



Herbs in Treatment Covid 19, Recommended or Not?

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ABSTRACT

Since March 2020, Covid 19 has been declared as global health issue. In common knowledge a good immune is the antidote of the viral infection. The aim of study is to identify the used of herbs in treatment of Covid 19. Design of this study is systematic literature review. Inclusion criteria is only included human based experimental study. Exclusion criterias are review article, lab-based study (pharmaceutical network/ docking), and grey literature. Formulated keyword used "herbs AND immune AND Covid 19" in English and Bahasa Indonesia. Quality assesment in this study using JADAD Score. Based on online searching in 5 search enggines (Google Scholar, Pubmed, Sage Jurnal, Science Direct and Garuda), there are 5 clinical trials in final result. There was 40% publised in Pyhtomedicine Journal and each 20% others published in Integrative Medicine Journal, American Blood Journal, Medtrix. The used of herbs in management of Covid 19 given as prevention in healthy people, complementary or alternative medicine in confirmed or suspected case. Implication on clinical practise, the herbs could be recommended if the safety is proven by National Agency of Drug and Food Control. There was potential effect of herbs to reduced symptom of Covid 19.

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ABSTRAK

Kata kunci:

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Sejak Maret 2020, Covid 19 telah dinyatakan sebagai masalah kesehatan global. Secara umum, kekebalan yang baik adalah penangkal infeksi virus. Tujuan dari penelitian ini adalah untuk mengidentifikasi penggunaan herbal dalam pengobatan Covid 19. Desain penelitian ini adalah studi literatur sistematis. Kriteria inklusi hanya termasuk studi eksperimental berbasis manusia. Kriteria eksklusi adalah artikel review, studi berbasis lab (jaringan farmasi/ docking), dan literatur abu-abu. Kata kunci yang diformulasikan menggunakan "herbs AND immune AND Covid 19" dalam Bahasa Inggris dan Bahasa Indonesia. Penilaian kualitas dalam penelitian ini menggunakan JADAD Score. Berdasarkan penelusuran online di 5 mesin pencari (Google Scholar, Pubmed, Sage Jurnal, Science Direct dan Garuda), ada 5 uji klinis dalam hasil akhir. Ada 40% diterbitkan dalam Pyhtomedicine Journal dan masing-masing 20% lainnya diterbitkan dalam Integrative Medicine Journal, American Blood Journal, Medtrix. Penggunaan jamu dalam penanganan Covid 19 diberikan sebagai pencegahan pada orang sehat, pengobatan komplementer atau alternatif pada kasus konfirmasi atau suspek. Implikasinya pada praktik klinis, jamu dapat direkomendasikan jika terbukti keamanannya oleh Badan Pengawas Obat dan Makanan. Ada potensi efek herbal untuk mengurangi gejala Covid 19.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that is known as Covid 19, which has become a worldwide pandemic. The first identification of this virus infection was in December 2019 in Wuhan, China (Sheng, 2020). The rapid spread of the virus in 2 weeks has hit 114 countries with a total of 118,000 cases and 4291 deaths. Based on this impact, WHO declared a Covid 19 pandemic on March 11, 2020 (WHO, 2020). In January 2021, the number of cases continues to increase to 89,416,559 confirmed cases, including deaths 1,935,028 (WHO, 2021)

CDC (2020) sets standards for preventing transmission by using face mask, washing hands and maintaining social distancing. This is related to the transmission of Covid 19 through droplets. Airborne or aerosol transmission may also occur in certain situations, such as during intubation. In this situation, the precautionary standard must be increased, namely the use of N95 masks and cover all. Other efforts made are 3T (testing, tracing and treatment). Testing is done in diagnosing positive cases through the RT PCR swab test while the rapid test is used as a screening. Next, close contact tracing of suspected and positive cases was carried out. Treatment is carried out by self-quarantine for cases of mild infection, while cases of severe infection need special management in health services (Kemenkes RI, 2020).

The current management of Covid 19 has experienced gaps in many aspects related to the imbalance of the number of resources and needs, especially in the 3T protocol. This is because the 3T procedure is not an easy task. Actions do not guarantee the effectiveness of reducing transmission in communities even like Korea, which has done digital tracing (The Conversation id, 2020). The tracing procedure preceded by RT PCR testing should take at least 3-12 days. During this time the patient tends to be impatient with uncertainty. Meanwhile, the standard therapy accepted by the FDA is antiviral redemsevir and conventional therapy does not guarantee a cure above 90% in severe cases (NIH, 2020).

Another mechanism that can be a solution is to increase immunity. Strong immunity will provide immunity against viral infections and speed healing. This rationale has implications for the demand and consumption of spices and herbal plants in the world market (Marketwatch, 2020). Reflecting on China as a pioneer of Covid 19, Hartati et al (2020) mentioned the opportunity for herbal and empon-empon as a reflection of the success of TCM in Covid 19 management. However, the use of immunomodulators must pay attention to the immune response mechanism against the Covid 19 virus. In pathogenesis, SARS Cov 2 targeting type 2 alveolar cells and duplicating RNA so that neutrophils and monocytes / macrophages produce abundant pro-inflammatory cytokines resulting in cytokine storm (Prompetchara et al., 2020) (NIH, 2020). This situation worsens the condition of the infection. Based on these opportunities and challenges, researchers are trying to conduct a literature study on herbs that can be used in Covid 19 therapy. The aim of this study is to determine the use of herbs in Covid 19 therapy.

METHOD

Design of this study used a systematic literature review. This methodology is a literature study that aims to provide a valid and reliable source of knowledge through a rigorous

search system. According to Vicente-Saez & Martinez-Fuentes (2018) there are several steps in this study including: formulation of research problems; develop valid protocols; literature search, inclusion-based screening, quality assessment, data extraction, analysis and synthesis.

Keywords formulation

Keywords formulation used based on population, intervention, comparison, and outcome (PICO) approach. Population in this research is Covid 19 patient. Interest of intervention is the used of herbs. Comparison is regular treatment. Outcome is immune asses in mortality or morbidity and severity of the symptom.

Searching Protocols

Based on the short description of PICO and Medical subheading, the keywords to be used in the search are "covid 19 AND herbs AND immune" and in Indonesian "Covid 19 DAN herbal DAN imunitas". In accordance with the research objectives, this literature study will produce recommendations for herbal therapy in the management of Covid 19. The inclusion criteria in this study is original research formed in clinical trials on Covid 19 patients, published in 2020-2021, accessible in full text, published in English and Indonesian. While the exclusion criteria were gray literature (proceedings, thesis, and dissertation); review articles; and original lab-based or non-human research (pharmaceutical network / docking).

Searching Strategy

Searching strategy in this study was to search online literature on health-based academic search engines. There are 4 search engines used for English keywords: PubMed, ScienceDirect, SageJournal, Google Scholar. For searches with keywords in Indonesian done at the Garba Rujukan Digital (Garuda) portal.

Quality Assessment

The quality for this research follows clinical trials based on the Consolidated Standards of Reporting Trials (CONSORT) guideline using the JADAD Score (Augestad et al., 2012). JADAD Score assesses 3 important criteria: randomization, double blinding, and drop out (Hempel et al., 2011). Critical appraisal done by 2 researcher idепенently (NKDP and IGAS) before concluded as the result. If there is disagreement, the third researcher (MYK) will decide. Result of the appraisal written in table 1.

Data analysis and syntesis

Data collection process in this study is summarized in a PRISMA flowchart that describes the results of the article filtering at the identification, screening, and eligibility stages. PRISMA flowchart of this study captured in figure 1. The identification stage is the search results using keywords and filters the year of publication. The screening stage includes scanning the title and abstract, then the eligibility study includes full text analysis and quality assessment. Data extraction uses a table in Microsoft Word 2007. In the table, data is collected regarding the author, title, research design, number of samples, samples characteristics, herbal administration techniques, and the impact of herbal use in

the management of Covid 19. The synthesis analysis was conducted qualitatively by describing the characteristics of the sample articles, herbal variances and reviewing recommendations. Content summary of the data analysis and syntesis describes in details in table 2.

RESULTS

Articles Characteristics

Based on the findings of the final article (n = 5), there were 40% published in the Pyhtomedicine Journal and 20% each published in the Integrative Medicine Journal, American Blood Journal, and Medtrix. As for the research design, 80% were RCT studies and 20% were pilot control group sign studies. Of the total 4 RCT articles, 50% were randomized by blinding while the other 50% were randomized without blinding.

Participants Characteristics

In Yan et al's (2020) study with the herbal intervention of Jinhao Artemisia Antipyretic Granules (8g b.i.d.) and Huoxiangzhengqi oral liquid (10ml b.i.d.) participants were healthy people without suspected signs of Covid 19, not pregnant / breastfeeding, and had no comorbid. Meanwhile, research by Ashraf et al (2020) stated that honey and Nigella Sativa herbs were given to Covid 19 patients who were

proven from positive RT PCR results but did not have multiorgan failure, a sign of shock sepsis, did not need a mechanical ventilator, without comorbid hypertension and diabetes. El Sayed et al (2020) in the TaibUVID study herbal intervention was given to patients with Covid 19 symptoms immediately until the 9th day after the patient had a nasal swab. Hu et al (2020) provided Lianhuaqingwen capsules intervention in Covid 19 patients over 18 years of age who proved positive laboratory test results with fever and flu symptoms without severe and comorbid symptoms. Xiong et al (2020) research Xuanfei Baidu herbal decoction was given to moderate-severe Covid 19 patients who were admitted to Wuhan Hospital without an antibiotic regimen.

Herbs Characteristic

The findings in this study the characteristics of traditional Chinese herbs (TCM) were seen in 3 studies and 2 other studies in Saudi Arabia and Pakistan. TCM herbs are presented in granule and oral form (Yan et al, 2020), capsules (Hu et al, 2020), and decoction or sachets dissolved in water (Xiong et al, 2020). Herbal TCM consists of not only 1 type but in the form of a mixture of more than 3 types of herbs that have been packaged in certain compositions. Research by Ashraf et a (2020) honey and Nigella Sativa are packaged in capsules. While El Sayed et al (2020) TaibUVID which consists of nigella sativa seeds (6-15 grams), anthemis hyalina is packaged in the form of inhalants and dietary supplements.

Table 1.
Description of JADAD Score Quality Assesment

Author	Randomization		Blinding		Drop Out < 10%
	Randomized	Method of randomization is explained	Blinded	Method of Blinding is explained	
Yan et al (2020)	√	√ (cluster)	√	√	√
Ashraf et al (2020)	√	√ (lottery method)	√	√	√
El Sayed et al (2020)	-	-(pilot study)	-	-	√
Hu et al (2021)	√	√ (block random)	-	-	√
Xiong et al (2020)	√	√ (tossing coint)	-	-	√

DISCUSSION

The definition of herbal in the world of medical medicine according to WHO (2018) "Herbal medicines include herbs and / or herbal materials and / or herbal preparations and / or finished herbal products in a form suitable for administration to patients". Herbal ingredients can be part of a plant (leaves, roots, stems, fruits, rhizomes, or other fragments). Served in the form of juices, stews, oils, essential oils, resins, and dry powders. The preparation process can be carried out by boiling, drying, extraction with alcohol.

In Indonesia, the use of herbs is mostly regulated by the Food and Drug Supervisory Agency (BPOM). The BPOM classifies the use of herbs as traditional medicines in 3 terms, namely herbal medicine, lean herbal medicine (OHT) and phyto-pharmacy (FF) (Efizal, 2020). Jamu is a limited number of herbal uses for the purpose of maintaining health based

on empirical evidence. Smeentara OHT, the use of limited scale herbs with ingredients has been standardized through preclinical tests (in vivo and invitro). Meanwhile, phyto-pharmacy is the use of standardized herbs with health objectives in accordance with the results of preclinical and clinical evidence.

The trend of herbal use in Indonesia has been significantly affected by the Covid 19 pandemic. This is evident from the development of traditional medicines into Indonesian modern medicine (OMAI) in April 2020 (Food and Drug Supervisory Agency, 2020). In the launch of the OMAI informatorium, 62 OHT products and 25 FF products were recorded. As for herbal medicine is not included in OMAI. Meanwhile, until the informatorium was published, there were no OHT and FF that could cure Covid 19. The claimed role of herbs was to increase endurance and relieve symptoms.

Table 2
Table of Content Summary

No.	Author/ Tahun (Country)	Title	Study Design and total sample	Herbs administration	Impact to immunity among Covid 19 patient
1	Yan et al (Yan et al., 2020) China	<i>Effects and Safety of Herbal Medicines among Community-dwelling Residents during COVID-19 Pandemic: A Large Prospective, Randomized Controlled Trial (RCT)</i>	RCT Total sample 22.065 consists of 11,092 interventional group and 10.973 controlled group.	Jinhao Artemisia Antipyretic Granules (8g b.i.d.) and Huoxiangzhengqi oral liquid (10ml b.i.d.) given in 1 hour interval in 5 days	Herbs reduced 89,6% risk of common cold among patient 16-59 years old without HILI effect (<i>Herbal induced liver injury</i>)
2	Ashraf et al (Sohaib Ashraf et al., 2020) Pakistan	<i>Honey and Nigella sativa against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial</i>	RCT Total samples 313 people consists of 150 interventional group and 183 controlled group.	HNS (madu dan Nigella sativa) honey (1 gm/Kg/day) and Nigella sativa seeds (80 mg/Kg/day) given in 2-3 oral dose in 13 days	Herbs accelaret viral clearance based ont RT PCR evaluation.
3	El Sayed et al (El Sayed et al., 2020) Arab Saudi	<i>Promising preventive and therapeutic effects of TaibUVID nutritional supplements for COVID-19 pandemic: towards better public prophylaxis and treatment (A retrospective study)</i>	Pilot studi Total sample 20 people	Nigella sativa seeds (6-15 grams) ,anthesis hyalina (1-2 grams) and 500 ml water boiled in 5 minutes, cooled down and instill 1 mL clove oil. Formed in food suplement ingredients : Honey: 15 ml , Anthemis hyalina (Chamomile): 1 gram/ dose, Nigella sativa: 2 grams/dose oru 5 ml nigella sativa oil/dose and 1 cup orange juice,	TaibUVID inhalant more recommended rather than in food supllement. Oral route by suplement reported diarrhea and hyperglycemia in 13 patients. melaporkan diare dan hiperglikemia.
4	Hu et al (Hu et al., 2021) China	Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial	RCT Total 280 participants without control group.	4 capsules LH given 3 time/day in 14 days.	LH shorten length of stay in hospital (7vs 10 hari); reduced fever (2 vs 3 hari); fatigue (3 vs 6 hari); cough (7 vs 10 hari)
5	Xiong et al (Xiong et al., 2020) China	Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: a pilot randomized clinical trial	RCT Total 42 covid 19 patients; 19 in interventional group and 20 in control group	1 sachet XBD diluted in 200 mL water taken twice a day.	XBD induced imunity based on WBC and lomfosit and reduced imflamation based on CRP indikator.

In a global perspective, the use of herbs, especially during the Covid 19 pandemic, is widely used in Asia, known as Traditional Chinese Medicine (TCM). While herbs are still a strict consideration in Europe and America, known as Western Medicine. The reflection of this study seeks to facilitate these two perspectives, known as integrative medicine. The final output of the recommendation is herbs as a complementary or alternative therapy (Complementary and Alternative Medicine (CAM)) (Dong, 2013). Review of 9 guidelines with English-based sources (WHO, INI, and ECDC), Chinese Medicine, and other sources (Korean Medicine, Japanese Respiratory Society (JRS), and Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy (AYUSH)) the use of herbs during the pandemic by Ang et al (2020), there are 12 herbal formulas and 53 natural ingredients that are often used. This study states that the pharmacokinetic analysis of Citri Reticulatae Pericarpium (Chen Pi) is well combined with Glycyrrhizae Radix et Rhizoma (Gan Cao) with the utilization of relieving symptoms of fatigue, fever, cold sweats, and indigestion.

As for the position of herbs according to the National Agency for Food Safety, Environmental and Occupational Health (ANSES) France (2020) there are 4 important considerations related to the management of Covid 19. First, herbs are not recommended if they have anti-inflammatory effects that increase angiotensin-converting enzyme 2 (ACE2) receptors such as ibuprofen and NSAIDs that aggravate viral infections. Second, only use standardized herbs both in terms of preparation and clinical testing. Third, only use herbs that have specific immunomodulatory effects without causing cytokine storms which worsen the condition of Covid 19 patients. There are 4 herbs that are recommended as a home remedy, namely Echinacra Spp, Pelargonium sidoides, Astragalus membranaceus, Curcuma longa. These herbs have immunomodulatory, antioxidant, antifibrotic, and antiviral therapeutic effects. While Colchicine and TCM have anti-inflammatory and antiviral effects, they are recommended for clinical trials. The fourth consideration is that herbs containing polyphenols are proven to be effective at the beginning of Covid 19 infection

(*Andrographis paniculata*, *Pelargonium sidoides*, *Sambucus nigra*, etc.) In connection with the findings of this study, herbs play a role in the prevention of Covid 19 (Yan et al, 2020) home care setting . Three other studies as complementary therapies relieve the symptoms of Covid 19 (Hu et al, 2020; El Sayed et, 2020; Ashraf et al, 2020) While Xiong et al (2020) research herbal as an alternative therapy in Covid patients who do not receive antibiotics in the setting hospital care.

In an effort to provide education and increase awareness of safe herbal use, the public needs to know the stages of the OHT to FF test. BPOM (2020) states that at an early stage it is necessary to conduct a standard test of raw materials to determine the consistency of active substances. In 1 plant usually contains several active substances so that it is necessary to purify them to increase bioavailability and separate them from contaminants. Then proceed to preclinical testing on experimental animals to determine the toxicity and pharmacodynamic efficacy tests. The final stage is a clinical trial consisting of 4 phases. Phase I tolerability test in healthy subjects. Phase II efficacy tests in limited sick subjects. Phase III efficacy test in a wider range of sick subjects. Phase IV is the evaluation of products that are already circulating in the community. This phase is in line with the WHO guidelines (2005) in the clinical trial operational guide for herbs. The literature review results present herbs that have been carried out in phase I and II clinical trials.

Limitation of The Study

The findings of the research majority revealed herbs formed in TCM in China. Within the limitations of the researcher's knowledge this is related to herbs has been included in formal national health system in China compared in other countries in the world. To discover a novel herbs that potentially beneficial in treatment Covid 19, futher study should involved lab based research article.

CONCLUSIONS AND SUGGESTIONS

Based on findings of 5 articles, herbs are proven to relieve the symptoms of Covid 19. The role of herbs from these findings is that they are preventive, complementary therapies to relieve symptoms and as alternative therapies. The use of herbs in this finding is largely a standardized TCM and is recognized as part of the national health care system in China. This is a limitation of the study results because herbal standards in China cannot be compared to other countries that do not establish herbs as an integrated part of formal health services. The opportunity to use herbs must pay attention to safety and toxicity standards. As a recommendation, the use of empirical herbs in the form of food can be used to prevent Covid 19 at the household level.

Recommendation Based on the study results, herbs can be a treatment option during the Covid 19 pandemic. As a preventive measure, the use of simple herbs can be used. Based on the guidelines for the use of herbs and dietary supplements in the Covid 19 pandemic era by the BPOM (2020), there are 7 recommended plants to increase endurance. These herbs include turmeric, ginger, ginger, meniran, sambiloto, guava, guava leaves.

Herbal processing at the household level can be done using wet / dry simplicia. There are important things that need to be considered in the selection of simplicia. The first

is the truth of the plant and the quality / quality. Good quality is agreed in the absence of organoleptics (deterioration of shape, smell, and taste). This can lead to mycotoxin content in the body. When processing, there are important standards. The first is the tool used should be made of stainless steel to boil materials that have been washed clean. Use masks to prevent human contamination of herbal ingredients. The processing stages consist of: the material is washed in running water; drained, chopped and boiled in a temperature of 100 degrees Celsius for 15-30 minutes for wet simplicia; and steeped in warm water for 5 minutes for dry simplicia. If you want to use herbs, you should buy them at a pharmacy or licensed drugstore by paying attention to the KLIK standard. KLIK is an extension of Check Packaging, Labels, distribution permits, and expiration.

With regard to herbs during the Covid 19 pandemic, it is certainly related to the function of herbs as immunomodulators. In the early stages, the use of immunomodulators can be used as prevention but not in the long term. The use of herbs to increase endurance in pregnant women, lactating women, immunocompromised patients needs to be through consultation and doctor's consideration. Herbs to increase endurance are good for use in the early phases of Covid 19 infection to prevent cytokine storms that worsen Covid 19 infection. The use of immunomodulators for moderate-severe Covid 19 infection is not even recommended.

Conflict of Interest Statement

Authors do not have any conflict of interest regarding the topic and result of the study.

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