

The Potential of Herbal Combinations as Adjunctive Therapy for Standard Care of COVID-19 Patients: A Lesson Learned from Indonesia

Anna Rozaliyani^{1*}, Satria Pratama², Findra Setianingrum¹, Fenny Yunita³, C. Martin Rumende^{1,4}

¹Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

²Faculty of Military Medicine, The Republic of Indonesia Defense University, Bogor, West Java, Indonesia

³Faculty of Medicine, Universitas Tarumanegara, Jakarta, Indonesia

⁴dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

The pandemic of novel coronavirus disease (COVID-19) has become a global disaster that occurred between the end of 2019 and 2023. It caused immeasurable damage to almost all aspects of human life. The disease has opened a lot of new perspectives on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) origins and pathogenesis, the nature of the virus, the potential for new treatments, and new policies to overcome this pandemic. This review aims to know the potential of plants that are beneficial to combat the diseases, including immunomodulators in the management of COVID-19. Studies reporting COVID-19 with the keywords SARS-CoV-2, COVID-19, pathogenesis, clinical manifestations, medicinal plants, and their benefits were included. We also discussed the molecular pathways of the bioactive compound that may interact with the pathogenesis of COVID-19. Clinical management for COVID-19 is still being refined from time to time because many aspects are not yet fully understood and need further studies. Therefore, effective, non-invasive, and affordable treatment must be sought immediately to meet this very urgent need. The commotion situation of the COVID-19 pandemic has encouraged various efforts to develop new drugs, including alternative therapies from potential medicinal plants. The pharmacotherapeutic activity of Indonesia-based medicinal plants for COVID-19 has evolved, including *Phyllanthus niruri*, *Andrographis paniculata*, *Anacardium occidentale*, *Zingiber officinale*, and *Glycyrrhiza glabra*. The potential benefits of that combination of herbal medicinal plants also need to be explored for better contribution in managing COVID-19, particularly in Indonesia.

Keywords: Indonesia-based medicinal plants; COVID-19; pathogenesis; treatment

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*corresponding author

Email: annarozal1110@gmail.com

INTRODUCTION

In November 2019, the most terrible spread of the coronavirus was first reported in Wuhan, China, and caused the coronavirus disease (COVID-19). It became a pandemic that transmission originated from animals to humans, then thrived into a human-to-human spread caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). High transmission and pathogenicity of viruses have been reported to be a worldwide trend. The World Health Organization (WHO) declared COVID-19 as a global pandemic. The wide viral dissemination throughout the world is inevitable, since its pathogenesis is not yet fully understood (Davis et al., 2021; Hu et al., 2021; Kumar et al., 2021; Li et al., 2021; Rosenthal et al., 2022).

Based on data from WHO at the end of June 2023, the burden of positive COVID-19 cases reached more than 768 million confirmed cases worldwide, and over

6.9 million deaths have been documented (WHO, 2023). Europe is the continent with the highest number of COVID-19 cases (249,642,346 cases), while the United States is the country with the highest number of cases (107,298,305 patients). In Indonesia, COVID-19 affected 6,811,945 patients, while 161,870 patients died, and 6,641,275 patients recovered. Indonesia becomes the 20th place out of 231 countries and territories in the world that have been affected by the COVID-19 pandemic (Davis et al., 2021; Hu et al., 2021; Kumar & Al Khodor, 2020; Li et al., 2021; Rosenthal et al., 2022).

Most COVID-19 patients suffer from mild to moderate respiratory illness and then recover without certain treatment. Clinical symptoms of COVID-19 comprise fever, cough, fatigue, malaise, shortness of breath, and other complications. These clinical manifestations are related to multifactorial conditions, including comorbidities. Geriatric patients and patients with diabetes, cardiovascular disease, obesity, cancer, and

chronic respiratory diseases are more susceptible to get serious infections or even death (Hu et al., 2021; Kumar & Al Khodor, 2020; Oladele et al., 2020). There was no single treatment or vaccine that has been proven effective in reducing/inhibiting SARS-CoV-2. The limited effectiveness of existing drugs or vaccines has encouraged the exploration of traditional medicine owned by each region as a potential approach to be developed. For example, Traditional Chinese Medicine (TCM) was reported effective for curing children with fever symptoms due to influenza, as well as COVID-19 (Choudhry et al., 2020; Shah et al., 2022; Xiong et al., 2020).

Indonesia is one of the countries that has a very large amount of biodiversity (Rahayu et al., 2020). Around 28,000 plant species are found in Indonesia's tropical forests (Elfahmi et al., 2014). Approximately 80% of these plants are recognized to have medicinal properties (Elfahmi et al., 2014). Unfortunately, not all of them are utilized as herbal medicines optimally. The Indonesian people's cultural heritage has been used traditionally for generations to improve health status (Rahayu et al., 2020). Various studies have been carried out to explore the potential of plants that are beneficial to improve health status, including immunomodulators in treating COVID-19. Some medicinal plants have been developed for COVID-19 treatment, including *meniran* (*Phyllanthus niruri*), *sambiloto* (*Andrographis paniculata*), *jambu mete* leaves (*Anacardium occidentale*), *jahe emprit* (*Zingiber officinale*), and licorice (*Glycyrrhizae radix*) (Maharani & Fernandes, 2021; Tungadi et al., 2020; Xiong et al., 2020). In this review, we aimed to describe the SARS-CoV-2 profiles, the pathogenesis, as well as current therapeutics of COVID-19 and the potential of Indonesia-based medicinal plants.

METHOD

This manuscript appraises the possible mechanism of SARS-CoV-2 actions and potential Indonesia-based medicinal plants that have both biological and pharmacological activities as adjunctive therapy for standard care of COVID-19 patients. The search of literature for this manuscript used databases from Google Scholar, Medline, and PubMed Central using keywords: SARS-CoV-2, COVID-19, pathogenesis, clinical manifestations, medicinal plants, and their benefits. Cohort studies, editorials, case reports, reviews, and case series were also considered for critical appraisal. Articles that met the purpose of the manuscript were refined and compiled for manuscript preparation.

The Nature of SARS CoV-2

The SARS-CoV-2 virion has four structural proteins of the coronavirus consisting of the spike (S) glycoprotein, nucleocapsid (N) protein, membrane (M) protein, and envelope (E) protein (Figure 1). Those proteins are less conserved but have an important role in the life cycle of the virus. The primary role of the S protein is documented in the pathogenesis and organ tropism of the virus. It is responsible for viral entry via receptor recognition, as well as membrane fusion. The spike glycoprotein-S mitigates viral attachment to the receptor of angiotensin-converting enzyme 2 (ACE2) and fusion with the membrane of the host cell. Then, SARS-CoV-2 utilizes the serine protease TMPRSS2 (trans-membrane protease serine 2) for priming of S protein, infecting the target cells (Hoffmann et al., 2020; Kumar & Al Khodor, 2020; Wu et al., 2020).

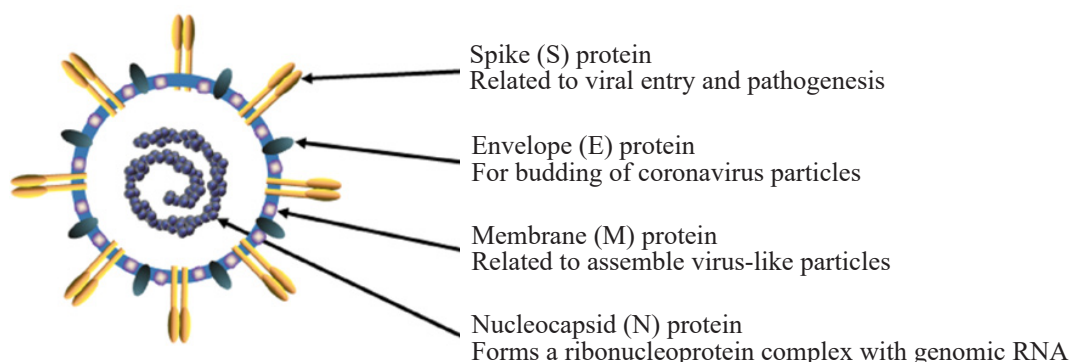


Figure 1. The structural protein of SARS-CoV-2 (Choudhry et al., 2020 with modification)

The proteins of SARS-CoV-2 spike consist of two subunits; the S1 receptor binding subunit and the S2 fusion subunit, to intercede binding of virion to receptor proteins and commence membrane fusion. Molecular analysis of the S protein recognized an insertion at the S1/S2 site, although the significance of this insertion remains undetermined. It appears that this unique insertion confers functional advantages for an easy cell infection and efficient dissemination across human hosts. The envelope (E) protein is the smallest structural protein but has an important role in the construction, formation of envelope, budding, and virulence. The membrane (M) protein has membrane-bending properties that contribute to stimulating viral assembly. The nucleocapsid (N) proteins fulfill several functions that encase viral RNA genomes into ribonucleoprotein complexes to preserve the genome. Several computational studies were conducted to explore the new therapies according to the SARS-CoV-2 structural protein (Choudhry et al., 2020; Gupta et al., 2021; Kumar & Al Khodor, 2020; Oladele et al., 2020).

Pathogenesis of COVID-19

The clinical symptoms of COVID-19 may mimic the common cold, including fever, cough, fatigue, and shortness of breath. The infection may progress to pneumonia, serious acute respiratory syndrome, multi-organs failure, and even mortality. Elderly patients (>60 years of age) and patients with chronic conditions are more susceptible to severe conditions (18.5%) when compared to children and healthy younger adults (6%) (Vincent & Taccone, 2020; Wang et al., n.d.).

Data on non-survivor patients revealed that the most common comorbidities in COVID-19 patients were hypertension (24–75%) and diabetes mellitus (16.2–35%). The SARS-CoV-2 binds to host cells via the ACE2 receptor, which is reflected by the lung’s epithelial cells, blood vessels, intestines, kidneys, and brain (Figure 2). The ACE2 expression is increased significantly in diabetic and hypertensive patients managed with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). It might increase the severity of SARS-CoV-2 infection as well. The virus can be transmitted from the mouth or nose of infected patients as small liquid particles when they talk, breathe, cough, sneeze, or sing. These particles might range from larger droplets to smaller aerosols (Wan et al., 2020; Wang et al., n.d.).

Therapeutic Strategies for COVID-19 Patients

There is no specific antiviral drug or COVID-19 vaccine that has proven effective in saving infected patients and protecting health workers or patients who are at high risk of infection. The SARS-CoV-2 pathogenesis includes hyperinflammation characterized by fulminant hypercytokinemia with multi-organ failure, immune-suppressed conditions, and reduced ACE2 which increases the permeability of pulmonary vascular and affects alveoli (Figure 3). It is activated by ORF3a, ORF3b, and ORF7a via the JNK pathway that causes lung deterioration. The virus mechanism of action can potentially be inhibited by combining drug treatment based on its pharmacological activity (Choudhry et al., 2020; Kumar & Al Khodor, 2020; Oladele et al., 2020).

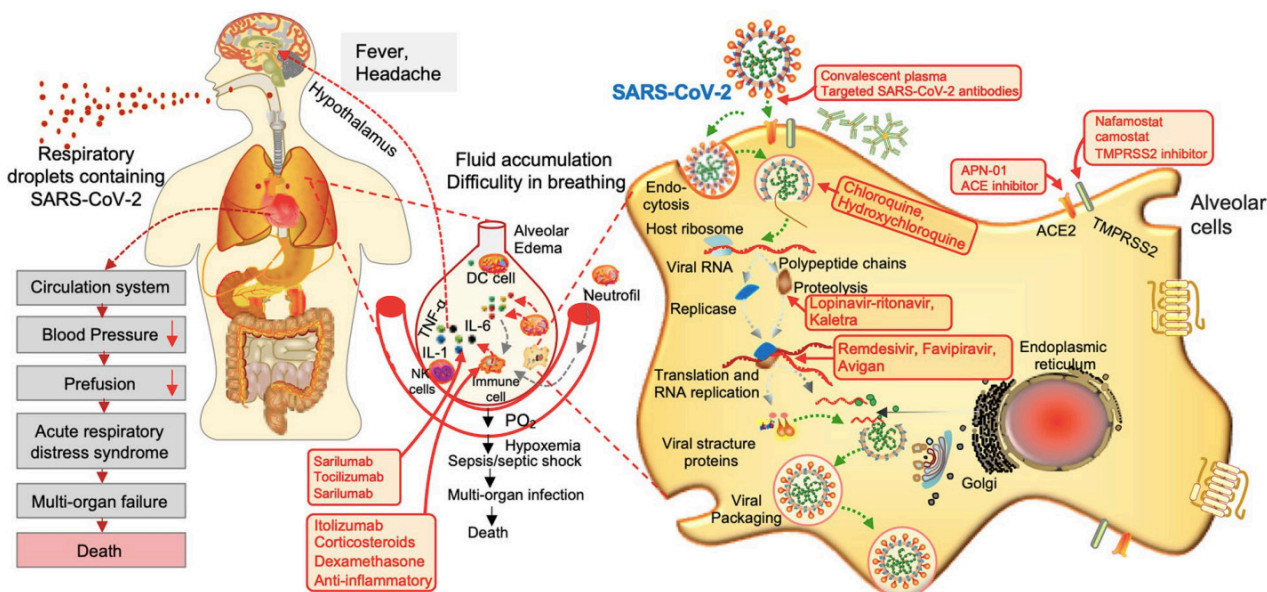


Figure 2. Model of SARS-CoV-2 infection and replication in host cells, and proposed treatment to inhibit the replication cycle of SARS-CoV-2 (M. Kumar & Al Khodor, 2020)

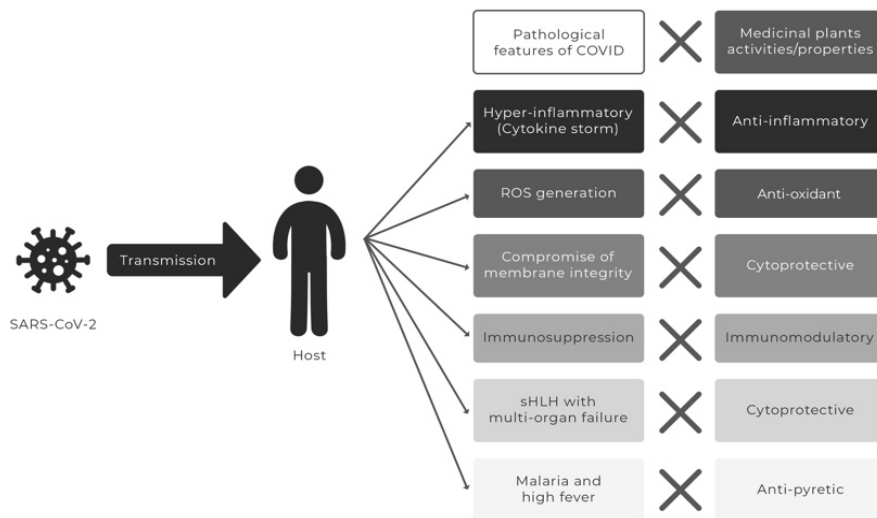


Figure 3. The COVID-19 pathological manifestation and potential of clinical medicinal plant properties

Various medicinal plants are being used for the treatment of COVID-19 globally. Traditional healing methods passed down from one generation to another have been developed in many countries around the world. The development of these potential uses of plants is linked to their affordability, safety, effectiveness, and cultural preferences. Several Indonesia-based medicinal plants have been explored as adjunctive treatments for COVID-19 based on their properties as an antiviral, anti-inflammatory, antipyretic, immunomodulatory, and anti-oxidant. Medicinal plants have been an essential part of human life since the beginning of civilization (Choudhry et al., 2020; Oladele et al., 2020).

The Potential of Native Indonesian Medicine Plants

Indonesia has a lot of potential natural materials that can be evolved as medicinal plants. The database from the National Agency of Drug and Food Control (NADFC/BPOM) states that there are around 283 medicinal plants which officially registered, however the rest of them are used traditionally but not yet registered (Elfahmi et al., 2014). The government supports the development of drugs from natural raw materials from Indonesia. Therefore, herbal medicines containing native Indonesian plants need to be promoted as adjuvants/complements in standard therapy for COVID-19. In China, the COVID-19 treatment protocol uses a combination of TCM with conventional therapy (Maharani & Fernandes, 2021; Shah et al., 2022; Tungadi et al., 2020).

Some Indonesia-based medicinal plants have been cultivated, including *meniran* (*Phyllanthus niruri*), *sambiloto* (*Andrographis paniculata*), *jambu mete* leaves (*Anacardium occidentale*), *jahe emprit* (*Zingiber*

officinale), and *kayu legi* or licorice (*Glycyrrhizae radix*) for anti-inflammatory and anti-oxidant properties in patients with respiratory infections, including COVID-19 (Figure 4). On the other hand, TCM intervention was reported as an important and effective therapy for COVID-19 treatment. Inflammatory cytokines e.g., ESR, CRP, and IL-6 levels were significantly reduced, and IFN- γ levels were increased in the group receiving conventional therapy plus TCM compared to the group receiving only conventional therapy (antibiotic and antiviral therapy) (Shah et al., 2022; Tungadi et al., 2020; Wan et al., 2020). These cellular mechanisms showed clinical impacts on shortening the disease infection time, slowing disease progression, and reducing mortality (Shah et al., 2022).

1. The aerial parts of *meniran* (*Phyllanthus niruri*)

The herbs belong to *Phyllanthus* (Euphorbiaceae) genus and spread widely in several regions. The active compounds in the aerial parts of *meniran* are trimethyl-3,4-dehydrochebulate and methylbrevifolin carboxylate, which were useful as therapy to prevent central and peripheral inflammation associated with increased production of the inflammatory mediators. *Meniran* has hepatoprotective, immunomodulatory, and anti-inflammatory activities. It reduced the effects of CCL4-induced hepatotoxicity by regulating L-carnitine, amino acid, and taurocholic metabolism. *Meniran* significantly reduced ALT levels, inhibited oxidative stress, increased hepatic cell membrane mobility, and reduced hepatic infiltration and hepatic focal necrosis. *Meniran* extract showed inhibition of chemotaxis of polymorphonuclear leukocytes (PMN) and monocytes, inhibition of CD18 expression, and inhibition of reactive oxygen species.

	Immunomodulator	Anti-inflammation	Antypiretic	Cough reliever, antitussive-expectorant	Analgesic	Anti-asthmatic	Antimicrobial, antibacterial, antiviral	Anti-oxidant	Hepatoprotector	Anti-vomitus	Anti-diarrhea	Gastroprotector-antiulcer
<i>Phyllanthus niruri</i>	✓	✓							✓			✓
<i>Andrographis paniculata</i>	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
<i>Anacardium occidentale</i>		✓	✓	✓	✓	✓	✓		✓	✓		
<i>Zingiber officinale</i>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
<i>Glycyrrhiza glabra</i>	✓	✓			✓	✓			✓			✓

Figure 4. Native Indonesian medicinal plants that have been cultivated for anti-inflammatory and anti-oxidant properties in patients with respiratory infections

Extract of *meniran* also revealed the inflammatory mediator's inhibition, including TNF-alpha and IL-6 (Fang et al., 2008; GUO et al., 2017; Hidayat & Patricia Wulandari, 2022; Upadhyay & Tiwari, 2023; Utami et al., 2022). The bioactive compounds of *meniran*, catechin and quercetin, showed effects on the decreased expression of TNF- α , IL-1, IL-6, and iNOS result in inhibition of inflammation in COVID-19 (Sukmanadi et al., 2020).

2. The aerial parts of *sambiloto* (*Andrographis paniculata*)

The aerial parts of *sambiloto* contains terpenoids, flavonoids, xanthenes, andrographolide A-F, grapholide, isoandrographanin, neoandrographolide, skullcapflavone, 7-O-methylwogonin with pharmacological activity as anti-inflammatory, reducing symptoms of upper respiratory tract infections, immunostimulants, anti-oxidants and antivirals. *Sambiloto* was documented to have anti-inflammatory pharmacological effects and anti-oxidants. Extract from *sambiloto* leaves can reduce the production of pro-inflammatory mediators, including NO, PGE2, TXB2, IL-1B, IL-6, and allergic mediators. The content of *sambiloto* also documented an anti-inflammatory effect. *Sambiloto* was also reported to reduce symptoms of respiratory tract infections such as sore throat, nasal secretions, phlegm, and cough, significantly. Its anti-inflammatory effect plays a role in reducing inflammatory mediators in sensory nerve endings in the respiratory tract. *Sambiloto* has antiviral activity against several viruses (DENV-1, HPV 16, HSV-1, influenza A virus, and HIV). It can inhibit DENV-1 and suppress the transcriptional activity of HPV16, as well as inhibit HIV replication (Attah et al., 2021; Hidayat & Patricia Wulandari, 2022; Hossain et al., 2014; Intharuksa et al.,

2022; Okhuarobo et al., 2014). Previous studies showed the role of *A. paniculata* in decreasing the number of infectious virions of COVID-19 and preventing cytokine storms (Siripongboonsitti et.al., 2023; Sangiamsuntorn et.al., 2021).

3. Leaves of *jambu mete* (*Anacardium occidentale*)

Various studies have proven that *A. occidentale* leaves extract by ethanol/water contains phenolic compounds such as quercetin, anthocyanins, and tannins and those compounds have several pharmacological effects such as anti-inflammatory, antioxidant, bronchodilator, and analgesic. The leaves of *A. occidentale* extracted by infusion with ethanol/water (40:60, v/v) showed significant activity in inhibition the secretion of proinflammatory cytokines, including IL-1 β and TNF- α (Souza et al., 2017). The compounds that inhibit IL-1 β and TNF-1 α play an important role in preventing inflammatory reactions, so *A. occidentale* extract has the ability as an anti-inflammatory agent. It has been used to treat bronchitis and inflammation, a sign of asthma. The bronchodilator effect was determined by measuring the percentage of the extract on histamine-induced bronchoconstriction. Its bronchodilator activity shows that this plant can stimulate β 2-adrenergic receptors. This stimulation causes the relaxation of smooth muscle by increasing the formation of cAMP. The β 2-adrenergic receptors could act as immunomodulators by increasing intracellular Ca²⁺ pressure and Ca²⁺ binding, thus having the effect of reducing intracellular Ca²⁺ concentrations (Baskar et al., 2019; da Silva et al., 2018; Souza et al., 2017). The *in silico* studies suggested that aghatisflavone (a bioactive compound of *A. occidentale*) play a key role to reduce TNF- α levels and inhibit SARS-CoV-2 Mpro (Chaves et.al., 2022; Lokhande et.al., 2020).

Table 1. The potential herbal components that have benefits for the management of COVID-19

Name of the plant	Bioactive compounds or treatment regiment	Molecular mechanism and/or clinical effect	Type of study
<i>Phyllanthus niruri</i>	Phyllanthin and hypophyllanthin	Inhibited target receptors (spike glycoprotein and main protease) of COVID-19 (Marhaeny et al., 2021).	<i>In silico</i> study
	Astragalin	Showed high binding affinities with the main protease of SARS-CoV-2 (Murugesan et al., 2021).	<i>In silico</i> study
	Catechin and quercetin	Inhibited the inflammation via the reduced expression of TNF- α , IL-1, IL-6, and iNOS (Sukmanadi et al., 2020).	<i>In silico</i> study
<i>Andrographis paniculata</i>	Patients received capsules containing 20.53 mg of andrographolide extract (APE).	Reduced the risk of severe COVID-19 by decreasing IL-1 β and showed beneficial effect of immunomodulator by preventing cytokine storms. (Siripongboonsitti et.al., 2023)	Double-blind clinical trial
	Andrographolide	Reduced the number of infectious virions of COVID-19 in a dose-dependent manner (Sangiamsuntorn et.al., 2021).	Model of human lung epithelial cells.
<i>Anacardium occidentale</i>	Agathisflavone	Showed inhibitory effect against SARS-CoV-2 M ^{pro} , presumably via interaction with allosteric site(s) and decreased the TNF- α levels in infected Calu-3 cells (Chaves et.al., 2022).	<i>In silico</i> study and enzymatic analysis
	Agathisflavone	Revealed to be a strong SARS-CoV-2 M ^{pro} inhibitor (Lokhande et.al., 2020).	<i>In silico</i> study
<i>Zingiber officinale</i>	Patients received <i>Zingiber officinale</i> (Tablet Vomigone 500 mg II tds) and <i>Echinacea</i> (Tablet Rucoldup I tds) for seven days in addition to the standard treatment (hydroxychloroquine).	Showed better clinical (coughing, dyspnea, and muscle pain) responses compared to standard treatment (Mesri et.al., 2021).	A clinical trial
	6-gingerol	Disturbed the entrance process of SARS-CoV-2 by inhibition of the enzyme ACE-2 in the host and the spike glycoprotein in the virus (Haridas et.al., 2021).	<i>In silico</i> study
	4-gingerol	Showed a stable bond to SARS-CoV-2 M ^{pro} with the lowest binding energy and interact via hydrogen and hydrophobic bonds (Wijaya et.al., 2021).	<i>In silico</i> study
<i>Glycyrrhiza glabra</i>	<i>Glycyrrhiza glabra</i> (GG) extract	<ul style="list-style-type: none"> Showed a 35%–40% marked reduction in lung viral load along with minimal lung pathology in the hamster model. Reduced the mRNA expression of pro-inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1). 	<i>In vivo</i> and <i>in vitro</i> study

Table 1. continued

Name of the plant	Bioactive compounds or treatment regiment	Molecular mechanism and/or clinical effect	Type of study
		<ul style="list-style-type: none"> Exhibited suppression effect to ROS, mtROS, and NET generation in a concentration-dependent manner in both human polymorphonuclear neutrophils (PMNs) and murine bone marrow-derived neutrophils (BMDNs) (Rizvi et.al., 2022). 	<i>In vivo</i> and <i>in vitro</i> study
	Glycyrrhizic acid and Nsp15 endo-glyasperin A	Showed interruption between virus and the ACE-2 receptor at entry-level and after entry into host cell. (Sinha et.al., 2020)	<i>In silico</i> study
	Glycyrrhizic acid (GA), Liquiritigenin (L) and Glabridin (G)	Showed inhibitory effect in the process of the catalytic activity of the main protease, facilitated by formation of complex with M ^{Pro} of SARS-CoV-2. (Srivastava et.al., 2022)	<i>In silico</i> study

4. Rhizoma of *jahé emprit* (*Zingiber officinale*)

Rhizoma of *Zingiber officinale* contains gingerols, phenolics, terpenes, shogaols, paradols, zingerone, zingiberene, quercetin, 6-dehydrogingerdione, gingerenone-A, β -bisabolene, α -curcumene, α -farnesene, and β -sesquiphellandrene which have various pharmacological activities, including anti-oxidant, anti-inflammatory, antimicrobial, protective effect against respiratory tract diseases, and improving respiratory symptoms. The mechanism of anti-oxidant activity is stimulating the anti-oxidant enzyme expression and reducing the formation of lipid peroxidation and reactive oxygen species as well. It can reduce the amount of inducible nitric oxide (iNOS) and prostaglandin E2 (PGE2). The mechanism of the anti-inflammatory activity of *jahé emprit* can reduce inflammation through the inhibition of Akt and NF- κ B, increase the activity of the anti-inflammatory cytokine, and reduce the number of pro-inflammatory cytokines. It inhibits the growth of various bacteria, fungi, and viruses through its ability to suppress the formation of bacterial biofilms, ergosterol biosynthesis, and interfere with the attachment and internalization of viruses in cells. It also helps relieve airways by inducing relaxation of the respiratory tract's smooth muscles, reducing airway resistance and cough symptoms (Ballester et al., 2023; Mao et al., 2019; Zhang et al., 2022). In addition, gingerol showed benefits in disturbing the entrance process of SARS-CoV-2 (Haridas et.al., 2021).

5. Radix of *kayu legi* or licorice (*Glycyrrhiza glabra*)

Licorice radix contains saponins, flavonoid glycosides, triterpene saponins, glycyretinic acid, chalcone,

glabridin, licoridin, glykomarin, glycyrisic acid, liquiritigenin, isoliquiritigenin, and licochalcone A. It has pharmacological activities including detoxification, hepatoprotector, relieving shortness of breath, reducing coughing, and sheds phlegm, as well as anti-inflammatory and antitumor. It has the potential to inhibit airway hyperresponsiveness (AHR) and reduce eosinophil infiltration in the lungs. The contained flavonoids show anti-inflammatory activity, one of which is by repressing the inducible nitric oxide synthase (iNOS) expression. Licorice could down-regulate iNOS through the JAK2/STAT3 signal pathway. It has a detoxifying effect and reduces the side effects of drugs because its macromolecular and micromolecular components can form complexes and affect the solubility, permeability, distribution, and metabolism of medicinal ingredients. Licorice has also been reported to be used quite often in COVID-19 patients (Chen et al., 2020; Jiang et al., 2020; Luo et al., 2020). The extract of *Glycyrrhiza glabra* was reported to play a role in reducing the mRNA expression of pro-inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1) (Rizvi et.al., 2022).

Herbal combinations as adjunctive therapy for COVID-19

One of the new innovations in the Indonesian herbal medicine industry is the production of a combination of medicinal plants containing five active ingredients: *Phyllanthus niruri*, *Andrographis paniculate*, *Anacardium occidentale*, *Zingiber officinale*, and *Glycyrrhiza glabra*. The details of each of this herbal component in COVID-19 was explained in Table 1. This combination of herbs is expected to provide various

benefits from the five active substances, including the role of anti-inflammatories, anti-oxidants, bronchodilators, analgesics, antivirals, etc. The potential benefits are also intended to provide a synergistic effect in improving patient's condition, including optimizing its role as an immunomodulator. This herbal combination is also supposed to be an adjunctive therapy for COVID-19 patients. It has been produced on a national industry scale and has an official distribution permit (BPOM, 2020).

In addition to the various benefits previously described, we have to anticipate the risks of using this product. In this critical pandemic situation, adverse events may have a lower risk compared to the risk of COVID-19 progression itself. We must consider wisely the possibility that the potential benefits of this product outweigh the risks in general (Kumar & Al Khodor, 2020; Oladele et al., 2020; WHO, 2023).

Establishing the efficacy and safety of traditional and natural medicines through rigorous clinical trials is essential to be part of official therapeutic recommendations. These studies were expected to encourage the progress of Indonesian-based herbal medicine industries. Further studies are mandatory to promote the potential of the Indonesian-based herbal medicine industry, as well as support from the government and all related parties (Kumar & Al Khodor, 2020; Oladele et al., 2020; WHO, 2023).

CONCLUSION

The pathogenesis of COVID-19 is still being explored and has become the basic development of more effective treatments. This pandemic situation encourages several efforts to evolve new drugs, including medicinal plants. The pharmacotherapeutic activity of Indonesia-based medicinal plants has also been explored, including *Phyllanthus niruri*, *Andrographis paniculata*, *Anacardium occidentale*, *Zingiber officinale*, and *Glycyrrhiza glabra*. The combination of these five ingredients is supposed to provide a synergistic effect to improve patient's condition, including for COVID-19 cases. The herbal combination has the potential to provide a synergistic effect, but this is still limited to *in silico* and animal research. Potential risks also need to be anticipated, including the possibility of various side effects. Establishing the efficacy and safety of this herbal medicine is essential through rigorous clinical trials to provide robust scientific evidence.

CONFLICT OF INTEREST

The authors stated there are no conflicts of interest.

AUTHORS' CONTRIBUTION

Conceptualization and study design, AR, SP; investigation, AR, SP, FY, FS; writing the original draft preparation, AR, SP; review and editing, AR, FY, FS, CMR. All authors have read and given approval for the manuscript to be published.

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