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REVIEW

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Natural products as home-based prophylactic and symptom management agents in the setting of COVID-19

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Coronavirus disease (COVID-19) caused by the novel coronavirus (SARS-CoV-2) has rapidly spread across the globe affecting 213 countries or territories with greater than six million confirmed cases and about 0.37 million deaths, with World Health Organization categorizing it as a pandemic. Infected patients present with fever, cough, shortness of breath, and critical cases show acute respiratory infection and multiple organ failure. Likelihood of these severe indications is further enhanced by age as well as underlying comorbidities such as diabetes, cardiovascular, or thoracic problems, as well as due to an immunocompromised state. Currently, curative drugs or vaccines are lacking, and the standard of care is limited to symptom management. Natural products like ginger, turmeric, garlic, onion, cinnamon, lemon, neem, basil, and black pepper have been scientifically proven to have therapeutic benefits against acute respiratory tract infections including pulmonary fibrosis, diffuse alveolar damage, pneumonia, and acute respiratory distress syndrome, as well as associated septic shock, lung and kidney injury, all of which are symptoms associated with COVID-19 infection. This review highlights the potential of these natural products to serve as home-based, inexpensive, easily accessible, prophylactic agents against COVID-19.

KEYWORDS
acute respiratory distress syndrome, coronavirus disease, diffuse alveolar damage, natural products, pulmonary fibrosis, severe acute respiratory syndrome coronavirus 2

1 | CORONAVIRUS AND ASSOCIATED CLINICAL SYMPTOMS

Coronaviruses (CoV; *Cronaviridae*) are a group of viruses discovered in the 1930s that mainly cause respiratory, gastrointestinal, liver, and neurological diseases in animals (Weiss & Navas-Martin, 2005). These viruses are termed zoonotic and can be transmitted from animals to humans due to pathogen spillover (Salata, Calistri, Parolin, & Palù, 2019). The word "Corona" is derived from the Latin word which means "crown" signifying the crown-like projections found on the surface of this virus. Coronaviruses are spherical, positive single-stranded RNA viruses made of spike (S) protein required for attachment, membrane (M) protein that maintains virion shape, envelope (E) protein for assembly and release of viral particles, and nucleocapsid (N) proteins for RNA binding and viral packaging (Fehr & Perlman, 2015). Figure 1 shows the structure of the SARS-CoV-2 virus. Seven types of coronaviruses are known to cause infections in humans. Among these, four (NL63, 229E, OC43, and HUK1) cause common cold with associated mild respiratory tract infections (Singhal, 2020). The remaining three strains cause severe and acute respiratory tract infections, which are responsible for three major human pandemic outbreaks in the 21st century namely severe acute respiratory syndrome (SARS, caused by SARS-CoV in 2002), Middle East Respiratory Syndrome (MERS, caused by MERS-CoV in 2012), and Corona Virus Disease 2019 (COVID-19, caused by SARS-CoV-2 in 2019) (Fan, Zhao, & Zhou, 2019; Guo et al., 2020).

1.1 | SARS and MERS

SARS emerged first in China in 2002 and spread across the world infecting around 8,096 individuals with 10% fatality (Gu &

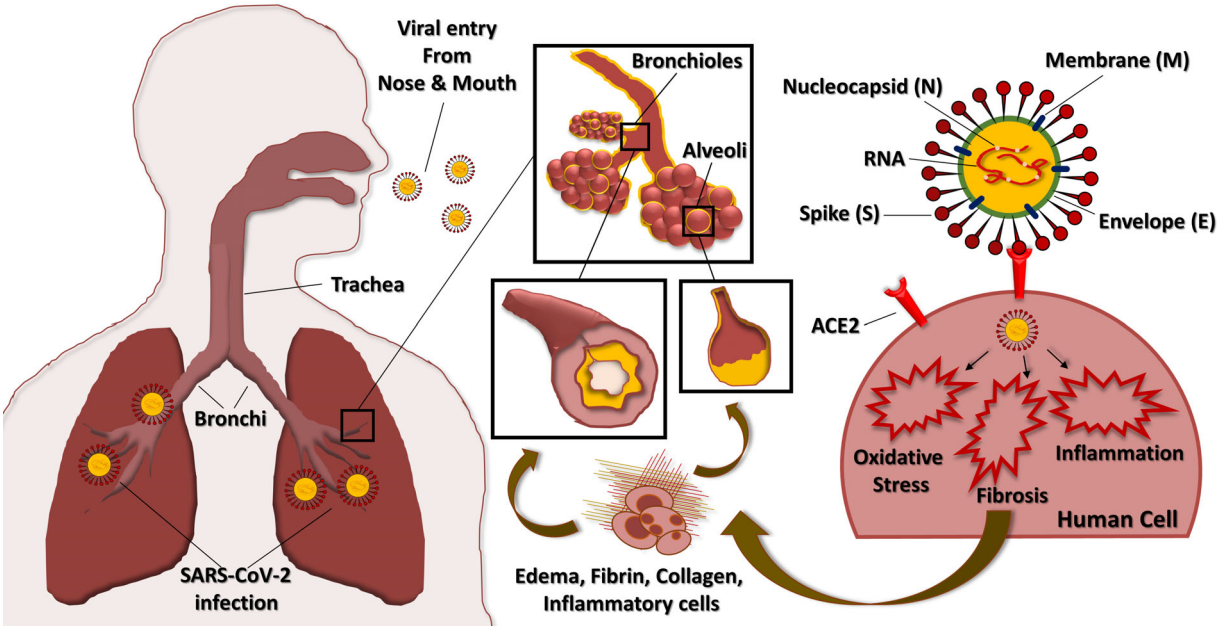

FIGURE 1 Structure of SARS-CoV-2 virus showing the single-stranded RNA and nucleocapsid (N) along with spike (S), envelope (E), and membrane (M) proteins. Schematic representation shows viral entry through the respiratory tract causing lung infection by damaging bronchioles and alveoli. This is associated with edema or swelling and elevated levels of fibrin, collagen, and inflammatory cells leading to pulmonary fibrosis. The spike (S) protein of SARS-CoV-2 binds to ACE2 on the human bronchial and alveolar epithelial cells and activates fibrosis, oxidative stress, and inflammatory responses leading to acute lung infection. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 [Colour figure can be viewed at wileyonlinelibrary.com]

Korteweg, 2007). MERS emerged in Saudi Arabia in 2012 and spread mostly to the Middle East with a few cases in Europe, Asia and North America (Hemida, 2019). It accounted for around 2,494 cases with a higher mortality rate of 34.4% (WHO, 2019). Since 2012, there have been a few active sporadic outbreaks of MERS (Ramadan & Shaib, 2019). The symptoms of SARS and MERS are similar and include fever, cough, shortness of breath, myalgia or fatigue (muscle pain), and diarrhea. In severe cases, both these infections result in pneumonia, severe respiratory infection, acute respiratory distress syndrome (ARDS), sepsis, and multiple organ failure (Al Hajjar, Memish, & McIntosh, 2013; Peiris, Yuen, Osterhaus, & Stöhr, 2003). There is an increased risk of progression associated with age and comorbid conditions such as diabetes, hypertension, cardio, pulmonary, and renal diseases. Pathological analysis of SARS and MERS reveals diffused alveolar damage (DAD), edema, elevated levels of collagen, fibrin and inflammatory cells in alveoli leading to decline in lung function and acute lung injury (Alsaad et al., 2017; Franks et al., 2003). Bats were reported to be the natural hosts for SARS and MERS coronaviruses which were transmitted to intermediate hosts, and finally to Humans (Omrani, Al-Tawfiq, & Memish, 2015; Salata et al., 2019). The transmission of SARS and MERS was by direct contact or through droplets of coughs and sneezes from the infected patients (Killerby, Biggs, Midgley, Gerber, & Watson, 2020; Peiris et al., 2003). Treatment for SARS and MERS involved administration of antiviral drugs in combination with corticosteroids and interferon-α (IFN-α), however, the treatment had minimal benefits to patients and severe adverse effects (Al Ghamdi et al., 2016; Tai, 2007).

1.2 | COVID-19

COVID-19 first emerged in December 2019 in China causing acute respiratory tract infections (Guo et al., 2020). This new virus is highly contagious and has spread rapidly across the globe. WHO declared the outbreak as "Public Health Emergency of International Concern" (WHO, 2020b). By the end of May 2020, the virus had spread to 213 countries or territories with greater than six million confirmed cases and about 0.37 million deaths. Furthermore, during this period, there was a steep rise in the number of reported cases and associated mortality (WHO, 2020d). Although the overall fatality rate for COVID-19-infected patients is lower (5.9%) compared with SARS- and MERS-infected subjects, the spread of the disease has been exceptionally rapid, causing a global pandemic. Figure 2 shows the COVID-19 global pandemic curve with the total number of confirmed cases and deaths. The current statistics on the extent of COVID-19 infections globally could be a significant underestimate given the lack of enough testing kits and a large number of asymptomatic carriers.

COVID-19 has very close similarities to the SARS virus and hence is named SARS-CoV-2 (Wu et al., 2020). Bats are believed to be the primary source of the virus and although the exact mechanism of transmission to humans is unclear, it is considered to have resulted

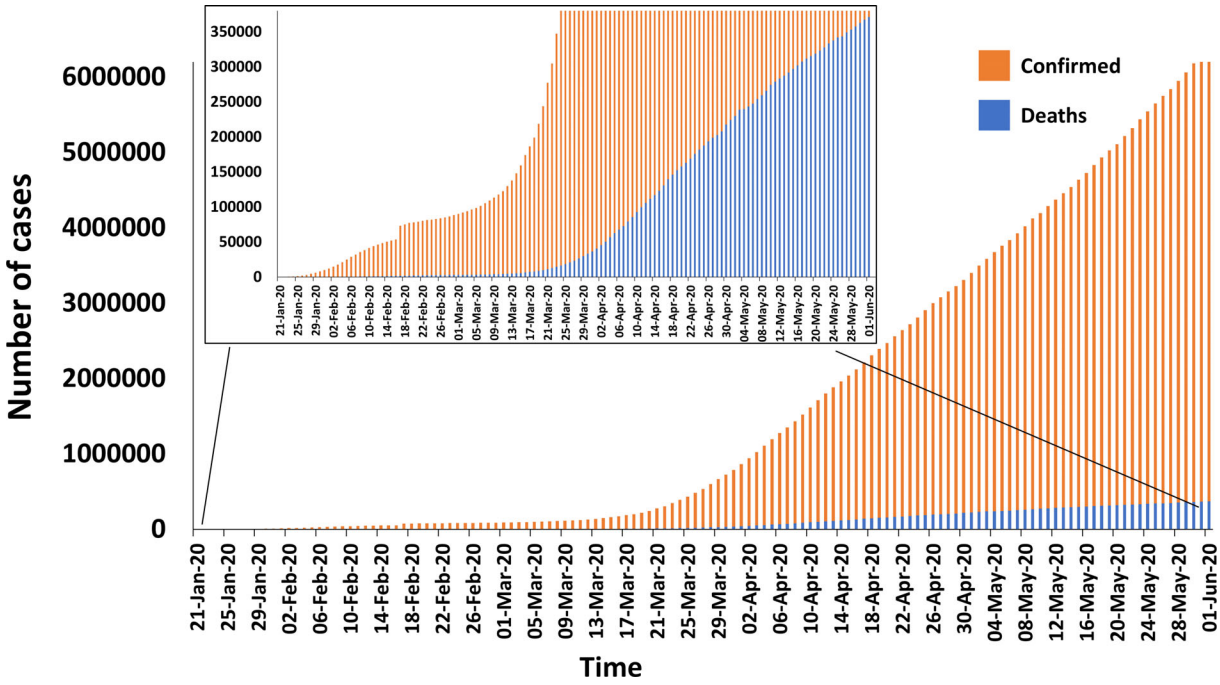

FIGURE 2 COVID-19 pandemic curve showing the total number of confirmed cases (orange bars) and the total number of deaths globally (blue bars). In-set highlights the increasing number of deaths (WHO, 2020d) [Colour figure can be viewed at wileyonlinelibrary.com]

either from direct contact, consumption of meat or through intermediate hosts (Guo et al., 2020).

1.2.1 | Symptoms

Patients with mild infection show fever, fatigue, dry cough, slight nasal congestion, and muscle pain. In severe cases, shortness of breath (dyspnea) associated with dry cough or sputum/ phlegm production (expectoration), along with signs of pneumonia are observed (Guan et al., 2020). In critical cases, patients show ARDS associated with complete respiratory failure, sepsis, septic shock, and multiple organ dysfunction including heart, liver, and kidney. These patients need ventilators in the intensive care unit (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020). Elderly patients with chronic comorbidities like diabetes, hypertension, cardiovascular, and cerebrovascular diseases are at greater risk of contracting COVID-19 (Lai et al., 2020). Laboratory studies show low blood levels of lymphocytes and white blood cells, and high levels of C-reactive protein and lactate dehydrogenase in COVID-19-infected patients (Tian et al., 2020; Wang, Hu, et al., 2020, p. 13).

Post-mortem lung sections from COVID-19-infected patients revealed DAD with thickening of alveolar walls, edema, fibrin, and proteinaceous exudates in alveolar spaces, vascular congestion, and pneumocyte hyperplasia with viral inclusions and multinucleate giant cells (Tian et al., 2020; Zhang et al., 2020). The chest computed tomography (CT) of COVID-19 patients shows bilateral multifocal ground-glass opacity indicative of alveolar exudate and transudate, as well as pleural thickening (Guan et al., 2020; Wang, Hu, et al., 2020).

1.2.2 | Transmission

The transmission of COVID-19 virus occurs with close, prolonged, and unprotected contact with symptomatic or patients who test positive for the virus (person-to-person), (Ghinai et al., 2020), as well as via respiratory droplets (Cascella et al., 2020). Figure 1 shows the schematic representation of SARS-CoV-2 viral entry through the respiratory tract of a healthy individual leading to acute lung infection. It is thought that short distance aerosol transmission could also be a possible mode of transmission, although the evidence in support of this is not strong. Furthermore, the transmission of the infection from asymptomatic individuals has been reported leading to the fear of community transmission (Mizumoto, Kagaya, Zarebski, & Chowell, 2020; Rothe et al., 2020).

1.2.3 | Chronological progression and severity

A retrospective study conducted in China examined a total of 225 patients including 116 individuals who recovered from COVID-19 infection and 109 patients who succumbed to the infection. In this study, individuals who recovered had a median age of 40 years, whereas those who died were older with a median age of 69 years. Furthermore, the prevalence of comorbidities was significantly higher among the patients who failed to recover versus those who recovered. This included hypertension (36.7 vs. 15.5%), prior history of lung disease (20.2 vs. 2.6%), diabetes (15.6 vs. 7.8%), and heart disease (11.9 vs. 3.4%). Interestingly, the common symptoms associated with the infection like fever, muscle pain, fatigue, and cough were found to

the same extent in both the patient groups with the exceptions of shortness of breath (70.6 vs. 19%) and expectoration (32.1 vs. 12.1%). Furthermore, patients who died had a higher incidence of ARDS (89.9 vs. 8.6%), acute cardiac injury (59.6 vs. 0.9%), acute kidney injury (18.3 vs. 0%), septic shock (11.9 vs. 0%) compared with individuals who showed complete recovery (Deng et al., 2020). Another study described 80% of infected individuals to exhibit generic symptoms, with only about 15% showing dyspnea with rapid and shallow breathing, pneumonia, and disturbed pulmonary gas exchange. Included within this group of individuals showing progressive symptoms was a smaller subset (5%) who developed acute symptoms of lung infection, sepsis, and organ failure requiring ICU admission. Importantly, the course of progression of this viral infection is relatively slow spanning an incubation period of 5–20 days from the time of exposure to onset of symptoms. In individuals who progress to a more severe state, this usually happens by around day 10 after appearance of the initial symptoms (Thomas-Rüddel et al., 2020).

1.2.4 | Prevention

Preventive measures to control the spread of COVID-19 pandemic are crucial and should be followed strictly. Coronaviruses are inactivated by ethanol, chlorine-containing disinfectants, and lipid solvents. Washing hands regularly with soap and sanitizers containing 70% ethanol/isopropanol to prevent the spread of viral infection is the recommended standard (Kampf & Kramer, 2004). Environmental surfaces have to be cleaned regularly with detergent or bleach such as sodium hypochlorite (NaOCl) solution. Close contact with symptomatic individuals has to be avoided, while also avoiding touching eyes, nose, and mouth. Individuals with a prior history of respiratory distress should wear masks and cover their coughs or sneezes. Health care workers (HCWs) should follow appropriate safety measures during the diagnosis, hospitalization, and isolation of COVID-19 positive patients (WHO, 2020c). During sample collection, precautions should be taken to prevent direct contact or exposure to airborne droplets. It is very essential to quarantine symptomatic individuals prior to diagnostic testing with appropriate safety guidelines (Adhikari et al., 2020). HCWs caring for COVID-19 patients should self-monitor body temperature and respiratory symptoms. Strict hygiene protocols should be implemented in hospitals. Immunocompromised individuals should avoid public/private gatherings (Cascella et al., 2020).

1.2.5 | Social distancing, personal hygiene, quarantine, and isolation

Social distancing or physical space between two individuals should be maintained to prevent the spread of the COVID-19 pandemic. When symptomatic or asymptomatic COVID-19-infected person coughs or sneezes, the respiratory droplets (>5–10 μm size) (Atkinson et al., 2009) containing the SARS-CoV-2 virus are released into the air, which can infect a healthy individual within 1 m radius. The virus can enter into the subject through the mouth (oral), nose (mucosal), or eyes (conjunctiva). Given this, social distancing requires maintaining at least 2 m or 6 ft distance between individuals to avoid respiratory droplet transmission (Yu & Yang, 2020). It requires avoiding crowded places and public gatherings and implements staying at home and limiting the number of visitors. Respiratory hygiene should be followed by covering mouth and nose with a tissue or bent elbow while coughing and sneezing. In addition to the above, indirect transmission of the virus by contacting contaminated environmental surfaces has been described. Hence, touching eyes, nose or mouth should be avoided.

Quarantining refers to keeping an asymptomatic individual who has been exposed to COVID-19, in isolation (Sharma et al., 2020). Quarantine can be implemented at home (self-quarantine) or the individual can be secluded in a specially designed facility. Importantly, quarantined individuals should be monitored for sign of fever, cough, and any other respiratory symptoms for up to 14 days.

Isolation refers to segregating confirmed COVID-19 patients away from healthy individuals to avoid the spread of the infection. This can be implemented either at home or in a hospital/isolation facility (Wilder-Smith & Freedman, 2020; Tang et al., 2020). Infected patients are monitored and administered care to manage their symptoms.

1.2.6 | Treatment and management

To date, treatment is symptomatic and supportive, with oxygen therapy and mechanical ventilation for ARDS and hypoxemia; fluid bolus therapy, vasopressors, and antibiotics for septic shock, as well as treatment to mitigate co-infections (WHO, 2020a). There are no potentially effective drugs or vaccines available for the treatment of COVID-19 and this has resulted in an explosion in research aimed at developing specific drugs. In parallel, existing drugs are being repurposed to test their efficacy against the SARS-CoV-2 virus. For example, broad-spectrum antiviral drugs (Remdesivir, ribavirin, and IFN-α) (Dong, Hu, & Gao, 2020), antimalarial drugs (chloroquine and hydroxychloroquine) (Gautret et al., 2020), and combination of retroviral drugs (Ritonavir/lopinavir) (Wang et al., 2020) are being evaluated in COVID-19 patients. Early results suggest that patients treated with these repurposed drugs show no improvement in the mortality rate, while the viral RNA load seems to show a slight decrease. However, in most patients, increased adverse events have been observed (Cao et al., 2020), which in more pronounced in individuals with underlying comorbidities (Srinivasa, Tosounidou, & Gordon, 2017).

Given the lack of targeted drugs to treat COVID-19, different approaches to mitigate COVID-19-associated complications are being evaluated. In this context, this review highlights the potential beneficial effects of natural products that are actively used in alternative/traditional medicines to treat many of the acute pulmonary infections, routinely seen in COVID-19 patients. These natural products can also boost immunity which is key to resist COVID-19 infection.

2 | THERAPEUTIC PROPERTIES OF NATURAL PRODUCTS

Medicinal plants are the biggest age-old source of therapeutically beneficial phytochemicals used for maintaining good health, and to prevent and treat many diseases. These include plants and herbs that are both used in Ayurveda, a traditional and alternative medicinal therapy based on holistic body healing, which originated in the Indian subcontinent. A huge body of research is currently focused on understanding the therapeutic efficacy and mechanism of action of these phytochemical agents. The following sections describe dietary supplements and home-based remedies that have shown value as preventive agents for acute respiratory infections, pulmonary fibrosis, pneumonia, sepsis, and multiple organ failure; all of which are characteristic manifestations of severe COVID-19 infection. In addition, many of these agents boost the immune system and imbues protection against infective agents. Figure 3 summarizes the beneficial properties of natural products against viral or chemically induced fibrosis, oxidative stress, inflammatory response, and associated acute lung injury in the setting of COVID-19.

Mechanistically, the available knowledge base shows that oxidative stress and dysfunctional immune system, in addition to existing comorbidities, contribute to many of the complications associated with COVID-19 infection. For example, oxidative stress is an important factor resulting in pathogen-induced pulmonary fibrosis (Cheresh, Kim, Tulasiram, & Kamp, 2013). Along the same lines, an effective immune system is essential for surveying pathogens and neutralizing them in an efficient and timely manner to protect the individual from the infection. The medicinal plants described here contain diverse phytochemicals that have antiviral, antifibrotic, antioxidant, antiinflammatory, and immunomodulatory properties. These, when used in combination, could have a synergistic effect as prophylactic or supportive agents to minimize certain clinical symptoms observed in COVID-19-infected patients. In addition, certain species of bacteria, algae, and fungi also exert therapeutic effects against pulmonary fibrosis and acute lung injury. Table 1 summarizes the evidence in the literature supporting the therapeutic value of specific species of bacteria, algae, and fungi, as well as plants. The detailed summary of the therapeutic properties for each of the key natural products discussed in this review is provided in Table S1. Among these, we have identified ginger, turmeric, garlic, onion, cinnamon, lemon, neem, basil, and pepper as well as mushrooms as readily available home-based remedies that have shown efficacy against pulmonary symptoms associated with COVID-19 infections in various pre-clinical and clinical trials.

2.1 | Ginger

Ginger (*Zingiber officinale*) has therapeutic properties against pulmonary fibrosis, pneumonia, ARDS, sepsis, and acute kidney injury. In addition, ginger along with its phytochemicals has antiviral, antifibrotic, antioxidant, antiinflammatory, and hepatoprotective properties (Chang, Wang, Yeh, Shieh, & Chiang, 2013; Mao et al., 2019; Rahmani, shabrmi, & Aly, 2014).

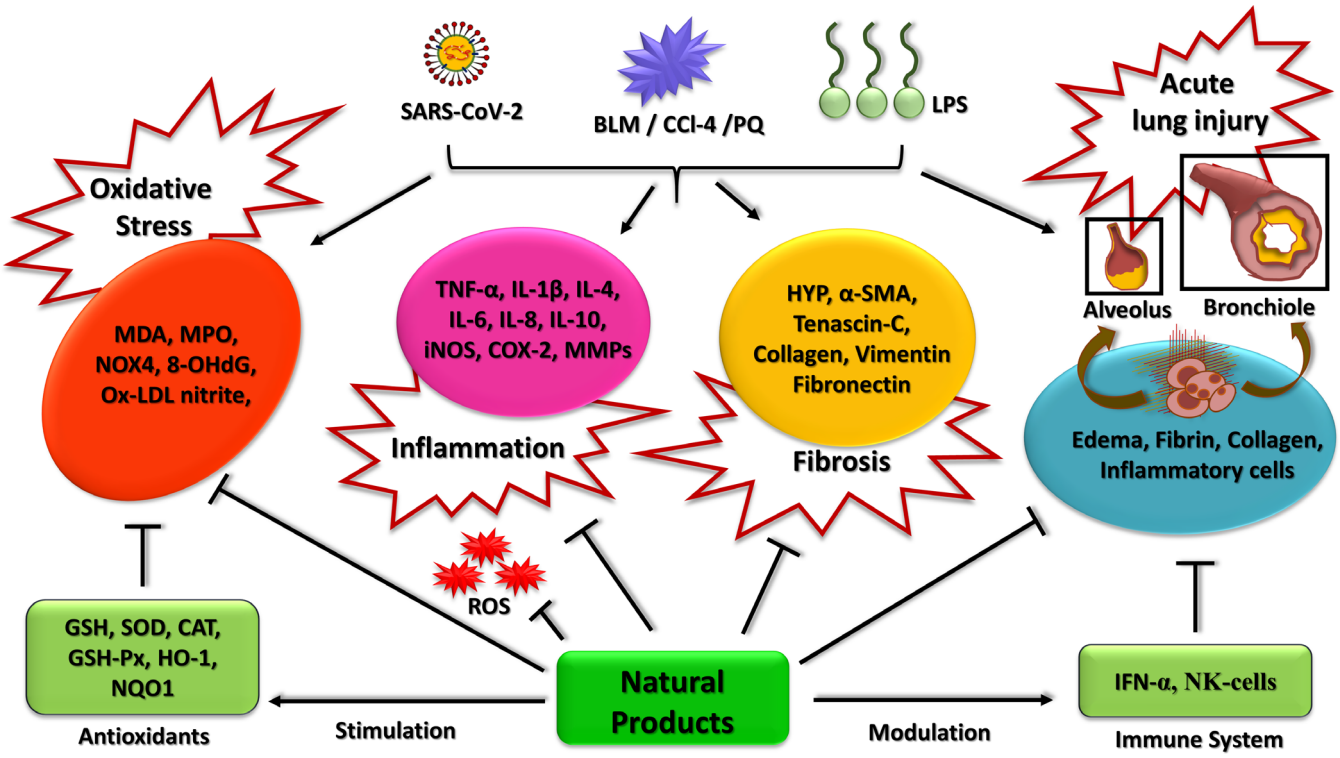

FIGURE 3 Schematic illustration summarizing the beneficial properties of natural products and their impact on oxidative stress, inflammatory response, pulmonary fibrosis, and acute lung injury [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Literature-based evidence supporting the therapeutic value of various species of bacteria, algae, fungi, and plants

Source	Species	Bioactive compound	References
Bacteria	Cyanobacteria (blue-green algae)	Phycocyanin	Leung, Lee, Kung, Tsai, & Chou, 2013; Li et al., 2017; Sun et al., 2011
Algae	*Laminaria japonica* (sweet kelp)	Fucoidan	Wang et al., 2019
Fungus	*Hirsutella Sinensis* (Caterpillar fungus) *Lentinula edodes* (shiitake) *Ganoderma Sinense* (purple Reishi)	Crude extracts, Lanostane-type triterpenoids	Chen et al., 2012; Di Pierro, Bertuccioli, & Cavecchia, 2020; Huang et al., 2015; Jung et al., 2019; Sato, Zhang, Ma, & Hattori, 2009; Shou et al., 2012; Sillapachaiyaporn, Nilkhet, Ung, & Chuchawankul, 2019
Plants	*Allium cepa* (onion)	Quercetin, Apigenin, selenium	Shahabi, Anissian, Javadmoosavi, & Nasirinezhad, 2019; Zhang, Cai, Zhang, & Chen, 2018
	Allium sativum (garlic)	s-allyl cysteine (SAC), Alliin (SAC sulfoxide) SMFM (sucrose methyl 3-formyl-4-methylpentanoate)	Nie et al., 2019; Tsukioka et al., 2017
	Andrographis panicula (green chiretta)	Andrographolide	Li et al., 2020; Zhu, Huang, Wang, Zhan, & Fan, 2011; Zhu, Zhang, Xiao, Chen, & Jin, 2013
	Arenaria kansuensis	β-carboline alkaloids	Cui et al., 2019
	Aucuba japonica (Japanese laurel) *Eucommia ulmoides* (Gutta-percha)	Aucubin	Qiu et al., 2018
	Azadirachta indica (neem)	Nimbolide, leaf extracts	Lee et al., 2017; Prashanth Goud, Bale, Pulivendala, & Godugu, 2019
	Carthamus tinctorius (safflower)	Hydroxysafflor yellow A	Jin, Wu, Wang, Zang, & Tan, 2016
	Centella asiatica (Indian pennywort)	Asiatic acid	Dong, Liu, Wei, Tan, & Han, 2017
	Cinnamomum verum or C. zeylanicum (cinnamon)	Cinnamaldehyde, Eugenol, linalool	Polansky & Lori, 2020; Zhuang et al., 2009
	Citrus limon (lemon)	Vitamin-C	Fisher et al., 2012; Rodrigues da Silva et al., 2018
	Corydalis bungeana	Corynoline	Liu et al., 2017
	Curcuma longa (turmeric)	Curcumin	Chen et al., 2017; Hosseini, Rasaie, Asl, Ahmadabadi, & Ranjbar, 2019
	Dioscorea nipponica	Trillin	Jiang et al., 2016
	Eclipta prostrata (Ecliptae Herba)	Eclipta herb extracts, Ecliptasaponin A	You et al., 2015
	Gastrodiaelata blume (Tien Ma)	Gastrodin	Zhang et al., 2017
	Humulus lupulus (hops)	Xanthohumol	Lv et al., 2017
	Mangifera indica (mango)	Mangiferin	Impellizzeri et al., 2015; Jia et al., 2019
	Nelumbo nucifera (lotus)	Neferine (bisbenzylisoquinline alkaloid)	Zhao et al., 2010
	Nigella sativa (fennel flower)	Seed extracts	Gholamnezhad, Shakeri, Saadat, Ghorani, & Boskabady, 2019; Poursalehi et al., 2018
	Ocimum sanctum (basil/tulsi)	Crude extracts	Mahajan, Rawal, Verma, Poddar, & Alok, 2013; Pattanayak, Behera, Das, & Panda, 2010
	Oryza sativa (Asian rice)	Isovitexin (from rice hulls)	Lv et al., 2016
	Paeonia lactiflora (common garden peony)	Paeoniflorin	Ji et al., 2016
	Piper nigrum (black pepper)	Piperine	Butt et al., 2013; Vijayakumar, Surya, & Nalini, 2004
	Pogostemon cablin (mint)	Pogostone, β-Patchoulene	Chen et al., 2017; Sun et al., 2016
	Rheum rhabarbarum (garden rhubarb)	Emodin	Guan et al., 2016; Tian, Yang, Liu, & Xu, 2018

(Continues)

TABLE 1 (Continued)

Source	Species	Bioactive compound	References
	Rhodiola rosea (Golden root)	Salidroside, crude extracts	Tang et al., 2016; Zhang et al., 2016
	Rosmarinus officinalis (rosemary)	Leaf extract	Bahri et al., 2017
	Salvia divinorum (magic mint)	Salvia + Ligustrazine	Huang, Li, Fan, Wang, & Zhan, 2013
	Salvia miltiorrhiza (red sage)	Tanshinone IIA	Tang et al., 2015
	Schisandra chinensis (Magnolia-vine) *Glycyrrhiza glabra* (Liquorice)	Schizandrin B + Glycyrrhizic acid	Zhang et al., 2017
	Sophora flavescens (Ku Shen)	Matrine + lycopene	Li et al., 2019
	Tanacetum parthenium (feverfew)	Parthenolide	Li et al., 2018
	Tripterygium wilfordii (thunder god vine)	Celastrol	Divya, Dineshbabu, Soumyakrishnan, Sureshkumar, & Sudhandiran, 2016, p. 2; Yang et al., 2020
	Zingiber officinale (ginger)	Zingerone and crude extracts	Mansouri et al., 2019; Rodrigues et al., 2018
Other bioactive compounds	*Foods rich in calcitriol*:Dairy products, orange juice, soy milk, and cereals	Calcitriol (vitamin D3)	Tan et al., 2016
	Foods rich in chicoric acid: *Cichorium intybus* (chicory) And also available in *Echinacea purpurea*, dandelion leaves, basil, and lemon balm	Chicoric acid	Ding, Ci, Cheng, Yu, & Li, 2019
	Foods rich in Epicatechin: Brewed green tea, Black tea, Black grapes, and blackberries	Epicatechin	Shariati, Kalantar, Pashmforoosh, Mansouri, & Khodayar, 2019
	Foods rich in resveratrol: Peanuts, pistachios, grapes, red and white wine, blueberries, and cranberries	Resveratrol	Sener, Topaloğlu, Sehirli, Ercan, & Gedik, 2007
	Foods rich in Sulforaphane:Broccoli sprouts, cauliflower, kale, and cabbage	Sulforaphane	Kyung et al., 2018
	Crude venom of *Naja naja atra*	Cobrotoxin	Cui et al., 2014

Ginger has significantly reduced pulmonary fibrosis and mitigated oxidative stress and inflammatory response in chemically induced pulmonary fibrosis in animal models. For example, bleomycin, a cytotoxic antibiotic used in cancer treatment, has idiopathic pulmonary fibrosis (IPF) as a side effect. In bleomycin-treated rats, zingerone, a bioactive compound in ginger has significantly reduced fibrosis score in histopathological sections of lungs, reduced levels of fibrosis marker, hydroxyproline and oxidative stress marker, and malondialdehyde (MDA). In addition, it increased levels of antioxidant markers like reduced glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) in the lungs (Mansouri et al., 2019). Similarly, in ethanol-treated rats that exhibit symptoms of diffuse alveolar damage and acute lung injury leading to ARDS, extracts of ginger mitigated abnormalities in alveolar air space, wall thickening, infiltration of multinucleated cells and pneumocytes, lung cell proliferation, and fibrosis in the ethanol-treated rats. In addition, ginger significantly reduced the oxidative stress markers namely 8-hydroxy-2′-deoxyguanosine (8-OHdG), oxidized low-density lipoprotein (Ox-LDL), and NADH oxidase levels. (Shirpoor, Gharalari, Rasmi, & Heshmati, 2017).

In a separate clinical study on 32 ARDS patients, 120 mg of ginger extract was shown to increase the tolerance of enteral feeding, significantly reduced nosocomial pneumonia and increased the ICU-free and ventilator-free days compared with the placebo group (Shariatpanahi, Taleban, Mokhtari, & Shahbazi, 2010). Ginger with its bioactive compounds has also ameliorated sepsis and acute kidney injury (AKI) induced by cecal ligation and puncture (CLP) in rats. Specifically, in this study, the authors demonstrated that 6-gingerol and 10-gingerol significantly reduced pathological levels of AKI markers, oliguria, blood urea nitrogen, urinary protein, serum creatinine levels, urinary sodium, and osmolarity in these rats. Both compounds have also reduced the levels of oxidative stress markers, MDA and nitrite, as well as increased the levels of antioxidants, GSH and SOD. In addition, they also reduced levels of inflammatory markers such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and kidney injury marker, KIM-1 (Rodrigues et al., 2018).

Pulmonary tuberculosis (TB) is another serious infectious lung disease leading to pulmonary fibrosis and acute lung injury (Ravimohan, Kornfeld, Weissman, & Bisson, 2018). In patients undergoing treatment for TB, ginger has significantly reduced levels of MDA and inflammatory markers such as TNF-α and ferritin (Kulkarni & Deshpande, 2016). Overall, these clinical studies suggest that use of ginger extract could have beneficial effects in individuals having pulmonary problems such as ARDS, pulmonary fibrosis, and pneumonia, as well as those having inflammatory conditions such as sepsis, all of which are symptoms seen in patients infected with COVID-19.

2.2 | Turmeric

Turmeric (*Curcuma longa*) has potential therapeutic effects on pulmonary fibrosis, severe respiratory disorders, lung infections, liver abnormalities. Curcumin, the bioactive compound in turmeric has been shown to have antifibrotic, antioxidant, antiinflammatory, and immunomodulatory activities (Jurenka, 2009; Menon & Sudheer, 2007; Srivastava, Singh, Dubey, Misra, & Khar, 2011).

Curcumin has significantly enhanced pulmonary function and ameliorated pulmonary fibrosis, oxidative stress, and inflammation in pulmonary fibrosis-animal models induced by virus, radiation, and toxic chemicals. Mice infected with Reovirus 1/L induce DAD with intra-alveolar and interstitial exudate and fibrosis, as well as pneumonia resulting in acute lung injury and ARDS. In these mice, curcumin has significantly reduced infiltration of inflammatory cells into interstitial and intra-alveolar space and decreased interstitial fibrosis in the lungs which are associated with the late phase of viral infection. Consistent with this, curcumin also reduced the fibrosis markers such as α-smooth muscle actin (α-SMA), tenascin-C and E-cadherin, as well as inflammatory markers like IL-6, IL-10, and IFN-γ (Avasarala et al., 2013).

In bleomycin-induced pulmonary fibrosis rats, curcumin increased the expression of cathepsins (CatK, CatL) which degrade collagen, and inhibited lung fibroblast proliferation by blocking transforming growth factor (TGF)-β1 (Smith et al., 2010; Zhang et al., 2011). In these rats, curcumin also suppressed the inflammatory cytokine TNF-α released by alveolar macrophages ameliorating pulmonary fibrosis (Punithavathi, Venkatesan, & Babu, 2000).

Paraquat is a toxic herbicide that leads to pulmonary fibrosis, edema, acute lung injury, and respiratory failure. In the paraquat-induced pulmonary fibrosis rat model, curcumin reduced the deposition of collagen fiber and inhibited fibrosis. In parallel, it also improved the tidal volume (volume of air taken during normal breath) and arterial partial pressure of oxygen (PaO_2) in the lungs (Chen, Yang, et al., 2017). In these rats, at the molecular level, curcumin decreased the levels of fibrosis marker hydroxyproline, as well as oxidative stress markers, and inhibited lung fibrosis (Hosseini et al., 2019). In another study, curcumin reduced levels of hydroxyproline and reactive oxygen species (ROS), and increased the levels of antioxidant marker heme oxygenase-1(HO-1), in mice irradiated with γ radiation showing symptoms of pneumonitis and acute pulmonary fibrosis (Lee et al., 2010).

In addition, it is well documented that impaired immune system with imbalances in inflammatory cells and cytokines can aggravate lung fibrosis (Hügle, 2011). In this context, it is important to note that curcumin is a potent immunomodulator and can regulate the function of dendritic cells, natural killer (NK) cells, neutrophils, macrophages, T cells, and B cells, as well as inflammatory cytokines (Gautam, Gao, & Dulchavsky, 2007). All the above pre-clinical findings strongly implicate turmeric as an agent that can improve lung function, and protect against acute lung injury and associated DAD, pulmonary fibrosis, and ARDS, all of which are observed in COVID-19 patients.

2.3 | Garlic

Garlic (*Allium sativum*) has potential therapeutic effects against respiratory tract infections, intra-alveolar edema and cell infiltration, pulmonary fibrosis, sepsis, and acute lung injury. Garlic along with its bioactive compounds, S-allyl cysteine (SAC), alliin, and diallyl thiosulfonate (allicin), has been shown to have antiviral, antifibrotic, antioxidant, antiinflammatory, and immunomodulatory properties (Arreola et al., 2015; Bayan, Koulivand, & Gorji, 2014; Shang et al., 2019).

Garlic has significantly inhibited pulmonary fibrosis and acute lung injury, and subsequently mitigated oxidative stress and inflammatory response in chemically induced pulmonary fibrosis, sepsis, and acute lung injury rat models. For example, in multiple studies using either bleomycin- or carbon tetrachloride (CCl_4)-induced pulmonary fibrosis rat model, SAC significantly reduced the fibrotic lesions, alveolar wall thickening, and collagen deposition. In doing so, it reduced the expression of various collagens, fibronectin, as well as levels of various fibrotic markers including hydroxyproline, α-SMA, and TGF-β, possibly by inhibiting phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT) and nuclear factor-κB (AKT/NF-κB) signaling pathways (Nie et al., 2019). SAC also reduced inflammatory cells in the alveolar spaces and attenuated lung injury by reducing the expression of inflammatory genes namely iNOS, TNF-α, and matrix metalloproteinase-9 (MMP-9), and reducing levels of oxidative stress markers like inducible NO synthase (iNOS) in lungs, total nitrites and nitrates (NOx), ROS, and lung lipid peroxides (Mizuguchi et al., 2006; Tsukioka et al., 2017).

Along the same lines, allilin (SAC sulfoxide) was shown to inhibit alveolar edema and damage, reduce neutrophils infiltration into alveoli and decrease inflammatory cytokines like TNF-α and IL-1β. In this process, allilin also inhibited the inflammatory response by inhibiting NF-κB and peroxisome proliferator-activated receptor γ (PPARγ) in lipopolysaccharides induced acute lung injury rat model (Wang, Guo, He, Chen, & Zhuang, 2017). Similarly, in CLP-induced sepsis and acute lung inflammation models in rats, SMFM (sucrose methyl 3-formyl-4-methylpentanoate) a natural compound isolated from garlic significantly inhibited alveolar damage, thrombotic lesions, and lung infection. In addition, SMFM also inhibited bacterial infection and proinflammatory cytokines TNF-α, IL-6, and IL-1β in the peritoneal fluid which are known to cause vital organ damage (Lee et al., 2015).

Garlic is also a potent immunomodulator (Ishikawa et al., 2006). In a clinical study on humans, dietary consumption of 2 g of garlic every

2–3 days, boosted the basal plasma IFN-α levels which are known to be protective against viral infections and prevent viral replication (Bhattacharyya, Girish, Karmohapatra, Samad, & Sinha, 2007). Importantly, these pre-clinical studies highlight the efficacy of garlic in mitigating pulmonary fibrosis, lung injury, and sepsis-associated organ failure, all of which are symptoms observed in patients with advanced COVID-19 infection.

2.4 | Onion

Onion (*Allium cepa*) has potential therapeutic benefits against acute respiratory tract infection and lung injury caused by collagen deposition, inflammatory cell infiltration, and pulmonary fibrosis. Onion along with its bioactive compounds, quercetin, apigenin, and selenium is known to exert antiviral, antifibrotic antioxidant, antiinflammatory, antiasthmatic and hepatoprotective properties (Kumar & Pandey, 2013; Marefati et al., 2018; Suleria, Butt, Anjum, Saeed, & Khalid, 2015).

Onion has been shown to significantly alleviate pulmonary fibrosis following attenuation of oxidative stress and inflammatory response in chemically induced pulmonary fibrosis rat models. For instance, in several bleomycin-induced pulmonary fibrosis rat models, quercetin, apigenin, and selenium have significantly reduced lung fibrosis by reducing collagen deposition, decreasing inflammatory cell infiltration, reducing alveolar wall thickness, and increasing alveolar air space. Similarly, quercetin has been shown to reduce the levels of fibrosis markers such as hydroxyproline, fibronectin, α-SMA, and several collagens in lung tissues of these mice. Quercetin has also ameliorated lung damage by enhancing levels of antioxidants (SOD and catalase), reducing the expression of oxidative stress markers (MDA), and decreasing inflammatory markers (TNF-α and MMP-7). At the molecular level, quercetin acts by inhibiting sphingosine kinase 1/sphingosine-1-phosphate (SphK1/S1P) signaling (Zhang et al., 2018).

Likewise, apigenin reduced expression levels of fibrotic marker hydroxyproline and leukocyte adhesion marker myeloperoxidase (MPO), besides enhancing antioxidant SOD activity. Apigenin and selenium independently ameliorated lung injury by reducing levels of inflammatory markers, TNF-α, and TGF-β1 (Chen & Zhao, 2016; Shahabi et al., 2019).

Along similar lines, in a rhinovirus-induced chronic obstructive pulmonary disorder (COPD) mice model, quercetin ameliorated lung injury by reducing infiltration of neutrophils, macrophages, and T cells into alveoli, and lowering the expression of inflammatory cytokines, TNF-α, IFN-γ, and IL-17A (Farazuddin et al., 2018).

In a separate clinical study, lower selenium levels were observed in patients with respiratory disorders admitted to the ICUs that correlated with decreased lymphocytes and increased C-reactive protein levels (Lee et al., 2016). In other studies, conducted on hospitalized patients with pneumonia and bronchiolitis, 1 mg of sodium selenite was found to reduce signs of respiratory infection and improve the recovery time. At the molecular levels, it increased the levels of antioxidant glutathione peroxidase as well as the leukocyte count (Hu, Liu, Yin, & Xu, 1998; Liu, Yin, & Li, 1997). Together, these pre-clinical and clinical studies highlight the potency of onion in ameliorating pulmonary fibrosis, acute respiratory tract infections, and lung injury which are the critical symptoms of COVID-19 patients.

2.5 | Cinnamon

Cinnamon (*Cinnamomum verum or C. zeylanicum*) along with its major bioactive compounds, cinnamaldehyde, eugenol, and linalool, has potent antiviral, antioxidant, antiinflammatory, and hepatoprotective properties (Jayaprakasha & Rao, 2011; Kawatra & Rajagopalan, 2015; Rao & Gan, 2014). Of the two varieties of cinnamon, on one hand, there is cassia that contains significant amounts of another bioactive compound coumarin, and on the other, there is ceylon (also known as true cinnamon) that has lesser amounts of coumarin. Coumarin if taken in larger quantities could be harmful. Care should be taken not to ingest cinnamon powder in large quantities as this could have potentially harmful effects (Grant-Alfieri, Schaechter, & Lipshultz, 2013). In light of this, Ceylon is more widely used.

Cinnamoni cortex (CC) extract has shown *in vitro* dose-dependent inhibition of wild-type SARS-CoV and a luciferase encoded HIV-containing SARS-CoV spike protein (HIV/SARS-CoV S pseudovirus). The antiviral activity against SARS-CoV could probably be due to the inhibition of viral replication and interference with viral endocytic pathways (Zhuang et al., 2009). Cinnamon extracts along with quercetin and selenium is also part of Gene-Eden-VIR/Novirin, a broad-spectrum antiviral herbal treatment. Clinical trials have shown its efficacy against several viruses including herpes simplex virus (HSV), Epstein–Barr virus (EBV) and human cytomegalovirus (hCMV) (Polansky & Lori, 2020).

Proteolytic activation of SARS-CoV-2 spike protein by the host cell proteases is essential for infection. Studies have shown the role of trypsin and cathepsin L in cleavage and activation of spike protein and its binding to ACE2, during the SARS-CoV infection (Belouzard, Chu, & Whittaker, 2009; Simmons et al., 2011). In this context, cinnamon as a trypsin inhibitor (Gopalakrishnan, Ediga, Reddy, Reddy, & Ismail, 2018; Shahwar, Raza, Shafiq-Ur-Rehman, Abbasi, & Atta-Ur-Rahman, 2012) could have a therapeutic role against the SARC-CoV-2 infection in COVID-19.

In CCL_4 and LPS-stimulated rat and mice, cinnamon extracts reduced MDA and increased levels of antioxidant markers catalase and SOD. It also reduced antiinflammatory markers TNF- α/IL-6, reduced phosphorylation of MAPKs (JNK, p38 and ERK1/2), and interfered with NF-κB activation by inhibiting the degradation of IκBα. It has also reduced necrosis and infiltration of lymphocytes in the liver of rats with hepatic injury (Hong et al., 2012; Moselhy & Ali, 2009). Overall, these studies implicate promising therapeutic roles of cinnamon against the SARS-CoV-2 infection in COVID-19.

2.6 | Lemon

Lemon (*Citrus limon*) has potential therapeutic benefits against pulmonary fibrosis, pneumonia, ARDS, sepsis, acute lung, kidney, and liver

injury. Lemons contain vitamin-C (Vit-C) or ascorbic acid (AA), which is an antifibrotic, antioxidant, antidiabetic, as well as an immunomodula tor. It is also documented to be protective against respiratory infections (Ashbel' & Arziaeva, 1965; Chambial, Dwivedi, Shukla, John, & Sharma, 2013; Hong, Lee, Lee, & Kim, 2018). Consistent with this, individuals with lower ascorbic acid levels are prone to severe infections and other acute diseases (Bakaev & Duntau, 2004).

In a case study involving a patient with dyspnoea, hypoxemia, and ARDS, placed on ventilator support, vitamin-C (50 mg/kg body weight every 6 hr) administered intravenously improved bilateral lung opacities as seen by chest X-ray, attenuated sepsis-associated ARDS, and was extubated (Bharara et al., 2016).

In an independent clinical study containing 595 critically ill surgical patients from ICUs, patients receiving antioxidant therapy (AA and α-tocopherol) had a relatively lower risk of pulmonary morbidity (a measure of ARDS and pneumonia), multiple organ failure and mortality compared with the standard of care patients. Importantly, patients on antioxidant therapy required mechanical ventilation and ICU admission for a shorter period of time (Nathens et al., 2002). In a separate clinical study, 57 elderly patients hospitalized for bronchitis and pneumonia were administered oral vitamin-C (200 mg/day) and compared with the placebo arm. Vitamin-C levels in the treated group were higher in the plasma and leukocytes, and these patients were showed pulmonary complications (Hunt, Chakravorty, Annan, Habibzadeh, & Schorah, 1994).

In a pre-clinical study comparing the effect of sepsis in mice lacking the capacity to synthesize vitamin-C (L-gulono-γ-lactone oxidase deficient, −Gulo) versus wild-type controls (+Gulo), lack of vitamin-C resulted in multiple organ failure, pulmonary edema, and proinflammatory response, all of which were attenuated by intraperitoneal infusion of vitamin-C (Fisher et al., 2014). Similar results were obtained in independent studies using sepsis and acute lung injury models treated with or without vitamin-C (200 mg/kg) (Fisher et al., 2011, 2012). Along the same lines, in paraquat-induced pulmonary fibrosis mice model, vitamin-C has blocked infiltration of lymphocytes, neutrophils, macrophages, and attenuates pulmonary fibrosis. It also significantly decreased collagen deposition and reduced levels of pro-inflammatory markers, TGF-β, IL-6, IL-17, and enhanced antioxidant markers namely catalase and SOD (Rodrigues da Silva et al., 2018).

Vitamin-C also has significant immunomodulatory properties. It gets accumulated in neutrophils and enhances phagocytosis, NK cell activity, and lymphocyte proliferation (Carr & Maggini, 2017; Wintergerst, Maggini, & Hornig, 2006). Taken together, preclinical and clinical studies suggest that vitamin-C could have promising therapeutic benefits in individuals with pulmonary fibrosis, pneumonia, ARDS, sepsis, acute lung injury, and multiple organ dysfunction all of which are observed in advanced COVID-19 patients.

2.7 | Neem

Neem (*Azadirachta indica*) has potential therapeutic benefits against pulmonary fibrosis pulmonary inflammation, acute lung injury, and alveolar damage. The bioactive compounds in neem are azadirachtin, nimbolinin, nimbolide, quercetin, and β-sitosterol. These are known to exhibit antiviral, antioxidant, and antiinflammatory (Alzohairy, 2016; Subapriya & Nagini, 2005; Tiwari, Darmani, Yue, & Shukla, 2010) properties.

In a bleomycin-induced pulmonary fibrosis mice model, nimbolide has been shown to significantly reduce pulmonary fibrosis by decreasing infiltration of white blood cells (monocytes, lymphocytes, and neutrophils) into the bronchoalveolar lavage (BAL) fluid. At the molecular level, nimbolide was shown to reduce the expression of fibrosis and oxidative stress markers, while increasing the expression of the autophagy mediator Beclin-1. Additional studies have implicated the inhibition of TGF-β/Smad pathway as a possible mechanism for its antifibrotic properties (Prashanth Goud et al., 2019).

In an independent study using cigarette smoke (CS)-lipopolysaccharide (LPS)-induced pulmonary inflammation mice model, administration of neem leaf extract (NLE) significantly reduced infiltration of macrophages and neutrophils into BAL fluid and prevented acute lung injury (Lee et al., 2017).

2.8 | Basil

Basil a.k.a. Tulsi (*Ocimum sanctum*) along with its bioactive compounds, quercetin, eugenol, and apigenin has been shown to exhibit antiviral, antioxidant, antiinflammatory, antiasthmatic, and immunomodulatory properties (Mahajan et al., 2013; Mediratta, Sharma, & Singh, 2002; Pattanayak et al., 2010; Saini, Sharma, & Chhibber, 2009). In healthy humans, 4 weeks oral administration of ethanol extracts of Tulsi significantly increased the levels of IFN-γ, IL-4, T-helper cells, and NK-cells (Mondal et al., 2011).

2.9 | Black pepper

Black pepper (*Piper nigrum*), known as “king of spices”, has antiviral, antioxidant, and antiinflammatory properties (Butt et al., 2013; Vijayakumar et al., 2004). The bioactive compound piperine is known to enhance the bioavailability of many drugs and phytochemicals by increasing their absorption from the gastrointestinal tract (Pattanaik, Hota, Prabhakar, & Pandhi, 2009). For example, 20 mg black pepper when taken along with 2 g turmeric was shown to increase the bioavailability of the latter by 2000-fold (Shoba et al., 1998). In light of this, one would envision that the bioavailability of the supplements discussed above could be enhanced by combining them with black pepper.

2.10 | Medicinal mushrooms

Medicinal mushrooms are an untapped resource which show potential antiviral, antiinflammatory, and immunomodulatory properties against various viruses like HSV, EBV hepatitis C virus, (HCV), human

immunodeficiency virus (HIV), H1N1 strain of flu, and influenza (Ellan et al., 2019; Linnakoski et al., 2018; Muszyńska, Grzywacz-Kisielewska, Kała, & Gdula-Argasińska, 2018). The secondary metabolites from these mushrooms such as alkaloids, non-ribosomal peptides, polyketides, and terpenoids have shown protease inhibitory activities against HIV-1 and hepatitis C virus (El-Fakharany, Haroun, Ng, & Redwan, 2010; Sato et al., 2009; Sillapachaiyaporn et al., 2019). Some of the medicinal mushrooms like Ganoderma species [(*G. lucidum*, (Reishi) *G. colosum*,(Lingzhi) *G. sinense* (Purple Reishi)], *Auricularia polytricha* (wood ear/jelly ear), *Chrysosporium merdarium*, *Cordyceps militaris* (caterpillar fungus), *Lignosus rhinoceros* (tiger milk mushroom), *Agaricus bisporus* (button mushrooms) (Lu et al., 2020; Ying et al., 2016) might also have protease inhibitory activities against the SARS-CoV-2 papain-like protease (Suwannarach et al., 2020). These mushroom extracts have bioactive polysaccharides (β-glucans) and galactomannan that are known to have immunomodulatory properties and stimulate the production of antiviral cytokines such as TNF-α, NK-cells, and macrophages (Jung et al., 2019). Mushroom extracts from *Lentinula edodes* (Shiitake) mycelia (AHCC) are extensively studied for their immunostimulant effects against various viruses and could have therapeutic effects against COVID-19 (Di Pierro et al., 2020).

2.11 | Papaya leaf

Papaya (*Carica papaya*) along with its bioactive compounds show antiviral, antioxidant, and antiinflammatory properties (Joseph, Sankarganesh, Ichiyama, & Yamamoto, 2015; Panzarini, Dwikat, Mariano, Vergallo, & Dini, 2014). Thrombocytopenia or low blood platelet count could be another risk factor correlating with both, severity and higher mortality in COVID-19 patients (Lippi, Plebani, & Henry, 2020). Similarly, low platelet count is also associated with IPF, multiple organ failure and acute kidney injury (Nguyen, Cruz, & Carcillo, 2015; Steiropoulos et al., 2014). Thrombocytopenia is a common clinical manifestation in dengue patients and studies suggest that activation of platelets leads to prothrombotic state in these patients (Jayashree, Manasa, Pallavi, & Manjunath, 2011; Ojha et al., 2017). Papaya leaf extract enhances thrombopoiesis and has significantly increased the platelet count in dengue patients and in mouse model (Dharmarathna, Wickramasinghe, Waduge, Rajapakse, & Kularatne, 2013; Subenthiran et al., 2013). Papaya leaf extracts might increase platelet count in COVID-19 patients and may show possible beneficial effects. An invitro study suggests that papaya leaf extracts might stabilize erythrocyte membrane thereby preventing hemolysis (Ranasinghe et al., 2012).

2.12 | Hot water

Inactivation of the virus is a critical step for containing the spread of COVID-19 pandemic. Studies show that heat can render the virus inactive and non-infectious. Consistent with this, SARS coronavirus was shown to survive at 4°C as well as at body temperature (37°C) but was inactivated at temperatures greater than 50°C (Rabenau et al., 2005). Similarly, UV radiation for 60-min was also shown to inactivate the virus (Duan et al., 2003). In turn, these findings highlight the importance of boiling water before drinking. In addition, inhaling steam generated from water containing turmeric and tulsi is effective against respiratory tract infections (Saleem, Rani, & Daniel, 2019; Shuman, Raju, & Jogdeo, 2018; Singh, Singhi, & Walia, 1990). Furthermore, fumigating living rooms with medicated smoke from burnt neem leaves has also been shown to be effective in combating the virus (Khedekar, Goel, & Ojha, 2016). Taken together, the prophylactic measures to protect against coronaviruses could include avoiding cold beverages, boiling/or UV-based sterilization of drinking water.

2.13 | Mechanism of SARS-CoV-2 infection and natural products bioactivity

The spike protein (S-protein) of SARS-CoV-2 virus recognizes and binds to the angiotensin-converting enzyme 2 (ACE2, Figure 1) on bronchial and alveolar epithelial cells and vascular endothelial cells (Zhang, Penninger, Li, Zhong, & Slutsky, 2020). The viral membrane fuses with the host membrane, and the viral RNA along with nucleocapsid proteins is released and replicated further in the host cells. The viral infection triggers apoptosis of epithelial and endothelial cells leading to secretion of inflammatory cytokines, IL-1β, IL-4, IL-10, TNF-α, and IFN-γ, that destroy the host cells (Fu, Cheng, & Wu, 2020). SARS CoV papain-like protease (PLpro) upregulates the expression of TGF-β1, a profibrotic cytokine (Li et al., 2012). The activation of TGF-β1 by proteolytic cleavage of its latent complex form is carried out by MMP-9 and MMP-2 (Kobayashi et al., 2014; Wang et al., 2006). Interestingly, as shown in Figure 4, the bioactive compounds inhibit TGF-β1 activation by suppressing these MMPs (Kim et al., 2013; Kumar, Kumar, Saravanan, & Singh, 2012).

TGF-β1 induces proliferation of fibroblasts and their differentiation into myofibroblasts that secrete extracellular matrix (ECM) leading to fibrosis (Liu et al., 2016; Michalik et al., 2018). In the canonical pathway, TGF-β1 phosphorylates the downstream effector proteins Smad2 and Smad3 that further activate the expression of pro-fibrotic proteins namely fibronectin, collagen type I/III, α-SMA, and vimentin (Malmström et al., 2004). The bioactive compounds inhibit the phosphorylated Smad2 and Smad3, and enhance the expression of Smad7 (a TGF-beta antagonist), leading to downstream suppression of fibroblast proliferation and their differentiation into myofibroblasts, as well as inhibition of pro-fibrotic gene expression (Nie et al., 2019; Smith et al., 2010).

In the non-canonical pathway, TGF-β1 activates p38 mitogen-activated protein kinase (MAPK) that induces epithelial to mesenchymal transition (EMT) (Wang et al., 2017; Zhang, 2009). In addition, TGF-β1 induces NOX4 expression and suppresses antioxidants, resulting in ROS generation and oxidative stress (Liu & Desai, 2015; Liu & Gaston Pravia, 2010). Bioactive compounds inhibit p38 MAPK, thereby ameliorating EMT (Avila-Carrasco et al., 2019; Cai et al., 2018). They also inhibit PI3K leading to downstream suppression of ROS and oxidative

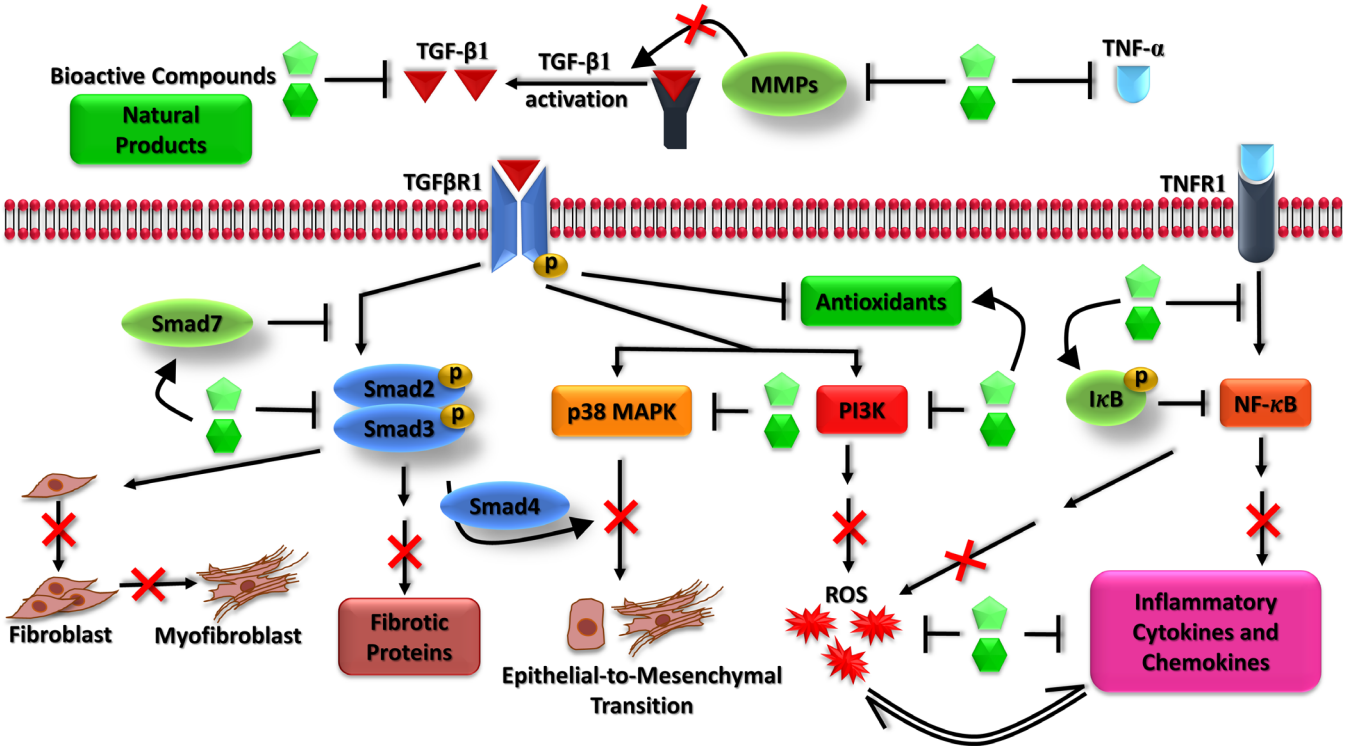

FIGURE 4 Inhibitory mechanism of bioactive compounds in TGF-β1 and NF-κB signaling pathways in pulmonary fibrosis. NF-κB, nuclear factor-κB; TGF, transforming growth factor [Colour figure can be viewed at wileyonlinelibrary.com]

stress (Huang, 2013; Park, Kim, & Lee, 2009). The non-structural proteins (nsp1, nsp3a, and nsp7a) and spike proteins of SARS-CoV activates NF-κB, resulting in the inflammatory response and ROS, which further drives the pathogenesis (Liao et al., 2005). S protein also degrades IκB-α, resulting in activation of NF-κB, that further upregulates TNF-α and IL-6 (DeDiego et al., 2014; Wang et al., 2007). Bioactive compounds inhibit expression of TNF-α and enhance IκB-α expression, together leading to suppression of NF-κB-mediated expression of inflammatory cytokines and chemokines. These compounds also have direct inhibitory effect on ROS and inflammatory cytokines and enhance the expression of antioxidants. It has also been shown that the SARS-CoV virus downregulates the ACE2 expression, and this could further trigger acute lung injury (Glowacka et al., 2010; Kuba et al., 2005).

3 | DISCUSSION

COVID-19 causes acute respiratory tract infections, pulmonary fibrosis, sepsis, and multiple organ failure, all of which could result in mortality. Study on the severity and progression of COVID-19 suggests that, among the patients who died, 70% had shortness of breath and 32% had expectoration. This implies that underlying pathogenesis like the initiation of fibrosis and alveolar damage might begin early during the 14–20 days of incubation period after exposure to the virus. Natural products taken during these initial stages of viral infection could prevent further progression of the infection and stabilize the initial symptoms. Furthermore, among the patients who died, around 89% had ARDS, suggesting that the major cause of mortality was the acute lung infection, pulmonary fibrosis and pneumonia. Natural products that are effective against these pulmonary conditions could be beneficial supplements to promote the recovery of patients showing these advanced COVID-19-related symptoms.

Considering the widespread global outbreak of COVID-19, controlled clinical trials might not be feasible. In some clinical settings, antimalarial, retroviral drugs, and corticosteroids are being repurposed and are showing adverse side effects. In this context, given the therapeutic efficacy of many of the natural products, these could be administered in combination with the clinical standard of care to mitigate treatment-related side effects. Importantly, unlike chemotherapeutic supplements, natural products have no adverse effects.

In summary, natural products have shown therapeutic efficacy against multiple symptoms observed in advanced COVID-19 patients. They are highly tolerated with no side effects and can be used in combination with existing clinical standard of care. In this setting, natural products have the potential to serve as prophylactic agents in populations that are at risk to develop COVID-19 infection. These include elderly individuals as well as those who have underlying comorbid conditions. In addition, in symptomatic patients, natural product supplementation can halt the progression of the infection. In the case of patients who have progressed to an advanced stage, natural products can mitigate many of the complications and reduce mortality. Importantly, natural product supplementation constitutes home-based remedies that are inexpensive and can be easily implemented on a community-wide scale.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Sai Manohar Thota conceptualized, designed, searched databases/articles, and wrote the manuscript. Venkatesh Balan and Venketesh Sivaramakrishnan contributed to manuscript writing and provided scientific guidance.

DEDICATION

Dedicated to India and her Traditional Medicine System—Ayurveda.

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SUPPORTING INFORMATION

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