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The Potential Roles of *Jamu* for COVID-19: A Learn from the Traditional Chinese Medicine

Dwi Hartanti, Binar Asrining Dhiani, Shintia Lintang Charisma, Retno Wahyuningrum*

Faculty of Pharmacy, Universitas Muhammadiyah Purwokerto, Indonesia

ABSTRACT

ARTICLE HISTORY

Received: June 2020 Revised: June 2020 Accepted: July 2020 As the pandemic of the coronavirus disease 2019 (COVID-19) continues while there is no drug and vaccine available, every effort to discover one should be considered. This review aimed to discuss the potential use of *jamu*, the Indonesian traditional herbal medicine, to deal with COVID-19 by following those of more-established traditional Chinese medicine (TCM). The online literature search using the PubMed database, as well as the circulars from the Indonesian Ministry of Health, were carried out to collect data up to June 07, 2020. The use of TCM for the treatment and prevention of COVID-19 has been officiated in the Chinese National Clinical Guideline on COVID-19 Associated Pneumonia, with shen-fu-tang + su-he-xiang pill and xiang-sha-liu-junzitang as the most frequently suggested formulae to treat severe and recovery stages of COVID-19, respectively. In Indonesia, the highly promoted product for the prevention of this disease is likely the adaptation of a TCM formula, while the use of some other formulae, which mainly containing Zingiberaceae, is suggested by the Government for the said purpose. The rationalization of the use of medicinal plants and suggested polyherbal formulae, based on their available pharmacological activity and the bioactive compounds, is also discussed in this review. The use of *jamu* for COVID-19, however, needs to be carefully considered for the limited scientific data available to support it.

Keywords: COVID-19; jamu; traditional Chinese medicine; herbal medicine

*corresponding author Email: retnowahyuningrum@ump.ac.id

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was announced as a global pandemic in February 2020. The cases exceeded 6.5 million cases and take toll death almost 400,000 people worldwide within four months, with the number of the total cases in America and Europe five times higher than those in Asia (WHO, 2020). Up to this day, there is no drug or vaccine available for COVID-19 therapy despite a massive effort from scientists around the world to discover them (Sanders et al., 2020). Repurposed drugs such as hydroxychloroquine, which initially seen as a prospective COVID-19 drug, have been proven to have no clinical benefit in the latest report, even though such a report has been claimed to be a flaw and resulted in an article retraction. The latest report on a double-blind, randomized, placebo-controlled trial of Remdesivir, a protide nucleotide analogs, resulted in shorter time recovery in hospitalized COVID-19 patients (Beigel et al., 2020). Hence, there is no clear evidence yet for any drug or vaccine that is beneficial for COVID-19 therapy.

The integrative treatment between conventional medicines with the centuries longstanding traditional ones, i.e., traditional Chinese medicine (TCM) and Ayurvedha, is believed to be useful for COVID-19

treatment. These traditional medicine systems have been part of Asian people's life to treat any kind of illness. TCM has been proven to provide beneficial prevention for viral infection diseases, including influenza, pandemic SARS, and H1N1 (Luo et al., 2020). Recently, a case report mentioned the recovery of a highly-suspected COVID-19 patient who consumed qingfei-pai-du formula (Ren et al., 2020). In the Chinese National Clinical Guideline on COVID-19 Associated Pneumonia, several formulae of TCM are suggested to treat each different disease stages (Chan et al., 2020). Jamu, the Indonesian traditional herbal medicine, is supposed to have similar potentials as those of TCM. However, the report on jamu for COVID-19 treatment is lacking up to this review is written.

In this review, the use of TCM, Ayurvedha, and *jamu* for COVID-19 cases are discussed. We will focus on the composition analysis on the most frequently suggested formulae in the Chinese Guideline and elaborate on their benefits claim. The information of the TCM formulae is then used for analyzing a registered *jamu* formulae that is highly promoted and claimed for COVID-19 treatment in Indonesia, i.e., Herbavid-19. We also list the medicinal plants and herbal medicine formulae mentioned in the circulars from the Indonesian Ministry of Health. Lastly, we explore the consideration that

Table 1. Plant constituents of the most popular herbal formulae for the treatment of COVID-19 (Ang et al., 2020)

Herbal formulae	Indicated for	The basic herbal composition
Shen-fu-tang + su-he-xiang pill	Severe stage	Panax ginseng C.A.Mey. roots, Aconitum carmichaelii Debeaux roots, Acorus calamus L. rhizomes, Curcuma longa L. rhizomes, Cornus officinalis Siebold & Zucc. pulps, Schisandra chinensis (Turcz.) Baill. fruits, Zingiber officinale Roscoe rhizomes, and Glycyrrhiza glabra L. rhizomes and roots + Liquidambar orientalis Mill. oleoresins
Xiang-sha-liu- junzi-tang	Recovery stage	Codonopsis pilosula (Franch.) Nannf. roots, preserved Astragalus propinquus Schischkin roots in honey, Atractylodes macrocephala Koidz. rhizomes, Wolfiporia extensa (Peck) Ginns sclerotia, Glycyrrhiza glabra rhizomes, and roots

needs to be applied for *jamu* usage for COVID-19, as well as the rationalization of the use of the suggested medicinal plants and polyherbal formulae. The data presented in this review were mainly retrieved from the online database PubMed (https://pubmed.ncbi.nlm.nih.gov/). The name of plants mentioned in this article is written according to the accepted name in The Plant List (http://www.theplantlist.org/).

TCM AND COVID-19

TCM is included in the sixth edition of the Chinese COVID-19 Guideline since the 2nd edition to the final 7th one (Chan et al., 2020). Further, 23 provinces in China have adapted this Guideline and issued TCM program in the provincial Guideline on COVID-19 prevention, while 26 provinces officially established the integrative TCM, which combined TCM with the conventional treatment for the COVID-19 patient (Luo et al., 2020; Yang Yang et al., 2020). More than 85% of the total confirmed COVID-19 patients were reported to have been treated with TCM. The treatment with integrative Chinese–Western medicine was given to all COVID-19 cases in Shanghai, while the first recovered patient in Beijing was also treated with this combination medication (Chan et al., 2020).

In the Chinese Guidelines, TCM is used for the treatment of mild, moderate, severe, and recovery stages of COVID-19, which utilized 23, 11, 31, and 21 herbal formulae, respectively. Among those 75 formulae, there are 17 most frequently recommended herbal formulae in different guidelines. The most popular herbal formulae are including shen-fu-tang + su-he-xiang pill and xiang-sha-liu-junzi-tang (Ang et al., 2020). A slight difference in the herbal compositions of those formulae in each Guideline is evidenced, with the basic herbal compositions is listed in Table 1. The exhaustive evaluation of the available data on the Chinese medicines for COVID-19, both traditional and modern, showed that the benefits of treatment are mediated by its capability for strengthening the body resistance and diminishing viral pathogenic factors (Zhou et al., 2020).

Glycyrrhiza glabra, Prunus armeniaca L., Ephedra sinica Stapf., Scutellaria baicalensis Georgi, and Atractylodes macrocephala were found to be the most frequently used plants used to treat COVID-19, which can be found in more than 35 herbal formulae (Ang et al., 2020). Glycyrrhiza glabra rich with glycyrrhizin, which showed antiviral activity against clinical SARS coronavirus isolates. Also, the well-recognized antiinflammatory and immunomodulatory activities of this plant might play significant roles in the treatment of COVID-19 (F. Chen et al., 2004; R. Yang et al., 2015). The potential efficacy of herbal medicines containing the later four plants in the treatment of COVID-19 might be related to their anti-inflammatory activities, which have been proven in various models (L. G. Chen et al., 2016; Liang et al., 2018; Minaiyan et al., 2014). Furthermore, amygdalin of Prunus armeniaca and extract of Scutellaria baicalensis protected bronchial epithelial cells in mice model with chronic obstructive pulmonary disease, while standardized extract of Scutellaria baicalensis ameliorated influenza A virus-induced acute lung injury (Jiao et al., 2019; W. K. Yang et al., 2019; Zhi et al., 2019).

Another prominent traditional medicine system included in the national Guideline of COVID-19 is Ayurveda, which is believed to improve the immunity system mediated by psychoneuroimmune mechanisms and the meaning response (Golechha, 2020; Rajkumar, 2020). One of the formulae championed for this purpose is chyawanprash, which is traditionally used for its immunomodulatory, antioxidant, and hepatoprotective activities as well as respiratory system rejuvenation effect (Sharma et al., 2019). The medicinal plants that are recommended in the guidelines are includes Allium sativum L., Cinnamomum verum J.Presl, Cuminum cyminum L., Curcuma longa L., Ocimum tenuiflorum L., Withania somnifera (L.) Dunal, and Zingiber officinale Roscoe. All of these recommended medicinal plants exhibited the immunomodulatory properties in the form of single plant preparation (Sheoran et al., 2017; Subhrajyoti & Shalini, 2020; Tabarsa et al., 2020).

Table 2. Rationalization of the use of the suggested medicinal plants for dealing with COVID-19 symptoms and maintaining the immune system

Plant name	Plant part	The main bioactive compounds	The underlying pharmacological activity
Curcuma longa	Rhizomes	Curcumin and a polysaccharide as immunomodulators (Salehi et al., 2019; G. G. L. Yue et al., 2010)	humoral antibody titers in mice (Afolayan et al., 2018). Curcumin modulated the immune responses
			Prolonged curcumin-injections was safe for functions of natural killer cells and antioxidative functions of macrophages as well as enhanced the mitogen and antigen-induced proliferation potential of T-cell (Varalakshmi et al., 2008).
			A polysaccharide stimulated in-vitro peripheral blood mononuclear cells (PBMCs) proliferation and cytokine production (G. G. L. Yue et al., 2010).
Curcuma zanthorrhiza	Rhizomes	Curcumin as immunomodulator	The methanolic extract showed significant inhibitory activity on CD18/11a expression (Harun et al., 2015).
Zingiber officinale var Rubrum	Rhizomes	6-gingerol, 6-shogaol, and The oleoresin microcapsules showed antioxidant activity (Jayanudin et al., 2019). 8-shogaol as antioxidants (Ghasemzadeh et al., 2016) The ethanolic extract had antioxidant activity (Ghasemzadeh et al., 2016).	
Psidium guajava	Leaves	Quercetin and other polyphenols as immunostimulant; quercetin, gallic acid, ferulic acid, and caffeic acid as antioxidant (Gutiérrez et al., 2008; Laily et al., 2015)	The water and ethanolic extracts exerted in-vitro immunostimulatory activity in the lymphocyte proliferation assay (Laily et al., 2015).
			The crude ethanolic extract, its fractions, and some isolated compounds exhibited immunomodulatory effects in the head kidney leukocytes of striped catfish (Nhu et al., 2020).
Phyllantus niruri	Aerial parts	Phyllanthin, hypophyllanthin, niranthin, phyltetralin, astragalin, quercetin, corilagin, catechin, geraniin, gallic acid, and ellagic acid as immunomodulator (Jantan et al., 2019)	The aqueous extract was capable of dose-dependently inducing proliferation of PBMCs, increasing the release of nitric oxide, and enhancing phagocytic activity of macrophages isolated from tuberculosis patients (Putri et al., 2018).
			The aqueous extract exerted anti-inflammatory and antinociceptive activities in rats carrageenan- and histamine-induced rats and acetic acid-induced mice, respectively (Adedapo & Ofuegbe, 2015).

Table 2. continued

Plant name	Plant part	The main bioactive compounds	The underlying pharmacological activity
Andrographis paniculata	Aerial parts	Andrographolide and other related diterpene lactones as immunomodulator; 5 - h y d r o x y - 7 , 8 - dimethoxyflavone, 5-hydroxy-7,8-dimethoxyflavanone, β-sitosterol, stigmasterol, ergosterol peroxide, 1 4 - d e o x y - 1 4 , 1 5 - dehydroandrographolide, and 19-O-acetyl-14-deoxy-11,12-didehydroandrographolide as antiinflammatory (Chao et al., 2010; Hossain et al., 2014).	and IFN-γ, as well as modulated the number of regulatory T cells in the carcinogen-induced esophageal cancerous rats (G. GL. Yue et al., 2019). The isolated anti-inflammatory compounds showed transcriptional inhibitory activity of NF-kappaB, as well as secretory reduction of TNF-alpha, IL-6, macrophage inflammatory protein-2 (MIP-2), and nitric oxide (NO) in LPS/IFN-gamma, stimulated RAW 264.7 macrophages (Chao et al., 2010).
Moringa oleifera	Leaves	Niaziminin B as immunomodulator; kaempferol-3-glucoside and chlorogenic acid as analgesic (Agarwal & Ambwani, 2018; Martínez-González et al., 2017)	The hexane and ethanolic extracts showed antinociceptive, antiinflammatory, and antiarthritis induced
Allium sativum	Bulbs	Diallyl monosulfide, diallyl disulfide, diallyl trisulfide, diallyl tetrasulfide, diallyl pentasulfide, and diallyl hexasulfide as immunomodulators (Oosthuizen et al., 2017)	

JAMU AND COVID-19

In contrast, the use of jamu is not recognized in the Guideline of COVID-19 Patients (Indonesian Society of Respirology, 2020). Despite a lack of scientific proof, several medicinal plants and herbal medicines have been championed and highly consumed by Indonesian in the hope that they will be protected from contracting the virus. Among those herbal medicines, Herbavid-19® was the highly promoted jamu for the COVID-19 medication. It consists of Arctium lappa L. fruits, Coix lacryma-jobi L. kernels, Curcuma zanthorrhiza Roxb. rhizomes, Forsythia suspensa (Thunb.) Vahl. fruits, Glycyrrhiza glabra L. roots, Imperata cylindrica (L.) Raeusch. rhizomes, Lonicera japonica Thunb. flowers, Lophatherum gracile Brongn. leaves, Mentha arvensis L. leaves, Pogostemon cablin (Blanco) Benth. leaves, and Nepeta tenuifolia Benth. Leaves. Herbavid-19® was registered with the claims of helping to maintain the immune system and relieve the symptoms associated with cough, fever, and sore throat (Indonesian NADFC, 2020b). Although Herbavid-19® is registered as traditional medicine made in Indonesia, its formula resemble the classical TCM yin-giao formula, which mainly consists of the primary plant materials of Lonicera japonica and Forsythia suspensa. Yin-qiao is traditionally used for the prevention and treatment of respiratory tract infection and has been proven to improve the function of the upper respiratory mucosal immune system of mice with bacteria- and virusesstimulated upper respiratory mucosal dysfunction (Liu et al., 2015). Yin-qiao-san is another modification of yin-qiao included in the Chinese COVID-19 Guideline, which is mostly used in combination for the treatment of mild and moderate stages of COVID-19. For mild cases, yin-qiao-san is particularly indicated for expelling phlegm, relieving cough, and restoring normal lung function in feverish patients (Ang et al., 2020; Xu & Zhang, 2020). Previously, yin-qiao-san, in combination with ma-xing-shi-gan, has clinically proven to reduce the time of fever resolution in patients with mild infection of H1N1 virus (Wang et al., 2011). However, yin-qiao-san is not included in the Chinese Guideline or evaluated in any on-going clinical trials of TCM for the treatment of COVID-19 (Yang Yang et al., 2020).

The Indonesian Government has suggested the use of some medicinal plants as immunostimulatory agents to deal with COVID-19 based on the available safety and efficacy data. These medicinal plants are *Curcuma longa*, *Curcuma zanthorrhiza*, *Zingiber officinale* Roscoe var *Rubrum*, *Psidium guajava* L, *Phyllantus niruri* L, and *Andrographis paniculata* (Burm.f.) Nees (Indonesian NADFC, 2020d). The use of *Moringa oleifera* Lam. and *Allium sativum* for their immunomodulatory activity and capability of relieving the symptoms of COVID-19

i.e., cough and sore throat, are also proposed by the Government. There are some herbal formulae intended for the same purpose as well (see Table 3), in which palm sugar (processed from exudates *of Cocos nucifera* L. or *Arenga pinnata* (Wurmb) Merr.) is commonly added to enhance the taste of the concoction (Ministry of Health of the Republic of Indonesia, 2020).

Recently, the Government published 'Informatorium Obat Modern Asli Indonesia (OMAI) di Masa Pandemi COVID-2019'. The OMAI term refers to standardized herbal medicine and fitofarmaka products, which according to the regulation of the Head of National Agency of Drug and Food Control no HK.00.05.4.2411, are those with standardized active constituents and have shown efficacy in preclinical or clinical studies. In total, there are 15 standardized herbal medicine and ten phytomedicine products available for dealing with COVID-19 symptoms or improving the immune system included in the informatory (Indonesian NADFC, 2020c). Furthermore, there are two immunomodulatory products registered as traditional medicines that are being clinically evaluated in patients with COVID-19 in June 2020. The first product is prepared from *Cordyceps* militaris (L.) Fr. sclerotia, while the second one is the polyherbal formula consist of Zingiber officinale var Rubrum rhizomes, Phyllanthus niruri aerial parts, Andrographis paniculata aerial parts, and Blumea balsamifera (L.) DC. leaves (Indonesian NADFC, 2020a; Uly, 2020).

CONSIDERATION OF JAMUUSES FOR COVID-19

The COVID-19 pandemic brings opportunities and challenges for researchers to discover effective treatments, including those originated from herbal medicines. Exploration of the active compounds from the natural product is a strategy that should not be missed, but the rush on claiming the efficacy without sufficient scientific evidence must be avoided. In Indonesia, herbal medicines are grouped into three categories, i.e., jamu, standardized herbal medicine, and fitofarmaka. The efficacy claim of jamu is based on the empirical data although the biological activity of commonly used plants in jamu has been scientifically investigated (Elfahmi et al., 2014). Indonesian Government encourages the use of the potential domestic resources for handling COVID-19. However, there is no herbal medicine that is registered for the prevention and treatment of COVID-19 in Indonesia. The claim of the efficacy of the products available for dealing with COVID-19 is more on the function of maintaining and increasing the human immune system. The widely used of herbal products, especially the products which claim formaintaining the human immune system and is associated with COVID-19 prevention or treatment, needs to be carefully considered and well

Table 3. Rationalization of the use of the suggested herbal formulae for dealing with COVID-19 symptoms and maintaining the immune system

Formula name: Plant constituents	The main bioactive compounds	The underlying pharmacological activity	Traditional uses
Formula 1: Cinnamomum verum barks, Citrus aurantifolia (Christm.) Swingle fruits, and Zingiber officinale var. Rubrum rhizomes	its analogs of Cinnamomum	leukocytes and enhancement phagocytosis of leukocytes by <i>Citrus aurantifolia</i> , amelioration of collagen type-II induced arthritis in mice by <i>Cinnamomum verum</i> , and antioxidant activity of	The variation of the <i>wedhang jahe</i> , traditionally used for warming the body, improving the appetite, aiding digestion, and helping with rheumatic pain (Beers, 2001)
Formula 2 : Alpinia galanga (L.) Willd rhizomes., Citrus aurantifolia fruits, and Curcuma longa rhizomes	Curcumin and a polysaccharide as immunomodulators	immune response by Alpinia galangal,	The modification of the classical <i>jamu kunyit asam</i> formula, traditionally used as a general tonic for maintaining overall health (Andrie et al., 2014)
Formula 3 : Curcuma zanthorrhiza rhizomes, Phyllanthus niruri aerial parts, and Zingiber officinale var. Rubrum rhizomes	phenolic compounds of <i>Phyllanthus niruri</i> as immunomodulators; 6-gingerol,	The immunomodulatory, anti-inflammatory, and antinociceptive activities of <i>Phyllanthus niruri</i> and <i>Curcuma zanthorrhiza;</i> the antioxidant activity of <i>Zingiber officinale</i> var. <i>Rubrum</i> (Adedapo & Ofuegbe, 2015; Putri et al., 2018)	The variation of the classical <i>jamu temulawak</i> , traditionally used for hepatoprotection (Tampubolon et al., 2014)
Formula 4 : Kaempferia galanga L. rhizomes, Oryza sativa L starches, and Pandanus amaryllifolius Roxb., leaves	as immunomodulator, essential	leukocytes and enhancement phagocytosis	The variation of the classical <i>jamu beras kencur</i> formula, traditionally used for a general tonic and invigorating, relieving tiredness, improving blood circulation and appetite (Beers, 2001)

communicated to the public. Nevertheless, scientific studies to prove the efficacy of popular products need to be conducted.

There are four aspects need to be considered in the use of jamu to deal with COVID-19. First, the safety of the product should be guaranteed. Although jamu is used for a long time, there is no such evidence that the use of COVID-19 treatment is safe. The use of herbal medicines for therapeutic purposes on COVID-19 focused on the symptoms relieving as it is generally showed the best benefits in the chronic, ongoing post-infection symptoms rather than its acute stage (Wardle, 2020). While most of the herbal medicines exhibit immunomodulatory properties, cytokine storms which is caused by the hyperstimulation of the immune system, is characterized as the most dangerous and potentially life-threatening event related to COVID-19 (Coperchini et al., 2020; Wardle, 2020). Second, the evidence of the safety and efficacy of herbal medicines should be obtained based on the clinical trials. As of March 2020, there are 14 clinical trials of TCM for the treatment of COVID-19 (Yang Yang et al., 2020). In June 2020, there are two clinical trials of Indonesian herbal products for the same purpose in Jakarta. However, until to date, there is no result of those studies being published. Before the clinical trial of the herbal products is conducted, pre-clinical data must show the promising results on its safety and efficacy for further development steps. The efficacy data obtained from both in-vitro and in-vivo studies can be used as the rationale for the further clinical trial of selected plants or polyherbal formulae for prevention and alleviating the symptoms of COVID-19. The main bioactive compounds and the underlying pharmacological activities of the suggested medicinal plants and polyherbal formulae associated with COVID-19 are listed in Table 2 and 3, respectively.

Third, the molecular mechanism underlined the pharmacological effects of herbal medicine in COVID-19 treatment is still unclear. So far, the available data are obtained from the in-silico experiments, e.g., screening of classical TCM used for treating viral respiratory infection demonstrated that the active compounds exerted its activities through regulation of viral infection, immune and inflammation reactions, as well as hypoxia responses. In addition, hesperidin, a flavonoid commonly found in Citrus sp. peels, which is popularly championed to be natural prevention of COVID-19 in Indonesia, was reported to bind strongly to human angiotensin-converting enzyme-2 (hACE-2) and RNA dependent RNA polymerase (RdRp) as SARS-CoV-2 infection potential targets (Joshi et al., 2020; Zhang et al., 2020). Lastly, the potential danger of the delay in medical treatment due to jamu consumption should be recognized. Since herbal medicines are sold

as over the counter product and can be accessed without a doctor's prescription, their use as self-treatment of COVID-19 by patients who experience symptoms is highly possible (Yichang Yang, 2020). *Jamu*, and other herbal medicines, in general, should not be used in an emergency condition, including in the acute phase of viral infection. Delay in getting the right treatment in COVID-19 cases prolong the recovery process. In fact, in some cases, this delay can be fatal if the virus continues to replicate quickly in the patient's body.

It is crucial to communicate the safe practice of *jamu* uses to the public. The products registered by the National Agency of Drug and Food Control are, at least, guaranteed to be safe to use, and hence should be the first criteria to be considered before consumption. Furthermore, the packaging, label, and expired date of a given product should be checked before it is used. In case *jamu* is self-prepared from raw material in the household setting, the selection and identification of the raw materials, the washing process, boiling process, the equipment used and also the overall sanitation and hygiene aspects need to be considered as they affect both its efficacy and safety (Ministry of Health of the Republic of Indonesia, 2020).

CONCLUSION

Unlike the prominent position of TCM for the treatment and prevention of COVID-19 in China, the use of *jamu* in Indonesia still has to take a long and steepy way to be used for this purpose. Further studies on the efficacy and safety of *jamu* products for COVID-19 in humans and also its molecular mechanisms are needed. Additionally, the safe use of both registered and suggested homemade *jamu* products should be well communicated to the public.

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