Small Molecule Drug Candidates for Managing the Clinical Symptoms of COVID-19: a Narrative Review

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Abstract
Towards the end of 2019, an atypical acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China and subsequently named Coronavirus disease 2019 (COVID-19). The rapid dissemination of COVID-19 has provoked a global crisis in public health. COVID-19 has been reported to cause sepsis, severe infections in the respiratory tract, multiple organ failure, and pulmonary fibrosis, all of which might induce mortality. Although several vaccines for COVID-19 are currently being administered worldwide, the COVID-19 pandemic is not yet effectively under control. Therefore, novel therapeutic agents to eradicate the cause of the disease and/or manage the clinical symptoms of COVID-19 should be developed to effectively regulate the current pandemic. In this review, we discuss the possibility of managing the clinical symptoms of COVID-19 using natural products derived from medicinal plants used for controlling pulmonary inflammatory diseases in folk medicine. Diverse natural products have been reported to exert potential antiviral effects in vitro by affecting viral replication, entry into host cells, assembly in host cells, and release. However, the in vivo antiviral effects and clinical antiviral efficacies of these natural products against SARS-CoV-2 have not been successfully proven to date. Thus, these properties need to be elucidated through further investigations, including randomized clinical trials, in order to develop optimal and ideal therapeutic candidates for COVID-19.

Key Words: Natural products, Coronavirus, SARS-CoV-2, COVID-19

INTRODUCTION
As we perceive, towards the end of 2019, Coronavirus disease 2019 (COVID-19) was discovered in Wuhan, China. The cause of the disease was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid dissemination of COVID-19 has provoked a global crisis in public health, with the World Health Organization (WHO) having declared COVID-19 a global pandemic by March 2020 (Zhu et al., 2020).

The clinical staging of COVID-19 includes asymptomatic, mild, moderate, severe, and critical forms of the disease. In the case of mild SARS-CoV-2 infection, patients might experience dry cough, fever, nasal congestion, muscle pain, and tiredness. In critical cases, COVID-19 provokes sepsis, acute severe infections in the respiratory tract, multiple organ failure, and pulmonary fibrosis. Following exposure to SARS-CoV-2, alveolar damage and initiation of pulmonary fibrosis might occur during the incubation period of 2-3 weeks. As a result, patients with COVID-19 present with sputum expectoration and shortness of breath. Older patients have a greater chance of developing severe or critical forms of the disease, especially those with chronic illnesses including hypertension, cardiovascular diseases, diabetes mellitus, and cerebrovascular diseases (Gustine and Jones, 2021).

Although the vaccines currently in use for immunization against COVID-19 include at least thirteen preparations (classified as four platforms) that are expected to be safe and efficacious for the prevention of severe/critical illness, the status of the pandemic has not yet been effectively controlled worldwide (Gumel et al., 2021). Therefore, novel therapeutic agents that can eradicate the core cause of the disease or
at least manage the clinical symptoms of COVID-19, should be developed to effectively control the global pandemic. The present recommendations of potential therapeutics for managing COVID-19 are based on empirical and historical data from various viral infections, including other types of SARS-CoV infections. In addition, drug repositioning techniques and virtual drug development tools have been utilized for making such recommendations (Jang et al., 2021). However, cutting-edge drug candidates have not yet been developed to date (Table 1).

On the other hand, natural products have been reported to exert a broad range of pharmacological effects and can thus be potentially developed as novel agents to treat various diseases. Some natural products have shown antiviral effects and consequently been utilized as prototypes during the development of novel antiviral agents.

In this context, in the current review, we attempt to discuss and rationalize the possibility of managing the clinical symptoms of COVID-19 using natural products derived from medicinal plants used for controlling pulmonary inflammatory diseases in folk medicine, based on a multitude of original research articles (Fig. 1).

**CHEMICAL AND BIOLOGICAL PREPARATIONS INVESTIGATED FOR THE MANAGEMENT AND/OR TREATMENT OF COVID-19 TO DATE**

**Glucocorticosteroids**

Because COVID-19 incites a multitude of systemic inflammatory reactions including severe pulmonary inflammation, glucocorticoids, which are a group of potent anti-inflammatory agents, might be a useful therapeutic option. However, chronic and/or megadose administration of glucocorticoids has been attributed to various adverse effects, including depression of...
immune function, hyperglycemia, lipodystrophy, and osteoporosis (Fardet and Fève, 2014; Ni et al., 2019). According to several clinical trials, the administration of dexamethasone to patients with COVID-19 who required oxygenation resulted in a decrease in death rates (Bartoletti et al., 2021). Administration of a low dose of glucocorticoids during a short period mitigated inflammation and retarded the progression of the disease (Hu et al., 2020). However, due to the adverse effects of glucocorticoids, including depressed immune function, a probable risk of aggravation of the disease exists, and there is no definite guarantee that chronic administration of glucocorticoids protects the human body from SARS-CoV-2 infection and the development of severe COVID-19 (Hu et al., 2020; Bartoletti et al., 2021).

Umifenovir, Ribavirin, Lopinavir, Ritonavir, Favipiravir

Umifenovir blocks the interaction between viral spike proteins and human angiotensin-converting enzyme 2 (Khamitov et al., 2008; Kadam and Wilson, 2017). Ribavirin showed the possibility of suppressing the proliferation of SARS-CoV-2 by inhibiting the activity of RNA-dependent RNA polymerase (Foolad et al., 2019). Lopinavir and ritonavir, both anti-HIV antiviral agents, have been shown to suppress the proliferation of SARS-CoV-2 by inhibiting 3-chymotrypsin-like proteases (Chu et al., 2004). Favipiravir is a prodrug of favipiravir ribofuranosyl-5′-triphosphate and has been reported to block viral replication by inhibiting the activity of RNA polymerase (Mentré et al., 2015). However, to date, clinical trials have not proven these agents to be effective in treating COVID-19.

Table 2. Natural products potential for managing the clinical symptoms of COVID-19

| Classification of natural products | Compounds and their mechanisms of action |
|-----------------------------------|----------------------------------------|
| Flavonoids                        | Apigenin (alleviates pulmonary injury through decreasing the levels of TGF-β1 and TNF-α) |
|                                   | Baicalin (prevents the interaction of S-protein of SARS-CoV with host angiotensin-converting enzyme 2) |
|                                   | Chalcones (suppresses the activity of proteases of SARS-CoV) |
|                                   | Kaempferol (suppresses the release of SARS-CoV from the infected cells by inhibition of the 3a ion channel) |
|                                   | Luteolin (inhibits the entry of SARS-CoV into host cells through binding to the surface spike protein) |
|                                   | Quercetin (suppresses the entry of SARS-CoV into the cell and the activity of SARS-3CLpro, a viral replication enzyme) |
|                                   | Scutellarein (suppresses the activity of the SARS coronavirus helicase, nsP13, through controlling ATPase activity) |
| Alkaloids                          | Cepharanthine (mitigates viral S and N proteins expression, thereby decreasing the replication of virus) |
|                                   | Fangchinoline (decreases viral S and N proteins expression, thereby decreasing the replication of virus) |
|                                   | Homoharringtonine (suppresses infection by coronavirus through affecting the replication of coronavirus and inhibits viral protein synthesis) |
|                                   | Indigo (suppresses the activity of 3CLpro, a viral replication enzyme) |
|                                   | Lycorine (suppresses the replication of SARS-CoV by interfering viral RNA translation) |
|                                   | Oxyosphoridin (inhibits the replication of SARS-CoV-2) |
|                                   | Tryptanthrin (inhibits the replication of human coronavirus) |
|                                   | Tetrandrine (inhibits viral S and N protein expressions, thereby decreasing the replication of the virus) |
|                                   | Tylophorine (suppresses the virulence of SARS-CoV by inhibiting the replication of virus and apoptosis of host cells induced by virus) |
| Other groups including triterpenoids | Ascorbic acid (exerts immunomodulating, antifibrotic, antioxidative activities, and protective effects against pulmonary infections) |
|                                   | Astragalosides (suppresses the production of nitric oxide and the release of pro-inflammatory cytokines) |
|                                   | Bananin (suppresses SARS-CoV NTPase/helicase and the replication of SARS-CoV) |
|                                   | Cinnamaldehyde (inhibits proteolytic activation of spike protein in SARS-CoV-2 by proteases in host cells) |
|                                   | Curcumin (protects acute lung injury, pulmonary fibrosis, and acute respiratory distress syndrome) |
|                                   | Diallyl thiosulfonate (exerts controlling effects on edema of alveolar inner region, pulmonary fibrosis, infections of respiratory tract, acute lung injury, and sepsis) |
|                                   | Emodin (suppresses the interaction between SARS-CoV spike protein and host angiotensin-converting enzyme 2 and the release of coronavirus from infected cells) |
|                                   | Glycyrrhizin (inhibits the replication, adsorption, and penetration of coronavirus) |
|                                   | Nimboline (mitigates lung injury and pulmonary fibrosis) |
|                                   | Piperine (exerts anti-inflammatory, antiviral, and antioxidative activities) |
|                                   | Saikosaponins (inhibits the penetration and attachment of human coronavirus) |
Remdesivir
Remdesivir is a monophosphate prodrug that is converted to an analog of adenosine nucleoside triphosphate after being metabolized in the human body. It blocks the normal replication steps of viruses, including SARS-CoV-2, by being involved in the viral replication process (Siegel et al., 2017). In 2020, remdesivir was approved for the treatment of COVID-19 by the United States Food and Drug Administration (FDA) through emergency use authorization, with full approval being granted subsequently (Baracco, 2021). However, the shortcomings of this agent are that it should be administered by injection, and the cost of treatment is very high.

Nitazoxanide, Chloroquine, Hydroxychloroquine, Pyronaridine, Artesunate
Nitazoxanide is an anti-helminthic agent that shows antiviral effects against diverse viruses, including SARS-CoV-2 (Rossignol, 2016). Chloroquine and hydroxychloroquine have been utilized as antimalarial drugs and immunomodulators for the regulation of chronic inflammatory diseases. They block viral entry into host cells by inhibiting the glycosylation of host cell receptors, proteolytic processing, and endosomal acidification (Savarrino et al., 2003; Al-Bari, 2017). A mixture of the antimalarial drugs, pyronaridine and artemesunate, has been investigated as an anti-SARS-CoV-2 agent based on the assumption that the actions of the drugs are similar to those of chloroquine and hydroxychloroquine (Krishna et al., 2021). However, none of these agents have been proven to be effective and safe in the treatment of COVID-19, despite undergoing clinical trials.

Tocilizumab, Baricitinib, Imatinib, Dasatinib, Cyclosporine, Ruxolitinib
Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor. It is used as an anti-inflammatory agent in patients with rheumatoid arthritis and as an immune function modulator. Tocilizumab might be an effective therapeutic candidate for COVID-19 because the levels of IL-6 are elevated in patients with COVID-19 (Xu et al., 2020). In addition, baricitinib, imatinib, dasatinib, ruxolitinib, and cyclosporine are immunomodulators that inhibit SARS-CoV-2 activity. However, tocilizumab failed to show efficacy in decreasing mortality in hospitalized patients with COVID-19, while Janus kinase (JNK) pathway inhibitors including ruxolitinib and other immunomodulators have not been proven to be effective and safe in treating patients with COVID-19, despite undergoing clinical trials (de Wilde et al., 2011; La Rosée et al., 2020; Li and De Clercq, 2020). Recently, among the aforementioned agents, baricitinib was authorized for the emergency treatment of COVID-19 by the FDA through emergency use authorization (Golettii and Cantini, 2021).

Camostat, Nafamostat
For SARS-CoV-2 to enter the host cell, the human transmembrane surface protease TMPRSS22 cleaves and activates the spike proteins of the virus. The serine protease inhibitors, camostat and nafamostat, demonstrated an inhibitory effect towards the activity of TMPRSS2. Owing to this, these two agents are expected to show potential antiviral activity against SARS-CoV-2. However, their clinical efficacy and safety in treating COVID-19 have not yet been proven (Hoffmann et al., 2020; Breining et al., 2021).

NATURAL PRODUCTS FOR POTENTIALLY MANAGING CLINICAL SYMPTOMS OF COVID-19
In this section of the review, we discuss and rationalize the possibility of managing the clinical symptoms of COVID-19 using natural products derived from medicinal plants used for controlling pulmonary inflammatory diseases in folk medicine (Table 2). As can be seen in the sections to follow, diverse natural products have been reported to exert antiviral effects by affecting viral replication, entry into host cells, assembly in host cells, and release (Fig. 2).

FLAVONOIDS
Apigenin
Apigenin, a natural product, has antioxidant, antiviral, anti-inflammatory, and antifibrotic effects (Kumar and Pandey, 2013; Suleria et al., 2015; Marefati et al., 2018). Apigenin was found to suppress pulmonary fibrosis by mitigating the infiltration of inflammatory cells and decreasing the fibronectin and hydroxyproline levels and deposition of collagen in animal models of lung fibrosis. Apigenin also decreased the expression of myeloperoxidase (MPO), a leukocyte adhesion marker, and increased the activity of superoxide dismutase. Furthermore, apigenin was reported to alleviate pulmonary injury by decreasing the levels of TGF-β1 and TNF-α (Chen and Zhao, 2016; Shahabi et al., 2019). These biological activities of apigenin suggest its potential for development into an agent that manages lung injury, acute respiratory tract infections, and pulmonary fibrosis, all of which are symptoms that are presented in patients with COVID-19.

Baicalin
SARS-CoV-2 exploits the angiotensins-converting enzyme 2 receptor of the host to enter the host cell. Baicalin, a natural product potential for eradicating the core cause of the disease and/or managing the clinical symptoms of COVID-19.
product derived from Scutellaria baicalensis, was reported to prevent the interaction between the S protein of SARS-CoV and the angiotensin-converting enzyme 2 of the host (Chen and Nakamura, 2004; Deng et al., 2012).

**Chalcones**
It was reported that a papain-like protease (PLpro) and a chymotrypsin-like protease (3CLpro) are viral proteases of SARS-CoV. These enzymes are viral replication enzymes involved in converting replicase polyepptides of coronaviruses into functional proteins. Chalcones derived from Angelica keiskei showed potential as anti-SARS-CoV agents by suppressing the activity of these proteases (Park et al., 2016).

**Kaempferol**
The derivatives of kaempferol, a natural product, suppressed the function of the 3a ion channel of SARS-CoV. It was postulated that the suppression of the 3a ion channel interferes with the release of the coronavirus from infected cells (Schwarz et al., 2014).

**Luteolin**
Luteolin, a flavonoid compound, showed anti-SARS-CoV activity in a wild-type SARS-CoV infection system. As a possible mechanism of action of this natural product, luteolin has the potential to inhibit the entry of SARS-CoV into host cells by binding to the surface spike protein of the virus (Yi et al., 2004).

**Quercetin**
Quercetin showed antiviral activity against various viruses, including murine coronaviruses (Chiov et al., 2016). Quercetin has been reported to suppress the entry of SARS-CoV into the cell (Chen et al., 2008) and inhibit the activity of SARS-3CLpro (Jo et al., 2020). 3CLpro is a viral replication enzyme that catalyzes the processing of replicase polyepptides of coronavirus into functional proteins. Quercetin was found to suppress pulmonary fibrosis by preventing the infiltration of inflammatory cells and deposition of collagen and depleting the fibronectin and hydroxyproline levels in animal models of lung fibrosis. It was also reported to reduce the damage to pulmonary tissues by decreasing the biological markers of oxidative stress and inflammation (Farazuddin et al., 2018; Zhang et al., 2018). These biological activities of quercetin suggest its potential for development into an agent that regulates lung injury, acute respiratory tract infections, and pulmonary fibrosis, all of which are symptoms observed in patients with COVID-19.

**Scutellarein**
The helicase protein in coronaviruses might be a pharmacological target for the development of potential therapeutics against the human coronavirus. Scutellarein, a natural product isolated from Scutellaria bacalensis, suppressed the activity of the SARS coronavirus helicase, nsP13, by controlling ATPase activity (Yu et al., 2012).

**ALKALOIDS**

**Cepharanthine**
Cepharanthine, a natural product isolated from the medicinal plant Stephania tetrandra, has been reported to exert antiviral effects against human hepatitis B virus, human immunodeficiency virus 1 (HIV-1), and human T-lymphotropic virus type 1 (Toyama et al., 2012; Zhou et al., 2012; Matsuda et al., 2014). Cepharanthine showed anti-inflammatory and antineoplastic effects and suppressed cell death provoked by human coronavirus-OC43 (HCoV-OC43) in the human pulmonary system. The molecule also mitigated viral S and N protein expressions, thereby decreasing the replication of the virus (Kim et al., 2019).

**Fangchinoline**
Fangchinoline, a natural product isolated from the medicinal plant Stephania tetrandra, has been reported to exert antiviral effects against HIV 1 (Wan et al., 2012). The molecule showed anti-inflammatory and antineoplastic effects. Fangchinoline suppressed cell death induced by HCoV-OC43 in the human pulmonary system. It also suppressed viral S and N protein expressions, thereby decreasing the replication of the virus (Kim et al., 2019).

**Homoharringtonine**
Homoharringtonine, a natural product, was shown to suppress the viral activities of the Newcastle disease virus, vesicular stomatitis virus, varicella-zoster virus, human echovirus 1, and hepatitis B virus (Romero et al., 2007; Dong et al., 2018; Andersen et al., 2019; Kim and Song, 2019). In addition, homoharringtonine showed potent antiviral effects against various human coronaviruses. It suppressed infection by coronavirus by affecting viral replication. It has been reported to be an inhibitor of protein synthesis (Lü and Wang, 2014; Cao et al., 2015; Dong et al., 2018).

**Indigo**
*Isatis indigotica*, containing indigo as the major active constituent, is a medicinal plant empirically used in Asian medicine for controlling hepatitis, encephalitis, and influenza (Qin and Xu, 1998; Ho and Chang, 2002; Chang et al., 2012). Indigo was shown to inhibit the replication of the Japanese encephalitis virus, possibly by interfering with the attachment of the virus to its receptor (Chang et al., 2012). Furthermore, indigo was shown to suppress the activity of 3CLpro (Lin et al., 2005; Berry et al., 2015).

**Lycorine**
Lycorine, a natural product isolated from Lycoris radiata (Spider lily), showed anti-inflammatory and antiviral activities against a multitude of viruses, including SARS-CoV, by suppressing viral replication (Li et al., 2005; Cao et al., 2013; Zhang et al., 2020). This inhibition of viral RNA replication may have been a result of interfering with viral RNA translation. In addition, lycorine was reported to inhibit influenza virus nucleoprotein movement from the nucleus and downregulate autophagy (Liu et al., 2011; He et al., 2013; Wang et al., 2014, 2019).

**Oxysophoridine**
Oxysophoridine is a natural product isolated from Siphocampylus verticillatus and Sophora alopecuroides. This compound exerts a multitude of pharmacological effects, including antioxidative, antineoplastic, anti-apoptotic, and anti-inflammatory properties (Yang et al., 2012; Yao et al., 2012; Rui et al., 2013; Wang et al., 2015; Cao et al., 2018). An in vitro
study showed that oxysophoridine might inhibit the replication of SARS-CoV-2 (Zhang et al., 2020). Owing to this, expedited investigations should be performed to determine the in vivo effect of this compound and elucidate its underlying molecular mechanism.

Tryptanthrin

Tryptanthrin is a major constituent isolated from the medicinal plant Strobilanthes cusia. This medicinal plant has been empirically used in Asian folk medicine to control infectious diseases including viral pneumonia, encephalitis, influenza, mumps, and cerebrospinal meningitis (Tanaka et al., 2004; Shahni and Handique, 2013; Gu et al., 2015; Lee et al., 2019). Tryptanthrin was shown to exert a potent antiviral effect on cells infected with HCoV-NL63 by affecting viral replication (Tsai et al., 2020).

Tetrandrine

Tetrandrine, a natural product isolated from the medicinal plant Stephania tetrandra, was reported to exert anti-inflammatory and antineoplastic effects (Kim et al., 2019). In human lung cells, tetrandrine prevented viral production following infection by the dengue virus (Liou et al., 2008). It also suppressed Ebola virus infection in human macrophages (Sakurai et al., 2015) and herpes simplex virus type 1 infection in ocular tissues (Hu et al., 1997). Furthermore, tetrandrine suppressed HCoV-OC43-induced cell death in the human pulmonary system. The compound also mitigated viral S and N protein expressions, thereby decreasing the replication of the virus (Kim et al., 2019).

Tylophorine

Tylophorine, a natural product of Tylophora indica, was shown to exert anti-inflammatory effects in patients with hepatitis C and inhibitory effects on the replication of the human hepatitis C virus (Raina and Raina, 1980; You et al., 2006; Yang et al., 2007; Pham et al., 2012; Wang et al., 2017). Tylophorine also suppresses the virulence of SARS-CoV by inhibiting viral replication and host cell apoptosis induced by the virus (Yang et al., 2010; Lee et al., 2012; Yang et al., 2017).

OTHER GROUPS INCLUDING TRITERPENOIDS

Ascorbic acid

Ascorbic acid has been reported to exert anti-diabetic, immunomodulatory, antioxidative, and antifibrotic effects as well as protective effects against pulmonary infections. Clinical and non-clinical investigations have suggested ascorbic acid as potentially having ameliorating effects in patients with pneumonia, sepsis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, multiple organ failure, and acute lung injury. These symptoms have also been observed in patients with COVID-19 (Hunt et al., 1994; Nathan et al., 2002; Wintergerst et al., 2006; Chambial et al., 2013; Fisher et al., 2014; Bharara et al., 2016; Carr and Maggini, 2017; Hong et al., 2018; Rodrigues da Silva et al., 2018). Thus, ascorbic acid may be used in the management of clinical symptoms of COVID-19.

Astragalosides

Astragaloside IV, derived from Astragalus membranaceus, has been reported to exert anti-inflammatory effects by suppressing the production of nitric oxide and the release of pro-inflammatory cytokines (Qi et al., 2017). These biological activities of astragaloside IV suggest a potential for its use as an agent for managing cytokine storm, which is the main cause of mortality in COVID-19.

Banannin

Banannin, a natural product, was shown to suppress the activities of ATPase and helicase of the SARS-CoV NTPase/helicase. Banannin has also been reported to suppress SARS-CoV replication in Frhk-4, a fetal rhesus monkey kidney cell line (De Clercq, 2006).

Cinanserin

Cinanserin is a natural product that suppresses the replication of SARS-CoV and is a potential inhibitor of SARS-CoV proteases. Binding of cinanserin to the active site of 3CLpro was shown to interrupt the processing of precursor polyproteins to the functional replicase which is required for viral replication (Chiow et al., 2016).

Cinamaldehyde

Cinamaldehyde, derived from Cinnamomi cortex, has been reported to exhibit anti-inflammatory, antiviral, and antioxidant activities (Jayaprakash and Rao, 2011; Rao and Gan, 2014; Kawatra and Rajagopalan, 2015; Polansky and Lori, 2020). Cinnamomi cortex, which contains cinamaldehyde as the major component, has been reported to mitigate the production of inflammatory markers such as IL-6 and TNF-α. In addition, the molecule decreased the phosphorylation of ERK1/2, p38, and JNK, and suppressed the activation of NF-κB by diminishing the degradation of IκBα (Hong et al., 2012). It was also postulated to possess inhibitory activity against proteolytic activation of spike protein in SARS-CoV-2 by proteases in host cells, since cinnamon was reported to be a trypsin inhibitor (Shahwar et al., 2012; Gopalakrishnan et al., 2018). All these investigations implicate a potential therapeutic role of cinamaldehyde as an agent for managing SARS-CoV-2 infection.

Curcumin

Curcumin, a well-known bioactive component of turmeric, has been reported to exert immunomodulatory, antioxidative, antifibrotic, and anti-inflammatory effects by controlling JNK as well as signal transducers and activators of the transcription (STAT) signaling pathway (Menon and Sudheer, 2007; Ju- renka, 2009; Srivastava et al., 2011; Kocaadam and Şanlıer, 2017). It has also been reported to ameliorate oxidative stress, pulmonary fibrosis, and inflammation in animal models of pulmonary fibrosis induced by chemicals, viruses, and radiation (Punithavathi et al., 2000; Lee et al., 2010; Hülge, 2011; Avasarala et al., 2013; Chen et al., 2017; Zahedipour et al., 2020). Curcumin was reported to modulate the function of natural killer cells, dendritic cells, T cells, neutrophils, B cells, and macrophages (Gautam et al., 2007). In this context, curcumin might show potential activities, including protection against acute lung injury, pulmonary fibrosis, and acute respiratory distress syndrome, as well as improving the overall function of the lungs. These are the optimal activities required
for the regulation of clinical symptoms observed in patients with COVID-19.

**Diallyl thiosulfonate**

*Allium sativum* containing diallyl thiosulfonate, alliin, and S-allyl cysteine as the major active components has been reported to exert therapeutic effects by controlling edema of the alveolar inner region, pulmonary fibrosis, respiratory tract infections, acute lung injury, and sepsis. Diallyl thiosulfonate and other components of *Allium sativum* showed antioxidative, antiviral, immunomodulatory, anti-inflammatory, and anti-fibrotic effects (Bayan et al., 2014; Arreola et al., 2015; Shang et al., 2019). These results implied that diallyl thiosulfonate and other phytochemicals in *Allium sativum* might be used to regulate the symptoms seen in patients with COVID-19.

**Emodin**

Emodin has been reported to suppress the interaction between SARS-CoV spike protein and the angiotensin-converting enzyme 2 of the host. It also suppresses the function of the 3a ion channel of SARS-CoV. This suppression is thought to interfere with the release of the virus from infected cells (Ho et al., 2007; Schwarz et al., 2011).

**Glycyrrizin**

Glycyrrizin, an active component isolated from Glycyrrhiza radix, has been reported to suppress the replication of SARS-CoV (Yang et al., 2020). In addition, glycyrrizin was reported to inhibit the replication, adsorption, and penetration of coronavirus (Cinatl et al., 2003; Fiore et al., 2008).

**Nimbolide**

Nimbolide, isolated from the medicinal plant *Azadirachta indica*, has been reported to exert antifibrotic activity in lung tissue, including reduction of biological markers of fibrosis and oxidative stress, through the suppression of the TGF-β/Smad intracellular signaling pathway (Prashanth Goud et al., 2019). These biological activities of nimbolide suggest its potential use as an agent to manage lung injury and pulmonary fibrosis, all of which are symptoms that occur in patients with COVID-19.

**Piperine**

Piperine, a bioactive compound derived from *Piper nigrum*, has been reported to exert anti-inflammatory, antiviral, and antioxidant activities (Vijayakumar et al., 2004; Butt et al., 2013). Piperine showed an effect of enhancing the bioavailability of an agent administered simultaneously with it by increasing the gastrointestinal absorption of that agent (Pattanaik et al., 2009). Therefore, piperine might be developed as a potentiator of orally administered agents aimed at treating or managing COVID-19.

**Saikosaponins**

Saikosaponins derived from an anti-inflammatory medicinal plant, *Bupleurum falcatum*, showed a multitude of biological activities, including immunomodulation, anti-hepatitis activity, anti-bacterial effects, and activity against nephritis. It has been reported that saikosaponin B2 exerted an antiviral effect by inhibiting the penetration and attachment of HCoV-229E (Cheng et al., 2006).

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**CONCLUSIONS AND FUTURE PERSPECTIVES**

After the outbreak of COVID-19, biomedical scientists worldwide have been investigating the development of novel therapeutics and safe and efficacious vaccines to mitigate the spread of the virus and retard the morbidity and mortality of COVID-19. Although several vaccines for COVID-19 manufactured by pharmaceutical companies are currently being used in clinics worldwide, the COVID-19 pandemic has not been effectively controlled, as there are various hurdles in rapid immunization drives, including the difficulties in mass production and the swift distribution of adequate doses to all populations globally. Therefore, novel therapeutic agents, preferably for oral administration, which can eradicate the core cause of the disease, and/or manage the clinical symptoms of COVID-19 should be developed to effectively regulate this global pandemic. As presented in this review, we attempted to postulate and scientifically rationalize the possibility of managing the clinical symptoms of COVID-19 using natural products derived from medicinal plants used for controlling pulmonary inflammatory diseases in folk medicine. Diverse natural products have been reported to exert potential antiviral effects *in vitro* by affecting viral replication, viral entry into host cells, viral assembly in host cells, and viral release. However, the *in vivo* antiviral effects and clinical antiviral efficiencies of these natural products against SARS-CoV-2 have not been successfully proven do date. Thus, these properties should be further elucidated through investigations, including randomized clinical trials, in order to develop optimal and ideal therapeutic candidates for COVID-19.

**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

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