

Potential of Jamu in Nanotechnology Perspective as an Alternative Treatment for Covid-19

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ABSTRACT

The world seems to be recovering at this time, especially because of the 2019 global coronavirus disease pandemic (COVID-19) caused by the Coronavirus 2 virus (SARS-CoV-2). This virus is similar to other β -coronaviruses through several steps to enter and bind angiotensin-converting enzyme 2 (ACE2) as the main receptor. This binding, particularly in the respiratory epithelium and alveoli of the lungs, affects harmony in human host cells. No specific vaccines and antivirals are available to date as drug investigations are still ongoing. However, many Indonesians consume herbal medicine, especially 'empon-empon' containing the Zingiberaceae family, to protect their health from COVID-19. So far, herbal medicine has shown good results to protect the Indonesian people in fighting SARS-CoV-2 empirically. In this review, we describe the characteristics of SARS-CoV-2, herbal ingredients that are active in fighting COVID-19, and applied nanotechnology challenges to COVID-19. Therefore, it is proposed to develop herbal medicine with a nanotechnology approach to increase the efficacy and potential of herbal medicine in fighting COVID-19. Moreover, the development of nanotechnology for Indonesian jamu will increase the value of Indonesian jamu and raise its reputation in the world.

Keywords: COVID-19; SARS-CoV-2; jamu, nanotechnology; 'empon-empon'

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INTRODUCTION

The COVID-19 pandemic has become a world problem as a global pandemic, where this case was first discovered in Wuhan Province, China, in December 2019 (Khanna et al., 2020)(Munster et al., 2020). The new coronavirus is the sole agent causing a new infectious disease known as severe acute respiratory syndrome coronavirus2 (SAR-Cov2). Coronavirus-2 is the seventh strain of the Coronaviridae family (Fuzimoto & Isidoro, 2020; Khanna et al., 2020). Coronavirus infections, including SARS-CoV2, can cause death due to pulmonary respiratory failure due to systemic cytokine storms (Liu & Ying, 2020).

Secretion of several cytokines and mediators, such as interleukin (IL) -1 β , IL-6, IL-7, IL-8, IL-18, interferon (IFN) - γ , tumor necrosis factor (TNF) - α , monocyte chemoattractant peptide (MCP) -1, and granulocyte-colony stimulating factor (G-CSF) have been shown to increase in COVID-19 patients (Borish & Steinke, 2003; Liu & Ying, 2020). In addition, pro-inflammatory cytokines play an important role in the process of disease pathogenesis. Production of IL-1 β occurs following viral attachment to a receptor such as a toll (TLR) and activation of the inflammasome. Elevated IL-6 levels are associated with the development of COVID-19, and

monitoring of this cytokine may be a potential marker in the prognosis of high-risk patients. TNF- α also plays a stimulating role in the development of inflammation and increases in the blood and peripheral tissues of COVID-19 patients (Borish & Steinke, 2003; Khanna et al., 2020). Studies on inflammatory diseases, such as Multiple sclerosis (MS), Inflammatory bowel disease (IBD), Rheumatoid arthritis (RA), and Ankylosing spondylitis (AS) have shown that increased production of IL-1 β , IL-6, IL-18, and TNF - α is directly related to disease activity. Therefore, it is speculated that the same applies to COVID-19, and the severity of the disease may be related to the production of inflammatory cytokines. The study was conducted to overcome this global pandemic to find drugs and antivirals (Liu & Ying, 2020).

There is no specific antiviral recommended, there is no vaccine available, and there is no medication approved for the treatment of COVID-19 being today. At present, the treatment is focused on the symptomatic of the disease, and the patients who have a severe infection are treated by oxygen therapy. In respiratory failure cases, mechanical ventilation is needed, while hemodynamic support is crucial for septic shock management (Hamid et al., 2020).

To treat COVID-19, the clinicians are using some of the drugs which potent to overcome this disease, not only the common antiviral such as remdesivir, favipiravir, and lopinavir-ritonavir that used against COVID-19 but also antimalarial such as chloroquine and hydroxychloroquine. As adjuvant therapies, dexamethasone and acetaminophen are using to fight SARS-CoV-2 as well. All of them are displaying acceptable outcomes; nevertheless, they still need more investigations to have the best treatment for COVID-19 (Pooladanda et al., 2020). So far, the main treatment for SARS-CoV-2 is using antivirals that prevent the virus from entering the cells and avoiding it from replication and the movement of infected cells to the others. Meanwhile, antibiotics have no contribution to defeating SARS-CoV-2 directly, but they could be helped if there is a secondary bacterial infection due to COVID-19 (Abd El-Aziz & Stockand, 2020). All of the compounds that have a good potent for COVID-19 are being examined mainly regarding the efficacy and the safety to beat 2019-nCoV. One of the most promising compounds is remdesivir, an antiviral drug with an action mechanism via terminating the RNA transcription prematurely, then inhibits the viral replication result in disturbs the ability of the virus to reproduce themselves (Jean et al., 2020).

Another alternative that researchers have taken to address this case is to use convalescent plasma (CP) to treat COVID-19, the classic adaptive immunotherapy that has been used to prevent and treat many infectious diseases for more than one hundred years. This plasma treatment could be more effective for COVID-19 patients in the early stages before the virus can do more serious damage to the lungs. CP is a promising and safe, effective method for the treatment of recurring and recurring pathogens, especially in the absence of proven antiviral compounds or vaccines (Rojas et al., 2020). Concerning this approach, the FDA has permitted the use of blood plasma from patients who have recovered from COVID-19 with high titers of antibody immune response (Chen et al., 2020).

Researchers around the world are not only exploiting specific vaccines and antivirals chemically and biotechnology but also exploring natural products and/or herbal medicines to treat COVID-19 (Ang et al., 2020). The various viral infection steps and replication can be inhibited by natural products, although the mechanisms are not yet fully characterized. Natural products contribute to reducing morbidity and mortality due to 2019-nCoV infection through their function as immunomodulators and suppressing the inflammatory process (McKee et al., 2020). Compounds that have the potential to inhibit coronavirus infection in humans include quercetin, myricetin, psoralidin, caffeic acid, tryptanthrin, lycorine, scutellarein, silvestrol, saikosaponin, isobavachalone,

and griffithsin. If the therapeutic activity of lycorine as an antiviral is not more than the level of plasma toxic concentration, this compound could be a good choice against the coronavirus. However, small molecules identified as the most potent for coronavirus inhibitors are categorized as polyphenols, which consist of conjugated fusion rings (Mani et al., 2020).

Known as a country that has a large biodiversity, Indonesian researchers also hardly exploit natural products for the treatment of COVID-19. A typical Indonesian natural product called jamu which has been practiced for centuries to maintain health and treat diseases. During the pandemic, many people in Indonesia consumed herbal medicine as a weapon to combat SARS-CoV-2 and so far, they have been healthy. However, the pharmacological activity associated with herbal medicine is quite abundant according to empirical data, so it is necessary to carry out further research to prove its efficacy scientifically and to ensure its safety (Elfahmi et al., 2014). To prevent cytokine storms, residents in several countries use herbs that have anti-inflammatory activity, one of which is Indonesia.

People in Indonesia from generation to generation know and consume traditional medicine or better known as jamu. Jamu, which comes from the ancient Javanese word "jampi" (magic potion), is commonly consumed to relieve pain and inflammation or to treat chronic diseases, such as rheumatism and cancer. In Indonesia, hundreds of ethnic groups have developed their own traditional recipes, most of which are derived from medicinal plants. These plant-based medicines contain one ingredient or a mixture of several elements. Plants in the Zingiberaceae (ginger) family, including Curcuma, Kaempferia, Zingiber, Alpinia, Elattaria, and Costus, have become mainstay elements in herbal medicine, along with other vegetable ingredients. Consumption of herbal medicine during the Coronavirus Disease 2019 (COVID-19) pandemic increased sharply, resulting in an imbalance in supply with the demand for these ingredients. Jamu, which is a traditional Indonesian medicine that has been known from generation to generation, is thought to increase immunity, making it the most popular alternative treatment during this pandemic. Nanotechnology development to increase antiviral activity and many natural products have been developed in dealing with COVID-19. Nanotechnology development can be adapted to detect, treat, and prevent this disease (Chan, 2020). In addition, nanoparticles can enhance the therapeutic effect and minimize drug side effects. The properties of nanoparticles are significant in antiviral treatment where high drug concentrations are required and overcome their limitations, such as bioavailability (Milovanovic et al., 2017).

Based on the description above, this review presents the results of nanotechnology modification to increase the efficacy of herbal medicine against SARS-CoV-2. Preparing jamu in nanotechnology will increase the value of the herbal medicine itself and provide a higher bioavailability as an alternative to fight COVID-19.

METHODS

This literature review was performed using the google search engine to find relevant references. The search terms encompass 'COVID-19', 'nanomedicine', 'herbal nanoformulations', 'herbal nanoparticles', 'jamu', 'natural products', 'herbal medicine', and 'herbal nanotechnology'. The period time for searching the references for this review is 11 May 2020 to 31 October 2020.

RESULTS AND DISCUSSION

The Characteristics of SARS-CoV-2

The best way to treat COVID-19 is by knowing the characteristics of SARS-CoV-2 first, clearly. SARS-CoV-2 is the seventh coronavirus that is known to cause human disease. Coronavirus (CoV) is a group of huge and enveloped viruses with positive-sense, single-stranded RNA genomes. CoV is a zoonotic pathogen that can infect humans via inter-species transmission. This virus could be divided into four types: alpha, beta, gamma, and delta coronavirus (Wang et al., 2020). Human coronavirus are dominantly associate with upper respiratory tract illness with the range from mild to moderate condition include the common cold (Vellingiri et al., 2020). CoV represents a continuous pandemic threat; humans have experienced two CoV-related health security crises since 2002 (Chang et al., 2020), i.e. severe acute respiratory syndrome coronavirus (SARS-CoV) which appeared in China and the middle east respiratory syndrome coronavirus (MERS-CoV) which emerged in Saudi Arabia in 2012 (El Zowalaty & Järhult, 2020).

Both SARS-CoV and SARS-CoV-2 are part of the β -genus of CoV. An envelope-anchored spike protein mediates CoV and goes through into the host cells by binding to the host receptor firstly and after that merge the viral and the host membranes (Shereen et al., 2020). A fined receptor-binding domain (RBD) of SARS-CoV spike particularly recognizes its host receptor angiotensin-converting enzyme 2 (ACE2) within the respiratory epithelium and alveoli of the lungs (Yan. et al., 2020). When compared with previously isolated SARS-CoV strains, 2019-nCoV tends to use the human ACE2 less efficiently than human SARS-CoV, which was found in 2002. But SARS-CoV-2 likely uses human ACE2 is more efficient than human SARS-CoV, which

emerged in 2003. Since the ACE2-binding interaction has proven to be one of the foremost vital determinants of SARS-CoV infectivity, SARS-CoV-2 has developed the capacity to infect humans and several capabilities to transmit among humans (Wan et al., 2020).

Processing of Transmission of SARS COV-2 to Host Cells

The process of SARS-CoV2 infection in host cells requires a special receptor, the ACE2 receptor. The interaction process between viral proteins and host cell ACE2 receptors is the first step in infection. Henceforth, the virus will have access to the host cytosol by carrying out proteolytic cleavage, where this process is influenced by the amount of acid from the spike protein by cathepsin or other proteases (Nugraha et al., 2020). The spike protein cleavage process occurs at two sites in the S2 portion. The first cleavage has a function of separating the RBD domains with S protein fusion, and the second cleavage serves to expose the fusion or splitting peptides in S2. The fusion between the virus and the host cell usually occurs within the endosome, which is acidified. This process is followed by the joining of two heptad replicates in S2 to form a six-helix antiparallel bundle. Overall, the occurrence of new S1 and S2 insertions is likely to influence the increase in spike protein cleavage by some proteases beyond that for other SARS-like viruses. The formation of the bundle leads to the mixing of the viral cell membrane and the host cell and results in the fusion and release of the viral genome into the cytoplasm (Huang et al., 2020; Jaimes et al., 2020).

Jamu for COVID-19

Naturally, there are hundreds of herbs that have been known to possess a significant amount of antiviral activity when used. They may be readily available in the garden or in the local market, and the others may prove quite hard to find. Olive leaf, balm from lemon leaf, ginger, chlorella, chamomiles, cayenne pepper, bilberry, black cohosh, chili, garlic, astragalus, licorice root, etc. are known used as antiviral, traditionally (James, 2015).

More advances, Traditional Chinese Medicine (TCM) was used to prevent and treat SARS in 2003 and also for the treatment of H1N1 infection in 2009. According to these experiences, TCM has been widely used in Chinese hospitals now to treat COVID-19. So far, the intervention of TCM can reduce the severe symptoms of patients (Xu & Zhang, 2020). However, the observation on SARS patients with emerging COVID-19 treated by TCM excluded the safety aspect. Considering the information that several herbs used in the TCM contain nephrotoxins and mutagens; meanwhile, the toxicological properties of most Chinese herbal medicines must still be fully understood (Yang et al., 2020).

Many natural products have good efficacy against viral infection as they can influence the role of viral proteins associated with virulence. Most of them have a common mechanism as an antiviral agent by inhibiting the viral replications. Chemical compounds from natural products such as lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, and 7-methoxycryptoleurine have antiviral activity in the nanomolar concentration and could be lead for further drug development (Islam et al., 2020).

During the pandemic, many people in Indonesia consumed 'empon-empon' as an alternative to protect themselves and to defeat COVID-19. 'Empon-empon' has a closed connection to jamu and more specific, 'empon-empon' is a part of jamu. 'Empon-empon' has two meanings (Riswan & Sangat-Remantyo, 2002), those are:

- Empon-empon is yard medicinal plants. Almost every family in the village in Java island has its own yard to cultivate medicinal plants. Hence, they can reach 'empon-empon' easily and use it to protect their health and curing their illness at any time.
- Empon-empon is also a group of medicinal plants belonging to the ginger family (Zingiberaceae) such as ginger (*Zingiber officinale* Roscoe), turmeric (*Curcuma longa* L.), Javanese turmeric (*Curcuma xanthorrhiza*), greater galangale (*Kaempferia galanga* L.), and galangale (*Alpinia galanga* (L.)). Some of them are used for flavors, dyes, spices, and ornamental plants.

Empon-empon containing bioactive curcumin, which has known for its therapeutic potential as an antibacterial, antifungal, and antiviral (Moghadamtousi et al., 2014). Curcumin is a complex molecule with numerous biological targets and diverse cellular effects, such as anti-inflammation, antioxidant, and anti-cancer. Furthermore, curcumin is non-toxic for humans at high doses (Epstein et al., 2010). Conforming to these investigations, 'empon-empon' has a good promising as a therapeutic agent for the treatment of COVID-19. Herbal medicine consists of several herbal mixtures, which are formulated with certain comparisons based on hereditary experiences. Herbal plants, as raw materials for herbal medicine, have been proven to have antiviral, anti-inflammatory, antibacterial activity, and so on. Several studies were conducted to prove that herbal plants, especially herbs, can be used as an alternative to the prevention and antiviral treatment of SAR CoV-2, either through pre-clinical or clinical approaches. Some herbal raw material plants as candidates for SAR CoV-2 antiviral can be seen in Table 1.

Nanotechnology for COVID-19

Nanotechnology approaches have been explored as a therapeutic agent against coronavirus, include nanomaterial, nanoparticles, nanocomposites, etc. The development of Ag nanomaterials is a novel therapeutic approach to fight the alpha-CoV porcine epidemic diarrhea virus (PEDV) was first introduced in 2018. This study illustrated that Ag₂S nanoclusters (NCs) might control the proliferation of PEDV in treated Vero cells. The result showed that prevention of the viral growth and inhibition of synthesis of viral negative-strand RNA is associated with the treatment with Ag₂S NCs. The Ag₂S NCs also demonstrated definitely govern interferon (IFN)-stimulating gene proliferation and clearly regulate the expression of pro-inflammatory cytokines. These processes provoked the protection of the cells from PEDV infection and proposed that Ag₂S NCs could be a great choice as a therapy tool for the next investigation (Du et al., 2018).

Nanoformulation has been deployed for diphyllin as a therapeutic agent to cure feline infectious peritonitis (FIP), disease because of feline coronavirus. By inhibiting the acidification of endosomal in fcwf-4-cells, diphyllin is a vacuolar ATPase that could halt the uncoating of the virus and break the cellular virus entry. Diphyllin formulated with poly(ethylene glycol)-block-poly(lactide-coglycolide) as a nanocarrier improved the diphyllin inhibitory activity against FIP and increased the safety profile. This study displayed that nanoformulation of diphyllin was successful in defeating coronavirus and the results suggested that the approach could be a promising treatment to overcome CoV infection (Hu et al., 2017). Furthermore, a nanospheres/microspheres (NS/MS) using a device from biopolymeric material having a great promising to beat coronavirus was developed to tackle human coronavirus NL63 (Chen et al., 2016).

Thereby, it can be concluded that nanotechnology could improve antiviral applications against vary of coronavirus. Nonetheless, it is needed more studies about the treatment for COVID-19 using nanomedicines, deeply, and comprehensively (Nikaeen et al., 2020).

Nanotechnology in Jamu

Nanotechnology is identical to nanoparticles; in the nano size, particles have different properties as compared to the macro size. The role of nanoparticles is applied to all of the matter, include natural products. The effectiveness of natural products in the prevention and treatment of diseases could be improved by making them into

Table 1. Herbal raw material plants as candidates for SAR CoV-2 antiviral

Material	Active compound	Prediction interaction of active compounds with SAR-Cov-2	References
<i>Zingiber officinale</i>	6 - Gingerol	Gingerol exhibits binding affinity of -11.4082 KJ/mol, -12.9523 KJ/mol and -12.8835 KJ/mol with COVID-19 viral RNA binding protein (6W4B), N Terminal RNA Binding Protein (6VSB), Spike glycoprotein (6M3M) respectively. Molecular interaction between COVID-19 viral spike glycoprotein with Gingerol forms hydrogen-bonded interaction with Glu63, Arg89, Thr92, Asp129 residues and form non bonded interaction with Glu63, Lys66, Arg89, Thr92, Leu168, Pro169 residues of COVID-19 spike glycol protein. Molecular interaction between COVID-19 viral RNA binding protein with Gingerol makes hydrogen bonded interaction with Val42, Pro58, Ser60, Thr68 residues and form non bonded interaction with Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Ile66, Thr68, Ile92 residues of COVID-19 spike glycol protein.	(Nugraha et al., 2020; Rathinavel et al., 2020)
Black pepper	Piperdardiine	Piperdardiine exhibited interactions with COVID19 and the residues SER46, MET49, HIE41, GLN189, ARG189, ASP187, MET165, HIE164, THR24, THR25, LEU27, ASN142, and GLY143 play a crucial role in binding with ligands.	(Nandi & Mitra, 2020; Rajagopal et al., n.d.)
<i>Curcuma longa</i>	Curcumin	The anti-inflammatory mechanism of curcumin is to inhibit the production and release of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, TNF- α . Meanwhile, dissolved curcumin directly into the lungs dramatically reduced the pro-inflammatory cytokines IL-1b, IL-6, TNF- α in LAB cells, lungs and serum of mice with severe pneumonia caused by Klebsiella. In addition, curcumin also decreases the expression of many other inflammatory mediators, including MCP1 (CCL2), MIP11 (CCL3), GRO α (CXCL1), GRO β (CXCL2), IP10 (CXCL10), SDF1 (CXCL12), MMP-2, IFN-g., and MMP-9, which regulates immune cell activity and inflammatory response and increases fibrosis in the lungs after infection.	(Liu & Ying, 2020; Nugraha et al., 2020)
<i>Curcuma longa</i>	Xanthorrhizol	Xanthorrhizol has anti-inflammatory activity by inhibiting inflammatory cytokines in adipose tissue and expression of tumor necrosis factor (TNF- α). Research has shown that xanthorrhizol prevents recruitment of immune cells into adipose tissue to downregulate inflammatory cytokine genes. Xanthorrhizol also has the activity of reducing interleukin (IL-1 β) gene expression in muscle. Other studies have shown that xanthorrhizol can reduce serum IL-6 levels and increase serum transformation growth factor (TGF- β) in patients with SLE with hypovitamin D.	(Kim et al., 2014; Nugraha et al., 2020)

Table 1. (continued)

Material	Active compound	Prediction interaction of active compounds with SAR-Cov-2	References
Citrus fruit	Naringin	Naringin pretreatment significantly inhibited LPS-induced expression of HMGB1 protein and proinflammatory cytokines (COX-2, iNOS, IL-1 β and IL-6) expression in vitro. HMGB1 is a ubiquitous DNA-binding core protein and can be actively released by immune cells, such as macrophages and monocytes, following inflammatory stimuli. HMGB1 also acts as a pro-inflammatory cytokine and regulates the storm of cytokines, up-regulating cytokines such as TNF- α , IL-6, IL-1 β , and IL-8.	(Cheng et al., 2020)

nanoparticles. One of the main reasons regarding the effectiveness of nanoparticles is the improvement of bioavailability. Having a good bioavailability will improve the pharmacokinetic profile that results in better therapeutic effects (Zhang et al., 2015).

Sulistyo and colleagues (2017) observed that green tea nanoparticles have better effects in ironized mouse model thalassemia as compared to the green tea as a free compound. The green tea extract prepared into nanoparticles using chitosan as a carrier crosslinked with sodium tripolyphosphate (Sulistyo et al., 2017).

Another benefit of the application of nanoparticles in the delivery of natural compounds is the system can reach the specific target sites such as certain tissues, organs, and cells. Delivery of natural products with nanoparticles device gives critical impacts, especially minimizing the adverse effects of the active substances. Using a self-nano emulsifying drug delivery system (SNEDDS), quercetin demonstrated a protective effect against liver damage. The histopathological observation displayed that the inflammatory infiltrations induced by paracetamol significantly ameliorated (Ahmed et al., 2014).

Nanoparticles can also deliver the natural products with controlled release, mainly by formulating the herbal with a polymer as a carrier. Formulation of acerola, guava, and passion fruits by-products inside PLGA (poly(DL-lactide-co-glycolide) matrix demonstrated an initial burst then gradually followed by a slower rate. The release of the drug from the nanoparticles at a controlled rate is a crucial key since the drug release kinetics determine the concentration of the drug in the target site (Silva et al., 2014).

All of the natural products in Indonesia which have therapeutic effects as a medicine empirically are categorized as jamu. Accordingly, the efficacy and the

value of jamu should be improved using nanotechnology approaches. Various methods of preparation of nanotechnology approaches could be applied in jamu i.e., nanosuspension, nanopolymerization, oil, solvent, and surfactant-co-surfactant mixture, self-nanoemulsion, nanoprecipitation, ultrasonication, solvent emulsion and evaporation, hot homogenization, nanoencapsulation, nanofiber fabrication, electrospinning, and spray drying (Gopi & Amalraj, 2016).

CONCLUSION

Jamu is a traditional Indonesian medicine made from a mixture of several plants such as 'empon-empon', which has been used for generations in Indonesia as a supplement or medicine to increase endurance and cure diseases. During the pandemic, many people in Indonesia consumed 'empon-empon' to protect themselves from SARS-CoV-2. Further evidence-based research in Jamu is needed to conform its efficacy. Through a nanotechnology approach, the value and potential of Jamu can be increased and become a promising therapeutic option for the treatment of COVID-19. Moreover, the development of nanotechnology for Indonesian jamu will increase the value of Indonesian jamu and raise its reputation in the world.

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