy for COVID-19, combining TCM methods with Western medicine may prove to be an efficacious way of mitigating the severity and progression of COVID-19 in hospitalized patients.

### **Curcumin**

From ancient times the medicinal properties of the polyphenolic compound [18], Curcumin, (also known as turmeric), has been elaborated, recorded in Unani, Ayurveda, and Chinese medicine [19]. Curcumin is extracted from the roots of a rhizome plant *Curcuma longa* (family Zingiberaceae). The notable medical properties which have brought this medicinal herb back to the limelight are its anti-inflammatory, anti-bacterial, antiviral, anti-angiogenic, anti-cancer properties [20]. Previously Curcumin was used to make a medicinal decoction in developing countries to combat viral epidemics caused by dengue virus [21], Zika virus, chikungunya, hepatitis C Virus [22]. One of the features all these authors noted was that curcumin exerts its anti-viral effects at initial steps in virus infection, by preventing virus-cell binding. Though the effectiveness of curcumin is researched, mentioned, it hasn't yet been approved by the FDA as a therapeutic agent [20]; instead, FDA categorized it as, "generally recognized as safe".

Since the onset of the SARS COVID-19 pandemic in March 2020, virologist, researchers have been studying the pathophysiology of the virus, and how it causes varying severity of disease in a different population with diverse manifestation from a mild sore throat,

the new loss of taste and smell to severe pneumonia, acute respiratory distress (ARDS) to Stroke, multi-organ failures [23]. The Allopathic and alternative medicine practitioners, researchers, scientists are all exploring various permutations and combinations of drugs to prevent, curb the COVID-19 infection. Due to its easy availability, repeated past success stories, and low cost, curcumin's effectiveness against the prevention and treatment of COVID-19 has also been studied.

The COVID-19 invoked pneumonia is due to the inflammatory derangement, "cytokine storm" [7] elicited by it. Curcumin is found to be effective by Zahedipour et al. [18] inhibiting the viral entry into the human cells (inhibits COVID-19 - ACE2 receptor binding), and by Prasad et al. [19] anti-inflammatory actions such as (a) by regulating the pro- and anti-inflammatory mediators [24], (b) by its action as an antioxidant, (c) enhancing apoptosis of the inflammatory cells [25] (d) decreasing collagen deposition, downregulating transforming growth factor II receptors. The former mechanism of inhibiting viral interaction with angiotensin receptors also mitigates the hypertensive effects of COVID-19 [26]. Thus far it's clear that curcumin can be used for supportive preventive and therapeutic purposes against COVID-19. However, further clinical trials are needed to fully evaluate the pharmacologic effects of curcumin.

## Elderberry

Elderberry (*Sambucus nigra*) is a dark purple berry of the European or black elder tree, which grows in the warmer parts of Europe, North America, Asia, and Northern Africa. It has been used in folk medicine for treating colds and flu. Its use has also been recommended in COVID-19 patients but we are yet to come with strong evidence to support this [27]. Due to its ability to modulate inflammatory cytokines, elderberry is also believed to have antiviral properties [28]. The phenolic acid components of elderberry demonstrate antiviral properties against human coronavirus HCoV-NL63 in vitro [29], which is different from COVID-19 but is a member of the coronavirus family. It has been suggested by randomized double-blind placebo-controlled trials that elderberry may reduce symptom duration when used for the treatment of influenza [30-32]. A similar clinical trial evaluated the use of elderberry in air travelers and reported that elderberry may reduce the duration of cold symptoms and severity [33]. Consumption of elderberry is considered safe when it's cooked and also consumed moderately. Due to the risk of cyanide toxicity, it is dangerous to consume uncooked elderberry, bark, root,

leaves, and unripe berries. Elderberry intake should be monitored cautiously in diabetic patients due to its ability to stimulate insulin and promote glucose metabolism [28]. Few noteworthy side effects of elderberry include nausea, vomiting, diarrhea, tachycardia, hypotension, hypokalemia, and dehydration as a result of diuresis [34]. Although preliminary research and studies suggest that elderberry may relieve flu symptoms or other upper respiratory tract infections, we are yet to come up with published research studies that have evaluated the use of elderberry for COVID-19 and demonstrate effectiveness for the particular category [27].

## Astaxanthin

Astaxanthin (AX) is a red fat-soluble pigment and one of the xanthophylls, derived from carotenes. AX is present in microorganisms and marine animals such as algae, yeast, crustaceans, salmon, and other fish supplies; however, the rich source of AX consumed by humans is obtained from *Haematococcus pluvialis* (a green microalga) [35-37]. AX is used as a food coloring agent and got the United States Food and Drug Administration (USFDA) approval to be utilized as a color additive to various food feeds [38].

The farmed Salmon fish contains 6-8 mg/kg flesh of AX contents. Similarly, the reported quantity of AX obtained from large trout in the Japanese market was 25 mg/kg flesh. The recommended daily dose of AX is 2-4 mg and is available in the market in the form of soft gel, capsules, cream, and in combo with other foods [35]. The antioxidant effect of AX was revealed in one of the randomized controlled trial (RCT). In this RCT, Park et al. concluded that AX was associated with reducing oxidative stress and inflammation secondary to lowering acute phase reactants and biomarkers, resulting in DNA damage. Additionally, dose-dependent heightened immune response due to overall T and B cell proliferation and increased natural killer (NK) cells cytotoxic effects were also reported, particularly in the 8mg AX group compared to 2 mg AX and control groups. However, this response was merely assessed in healthy females in their 20s; therefore, it requires further investigation in both genders [39]. It is suggested that the antioxidant activity of AX is better than the  $\beta$ -carotene. It is also anticipated to protect against cardiovascular diseases, certain cancers, and various immune-mediated conditions owing to the significant antioxidant properties [36].

It was found out in the rodents' model that the anti-inflammatory effect of 100mg/kg of AX was as efficacious as 10 mg/kg prednisolone [40]. Many studies have demonstrated that it alleviates inflammatory cell infiltration

and proinflammatory cytokine storm (e.g., IL-6, TNF- $\alpha$ , etc.) mainly via the NF- $\kappa$ B inhibition pathway in SARS-CoV-1 infection [King]. Because of the anti-inflammatory, immunomodulatory, and antioxidant properties, it is anticipated to be a potential adjuvant therapy in COVID-19 patients [41].

## N-Acetyl Cysteine (NAC)

N-Acetylcysteine is the acetylated version of the essential amino acid L-cysteine. (N-acetyl cysteine, N-acetyl-L-cysteine or NAC) are also interchangeably used for N-acetylcysteine. NAC is also acting as a precursor of reduced glutathione (GSH). Both NAC and GSH act as a scavenger of reactive oxygen species (ROS) and reduce the oxygen-free radicals, thus maintaining the cell's integrity. NAC has a broad range of uses; however, its role in facilitating mucolytic in various respiratory diseases and as an antidote for paracetamol (aka APAP) toxicity is more prevalent. It is available in oral, intravenous, and aerosol formulations [42-44].

A randomized placebo-controlled trial (PANTHEON) evaluating NAC's efficacy in the chronic obstructive pulmonary disease (COPD) population concluded that long term NAC use at a dose of 600 mg twice/day preclude exacerbation, notably in the setting of moderate disease severity [45].

As it has been studied substantially that the SARS-CoV-2 spike (S) glycoprotein has two subunits such as S1 and S2, which bind to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell membrane. S1 is responsible for expediting the bond formation between viruses and host cells. On the other hand, S2 promotes viral entry into the eukaryotic cell via fusion with the host cell membrane [46]. It is also suggested that human protease "furin" can further facilitate virus entrance [47].

Moreover, (Rangel-Mendez & Moo-Puc 2020) reported that many clinical studies had demonstrated the ACE inhibitory action of NAC [48]. Also, it is proposed that SARS-CoV-2 triggers cytokine storms resulting in lung inflammation due to activation of the Nf- $\kappa$ B pathway (a potent pathway for pro-inflammatory cytokine production). Likewise, NAC inhibitory action of the Nf- $\kappa$ B pathway was also revealed in the influenza A & B model *in vitro* [49]. Based on the results in a recent study reported by Andreou et al., the combination of NAC, copper, nitric oxide (NO), and remdesvir can play a promising role in the management of COVID-19 patients owing to the anti-inflammatory properties, inhibition of RNA polymerase

enzyme, reducing viral replication, and improving pulmonary oxygenation [50].

To conclude, NAC has both antioxidant and mucolytic activity, thus can be a potential therapy or adjuvant therapy in the management of COVID-19.

## Glutathione

Glutathione (GSH) is a vital cellular antioxidant that is present abundantly in all our cells; the liver and the lining of the respiratory tract have the most of this antioxidant. GSH plays a pivotal role to help resolve viral infections in our bodies. It not only detoxifies toxic compounds, but also plays a role in protein folding, vitamin C and E regeneration, maintenance of mitochondrial function, antiviral defense, the regulation of cellular proliferation, apoptosis, and the immune response. GSH deficiency is linked with rapid aging and various chronic diseases, such as diabetes, cardiopulmonary diseases, hepatic illnesses, and cancer. GSH deficiency may contribute to severe COVID-19 infection as well. Amid viral infection, increased viral replication leads to a higher viral load that causes profound oxidative damage to the lungs. GSH deficiency also causes high levels of inflammation responsible for ARDS (acute respiratory distress syndrome) and more susceptibility of fatality from SARS-CoV-2. According to an Italian study, GSH is particularly useful in preventing severe respiratory disease in the elderly patient population. Maintaining high cellular levels of reduced GSH is vital for health and immunity. Peak GSH levels can enhance the body's response to viral infections and help combat COVID-19. GSH levels can be restored with GSH supplements and via intravenous infusion [51]. Fatality rates are higher in elder males who have lower levels of blood reduced GSH [52], as the elderly population manifests a chronically low level of inflammation due to oxidative stress and production of inflammatory cytokines, that leads to increased severity of viral infections and could be attenuated by administration of antioxidants [53]. A notable rise in blood serum glutathione reductase (GR), due to oxidative stress imbalance, was seen in COVID-19 patients, especially when admitted to ICU [54]. A series of literature suggests that an endogenous deficiency of GSH may lead to serious manifestations and even death from COVID-19 [55]. Additionally, GSH affects the production of most inflammatory cytokines and is needed to maintain sufficient interferon (IFN)- $\gamma$  production by dendritic cells [56]. GSH also affects the secretion of cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , known to have pyrogenic properties [57].

## Medical Mushrooms

Medicinal mushrooms (MM) have been explored as therapeutic agents for several decades. They have an established history in ancient and traditional medicine all over the world. Medicinal Mushrooms or their derived preparations continue to be used in modern clinical settings in countries like Korea, Japan, China, and Russia [58]. They have been researched extensively for their immunomodulating, anti-inflammatory, anti-tumor, anti-viral, antioxidant, anti-bacterial, and anti-fungal effects, to name a few. They also have established protective action against the cardiovascular and hepatic system and are considered anti-diabetic [59]. The immunomodulatory action is due to bioactive polysaccharides or polysaccharide-protein complexes present in the medicinal mushrooms that have been found to augment the cell-mediated and innate immune response. These bioactive polymers stimulate the immune cells to mature, differentiate, and proliferate [58]. The induction of immunomodulatory cytokines and their receptor expression has been demonstrated by  $\beta$ -glucans, a polysaccharide component of medicinal mushrooms [60]. Other biological components of these medicinal mushrooms like proteins, lipopolysaccharides, and glucose-proteins have been explored as agents that enhance immunological response produced by the host cells.

The anti-viral action of medicinal mushrooms has been explored in several studies. Ren et al. [61] found that lentinan, an extract from *Lentinus edodes* mycelia, also known as LNT-1 downregulated the inflammatory cytokines (TNF- $\alpha$ , IL-2, IL-11), indicating an inhibitory effect on infectious hematopoietic necrosis virus. The GFAHP, a protein extract from *Grifola frondosa*, was shown to inhibit the replication of HSV-1 in-vitro and reduced the severity of ophthalmic manifestation in animal models. The D-fraction extract of *Grifola frondosa* also demonstrated inhibitory effects in HBV [62]. The  $\beta$ -glucans from *Lentinus edodes* were explored as a potential treatment for lung injury. It reduced inflammation of the lung epithelium and reduced the cytokine-induced activation of human alveolar cells.

*Inonotus obliquus*, commonly known as the chaga mushroom, has also demonstrated inhibitory actions against HSV. It stops the viral-induced fusion of the cell membrane thus preventing viral entry into the cell. It is also used to aid in breathing by suppressing nasopharyngeal inflammation [63]. The polysaccharides in *Inonotus obliquus* inhibit the JAK-STAT pathway,

which is responsible for its anti-inflammatory action. The chaga mushrooms inhibited nitric oxide production and inhibited the levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Metabolites extracted from *Agaricus blazei* Murill (AbM) were demonstrated to have anti-viral effect on influenza virus and H1N1 virus in vitro. AbM's anti-inflammatory action is by inhibiting pro-inflammatory cytokines like IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [64].

The antiviral, anti-inflammatory, immune-modulatory action, along with the inhibitory effect on cytokine expression can be beneficial in the management of COVID-19. Some of the medicinal mushrooms and their extracts mentioned above ameliorate the pro-inflammatory response and can be considered as a therapeutic agent during the cytokine storm. Moreover, the anti-inflammatory action of medicinal mushrooms, especially *Inonotus obliquus* can help reduce airway inflammation in mild to moderate COVID-19 cases.

## Propolis

Propolis is a complex substance, containing over 300 chemical substances. The major parts constituting propolis are resins, waxes, oils, and pollen, phenolic compounds, flavonoids, terpenes, esters, aromatic aldehydes and alcohols, beta-carotene, caffeic acid, and kaempferol. The composition of propolis is variable. It has antimicrobial, antineoplastic, anti-inflammatory, antioxidant properties [65]. It has been used for ages for medicinal purposes. It has proven pharmacological and pharmaceutical properties [66]. Hence it can be used potentially for the betterment of human and animal health [67]. However, the use of propolis in SARS-Cov-2-infected patients has yet to be probed into.

Previously several studies have shown that propolis exhibits antiviral properties against HSV-1, HSV-2, Influenza virus type A and B, Parainfluenza virus, Adenovirus, HIV, infectious bursal disease virus and avian reovirus, Newcastle virus disease, bovine rotavirus, pseudorabies virus, feline calicivirus, canine adenovirus type 2, and bovine viral diarrhea virus [65]. It is hypothesized that it hampers virus entry into the cells, thus impacting viral replication. *In vitro* studies have shown its effectiveness against several DNA and RNA viruses, including coronavirus [65,66] propolis also has a viricidal action on the enveloped viruses [68]. Another important propolis flavonoid is quercetin and it exhibits vital activity against SARS CoV 2 [65,69]. Quercetin along with vitamin c has aminopeptidase inhibitor activity, hence showing activity against SARS and MERS [69].

Propolis affects various biological systems [70]. Finally, the safety, health effects, low cost are supporting

features of usage of propolis against COVID 19. Caffeic acid phenethyl ester (CAPE) is an important component of propolis that down regulates RAC which is a signaling protein in human cells. It acts as a RAC/CDC42 activated kinase 1 (PAK1) blocker. Hence CAPE inhibits coronavirus induced fibrosis in the lungs [71].

### **Andrographis paniculata (paniculata)**

Andrographis paniculata has several common names; Indian Echinacea, Chuan Xin Lian, Chiretta, Kalmegh, and frequently used in traditional medicine for infectious diseases as it is thought to exhibit antioxidant, anti-inflammatory, and immunostimulating properties [72]. This bitter-tasting plant is used either or alone or with other herbs, research has shown Andrographis reduced severity and duration of the common cold and flu symptoms [72]. The antiviral property of Andrographis is contributed to the upregulation of cytotoxic lymphocytes (CTLs) and natural killer (NK) cells, which play a major role in destroying cells infected with foreign antigens like bacteria or viruses [72]. Enmozhi et al. [73] analyzed Andrographis compound in silico against SARS-CoV-2 and saw great binding in comparisons to other synthetic drugs like lopinavir, oseltamivir, and ritonavir. Andrographis also showed greater binding in comparison to other plant-based compounds like kaempferol, quercetin, demethoxycurcumin, curcumin, catechin, zingerol, and gingerol. Murugan et al. [74] also conducted a study to show the potency of Andrographis against COVID-19 using evidence to show microscopic mechanisms. The study revealed a high binding affinity of AGP3 protein of Andrographis to at least four target sites on the COVID-19 virus: 3CLpro, PLpro, RdRp, and spike protein, further enhancing its therapeutic effects on the virus. Chalichem et al. [75] explained the importance of repurposing currently proven therapeutic benefits of anti-viral agents like Andrographis. Researchers provided evidence of the antiviral property of Andrographis against life threatening HIV. Therefore, the defense against other viruses like COVID-19 cannot be eliminated and requires further research.

### **Probiotics**

Probiotic is a Greek word - Pro (meaning 'for'), and biotic (meaning 'life'). The World Health Organization defines probiotics as, "live microorganisms which when administered in adequate amounts confer a health benefit on the host". The various health benefits have been studied over the years; some of which are decreasing secondary infections after a course of antibiotics improves immunity, decreases serum cholesterol, protects against cancer

[76], and decreases respiratory infections secondary to the invasion of the gastrointestinal system [77]. Many scientists' have argued that these various health benefits are on account of the species of micro-organism deployed as the probiotic. For instance, Guillemard et al. showed how Lactobacillus casei reduced the incidence and duration of respiratory tract infection [78], Shimizu et al. [79] showed that Bifidobacterium Breve and Lactobacillus Casei Lowered the incidence of ventilator-associated pneumonia. Chong et al. [80] studied that Lactobacillus plantarum can be used in the prevention of upper respiratory tract infections. In March 2020, when the world was struck by the SARS COVID-2019 pandemic, and the world was least prepared for it. As of September 2020, the total number of cases in the United States alone is 280 million, and the number of deaths is 8,742. In a frantic effort to flatten the curve, open the economy safely from the lockdown Scientific fraternity, healthcare professionals are experimenting with multiple drugs, either alone or in combination with other drugs, both allopathic and alternative medical treatments to contain the COVID-19 virus. Probiotics have had their fair share of being speculated for both preventing and mitigating the effects of COVID-19 infection, and their complications.

Different microbiota occupies, form native colonies in different organs. While the gut and lungs are anatomically independent, there are potential links between the two, creating what is known as the gut-lung axis (GLA) [3] [81]. There are also studies to show that gastrointestinal cells, as well as hepatocytes also express angiotensin-converting enzyme 2(ACE2), transmembrane protease serine 2, the important receptor for SARS-CoV2 [82].

Binding to these receptors induces pro-inflammatory mediators, resulting in gastrointestinal symptoms, like diarrhea, abdominal pain, increase fecal calprotectin, and serum interleukin-6 [83].

Yang and Tu [84] further elaborate how there is the possibility that COVID-19 is transmitted by the fecal-oral route, as well as respiratory route. A small case series in China showed that in COVID-19 positive patients there is a microbial disturbance in the gut, known as dysbiosis [85]. Given the past successful experiments to clear influenza virus from the respiratory tract by probiotic remedy [80], GLA, the possibility of COVID-19 in dysbiosis state by infecting the gut as well, researchers are experimenting to see if probiotics can be low cost, effective treatment against COVID-19. So far only two types of non-pathogenic bacteria are found to effectively reduce the coronavirus receptor

expressions in animal model studies [86], Lactobacillus and Bi- fidobacteria. The speculation of the effectiveness of probiotics to prevent, mitigate COVID-19 is indirect since there is not yet approved to conduct a clinical trial with it. Meanwhile, there is also NIH funded research going on in Colorado State University (CSU) for engineering probiotics (Lactobacillus acidophilus) which express COVID-19 proteins to develop oral vaccines, and another to engineer lactobacilli which can be used for vaccine delivery [87].

## Conclusion

As the quest for an apt vaccine for COVID-19 continues, the world seeks viable treatment options available to mitigate the progression of the disease. The use of nutraceuticals enhancing the immune system is something that needs to be explored further to bring repurposed therapeutic products into the market quicker. Nutraceuticals have a demonstrated history of use in a spectrum of health conditions owing to a variety of potent immunomodulatory, anti-inflammatory, and antiviral properties. Deficiencies of many natural supplements have shown to increase susceptibility to viral infections, subsequently worsening the clinical outcomes. In this review, we have examined traditional medicine of India and China, nutraceuticals, and botanicals to demonstrate their efficacy in the fight against COVID-19; providing nutrient supplementation could help reduce the severity of symptoms and delay disease progression. Although nutraceuticals, like other supportive care options for COVID-19, may not be the sole solution to this pandemic, they may have a profound impact on preventative and supportive measures in these unprecedented times. More clinical trials are warranted to determine the effectiveness of using and capitalize on the substantial potential against viral infections, including COVID-19.

## Declarations

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