

Review Article

Potential Indonesian Herbs to Develop a Mix Herbal Immunomodulator Supplement: A Hermeneutic Systematic Review

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Abstract

To date, only few studies summarize which herbal plants mostly studied in immunity. This study aims to search for the most Indonesian herbs studied as immunomodulator, and to identify their potencies. The findings hopefully could lead to a new formula of herbal immunosupplement. This systematic review was designed with hermeneutic approach, following PRISMA guideline. Literature searching was performed in Google Scholar and Indonesian Scholar Database, using Boolean operator and citation tracking. Relevant articles were identified to list the most Indonesian herbs studied as immunomodulator. Quality assessment was conducted with Newcastle-Ottawa Scale and the extracted data were analyzed descriptively. Record identification hit 574 articles, of which were screened, resulting to 241 studies. Data extraction was taken from 17 studies. Among the most herbal studied, *Phyllanthus niruri*, *Andrographis paniculate* and *Nigella sativa* reveal to be the potential herbal plants to develop a new herbal mix immunosupplement, due to their proinflammatory and phagocytic-activator properties.

Keywords: *herbal medicine; Immunity; Immunomodulator; Supplement*

Introduction

Living in the era of COVID-19 pandemic forces us to quickly adapt with this situation, to stay healthy, and to prevent the disease transmission. Following the COVID-19, health protocol such as wearing facemask, washing our hands, keeping social distance, avoiding crowd, as well as maintaining our immunity system to function properly against the virus and other pathogens, are thus compulsory [1]. This latter could be achieved by several actions including taking well-balanced nutritious diet, regular exercise, and adequate sleep [2]. Currently, people are also interested in getting immunosupplements, especially those which are developed from natural substances [3]. Therefore, immunomodulator products derived from herbal plants are now being on high demand to be consumed as

immunity booster [4]. Indonesia, by nature, is rich of bioactive substances from plants that could be used as herbal medicine [4,5]. Several studies have showed that many Indonesian herbal plants demonstrate their activities against pathogens, either by fighting the pathogen itself or by stimulating the body's immunity [6]. The compounds or substances that can modulate the function and activity of the immune system are known as immunomodulators [7]. The function of immunomodulators is to improve the immune system by inducing and amplifying (immunostimulant) or suppressing abnormal immune reactions (immunosuppressants) [8]. There are many drugs or supplements on the market that claim to increase the body's immune system from herbal plants. These products either in a formula of a single herb or in a combination formula of several herbs, were found mostly in the form of tablets and syrup in a modern packaging. Since quite a few immuno-supplement drugs is available, it is only natural that people search for an effective herbal formula with not only many benefits but also less negative side effects. To the best of our knowledge, there has been only few studies which collect, summarize, and conclude which herbal plants that were mostly studied as immunomodulator agents. Therefore, this review aims to systematically search for Indonesian herbs which were mostly studied as immunomodulator agents and thus to identify their immunomodulator potencies. Furthermore, the findings hopefully will lead to a novel composition and new formulation of herbal plants that can be used as immunomodulators.

Methods

This study was designed as a narrative systematic review, using a hermeneutic approach for the literature review process. Hermeneutic framework for literature review consists of two interlinked hermeneutic circles, namely the search and acquisition circle, and the analysis and interpretation circle [9]. Literature searching was conducted using Boolean operator and citation tracking in Google Scholar database from 2011-2021. Following the PRISMA guideline [10], the relevant articles were screening for duplication, relevancy, and eligibility according to the inclusion and exclusion criteria (Table 1). Those studies were listed

to find the most herbal plants studied as immunomodulator agents. The first hermeneutic circle was then applied again for the second round to select studies related to those five most studied herbs in Google Scholar and Indonesian Scholar Database (GARUDA), using the same search terms and snowballing method. Quality assessment for selection studies was performed with the Newcastle-Ottawa assessment tool [11]. Next, the second hermeneutic circle, the analysis and interpretation circle, was then applied to mapping and classify the selection studies to answer the research questions. All studies related to those listed herbs were analyzed descriptively with meta-synthesis.

Table 1: Inclusion and exclusion criteria for screening relevancy and eligibility.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> -Experimental study on animals and on human -In vivo, ex vivo or in vitro -Focusing on immunomodulator activities -Herbs could be in a mono/combination formula -Open access, article could be retrieved 	<ul style="list-style-type: none"> -Review studies, Book, Thesis, Dissertation, Research report -Other languages than Indonesia and English -Experimental study on aquaculture and poultry -Focusing on anti-pathogen activities (i.e. antiseptics, antibacterial, antiviral, antifungus), toxicity and other activities (i.e. analgetics, diuretics, antidiabetics, antihypertension, anti-dyslipidemia, anticancer)

Results

The flow chart diagram on literature searching, using a modified PRISMA guideline with hermeneutical approach is presented in Figure 1 [10]. Database searching and citation tracking in Google Scholar database used search terms “herbal OR jamu OR extract OR extract AND immunomodulator” and “herbal OR jamu OR extract OR extract AND “respon imun OR immune response” hit 344 and 230 results, respectively. These 574 articles were then screened for duplication, relevancy and eligibility through the inclusion and exclusion criteria (Table 1). The resulted 241 studies were collected and listed to find the most immunomodulator herbs studied. They were meniran (*Phyllanthus niruri*), ginger (*Zingiber officinale*), sambiloto (*Andrographis paniculate*) and black cumin (*Nigella sativa*). Next, those four herbs were entered into the second round of the

first hermeneutic circle, using the similar search terms, and snowballing in Google Scholar and Indonesian Scholar Database (GARUDA). A total of 182 records were found and screened, resulting to 45 retrieved records. Quality assessment was performed with the Newcastle-Ottawa assessment tool by two reviewers [11], looking at the selection of the study groups, the comparability, and the ascertainment of either the exposure or outcome of interest, depending on the type of study (Table 2). A star is given when the study met the criteria for each of the three categories. Seventeen studies were ultimately selected for data extraction and data synthesis, following the second hermeneutic circle (analysis and interpretation). They reported either a single herbal plant (10 studies) or a mix of herbal plants (7 studies). The summary of selection studies is presented in Table 3.

Table 2: Results of quality assessment for selection studies.

Author, Year	Herbal Plants	Main Findings	the Newcastle-Ottawa Scale*			
			S	C	O/E	T
Arum I. L. et. al., 2011 [13]	Meniran	Treatment group showed higher numbers of activated lymphocyte and phagocytosis ability of macrophage than control group (p<0.05, respectively).	*	*	*	*** Good
Ifandari et. al., 2013 [16]	Meniran	Lymphocyte count isolated from mice spleen infected with S.typhii was higher in treatment than in control group (p<0.05).	*	*	*	*** Fair
Himawan, H.C., et. al. (2017) [25]	Meniran	Faster wound closing was found in treatment than in control group (p<0.05)	*	*	*	*** Good
Aldi, Y. et. al. (2018) [26]	Meniran	Treatment group showed higher macrophage phagocytic and capacity index than control group (p<0.05).	*	*	*	***Fair

Novianto F. et. al., 2016 [14]	Meniran and Temulawak	Treatment group showed higher physical fitness ($p<0.05$) and total leucocyte count ($p>0.05$) than placebo group.	*	*	*	***Fair
Darmawan, K.H. et. al. (2017) [27]	Meniran and Garlic	Formulation of the extract in nano increased phagocytosis ratio and index than the raw extract and control ($p<0.05$)	*	*	*	***Good
Sagala R. J. et. al.,	Meniran, <i>Piper crocatum</i> , and Thyphonium flagelliforme	Treatment group showed higher macrophage phagocytic and capacity index than control group ($p<0.05$).	*	*	*	***Fair
Qarni, U. A. and Rifa'I M. (2013) [15]	Sambiloto	Sambiloto ethanol extract increased regulatory T cell count isolated from mice spleen than control ($p<0.05$)	*	*	*	***Fair
Rahayu M.P. (2014) and (2015) [21]	Sambiloto	N-hexan fraction of Sambiloto increased phagocytic activity in macrophage and increased the amount of immunoglobulin G in mice induced by hepatitis B vaccine ($p<0.05$)	*	*	*	***Fair
Orienty, F.N. et. al. (2015)	Sambiloto	Sambiloto extract significantly reduced inflammatory cells in periodontitis.	*	*	*	***Fair
Aryani, D. K. A. et. al. (2018) [29]	Sambiloto	Sambiloto tablet group showed lower MIF expression than placebo ($p<0.05$)	*	*	*	***Good
Trimayanti Y. et. al. (2015) [30]	Sambiloto and black cummin	Combination of sambiloto and black cummin extract effectively reduced cutaneous anaphylactic reaction induced by ovalbumin than control group ($p<0.05$)	*	*	*	***Good
Saidah, S. et. al. (2015) [20]	Sambiloto and Cinnamon	Combination of sambiloto and cinnamon increased the amount of immunoglobulin M and G in mice induced by hepatitis B vaccine ($p<0.05$)	*	*	*	***Fair
Azimah, D. et. al. (2016) [17]	Sambiloto and Temulawak	Combination of sambiloto and temulawak significantly increased lymphocyte proliferation isolated from mice spleen ($p<0.05$)	*	*	*	***Good
Akrom et. al. (2015) [24]	Black cummin	Ethanol extract of black cummin seed increased the activity of macrophage phagocytosis and ROI secretion of Swiss mice infected with <i>L. monocytogenes</i> ($p<0.05$).	*	*	*	***Good
Nitihapsari, G. Y. et. al (2019) and (2020)[18,19]	Black cummin	Black cummin extract was effective in increasing TNF- α ($p<0.05$) but not IL-1 β levels of Balb-c mice infected with MRSA ($p>0.05$)	*	*	*	***Good
		MRSA ($p>0.05$)				
Ismail et. al. (2015)[31]	Black cummin and <i>Carthamus tinctorius L.</i>	Combination of extract of black cummin and <i>Carthamus tinctorius L.</i> increased macrophage phagocytic activity ($p<0.05$).	*	*	*	***Fair

Table 3: Summary of selection studies.

Herbal	Mono/Mix	Formulation	Subject/design	Type of studies	Intervention/Exposure	Immunomodulator potencies
Meniran	mono [13,16,25,26], combination [14,27,28]	pure extract [13,16,25,26,28], herbal mix drink [14] and nano [27]	mice [13,16,26,28], rats [25,27], human [14]/ in vivo [13,14,25], ex vivo [13,16,26] and in vitro [27,28]	pre-post group [13,14,25] post – control group [13,16,26–28] her	Salmonella typhimurium [13,16], incision [25], Staphylococcus aureus [26]	macrophage phagocytosis activity [13,26–28], proinflammation [13,14,16,25], antiinflammation [13].

Sambiloto	mono [15,21,29,32], combination [17,20,30]	pure extract [15,17,20,30,32], fraction [21], tablet [29]	mice [15,20,21,29], rats [30,32] / in vivo [20,29,32], ex vivo [15] and in vitro [20,21]	pre-post group [20,30] post – control group [15,21,29,32]	hepatitis B vaccine [20,21], silk ligature [32], <i>Plasmodium berghei</i> [29], incision [30].	macrophage phagocytosis activity [15,21], proinflammation [32], antiinflammation [29,30], antibody production [20]
Black cumin	mono [18,19,24], combination [[31]	pure extract [18,19,24,33] nano [27]	mice [18,19,31], rats [24], ex vivo [31] and in vitro [18,19,24]	post – control group [18,19,24,31]	[18,19,31]	macrophage phagocytosis activity [24,31], pro-inflammation [18]

Discussion

This study employs a hermeneutic approach to systematically review the most frequent herbal plants studied in Indonesian setting. Our findings reveal that studies on meniran (*Phyllanthus niruri*), sambiloto (*Andrographis paniculate*) and black cumin (*Nigella sativa*) demonstrate significant immunomodulator potencies. These herbals, either in mono or in mix formula, under pathogenic or non-pathogenic exposure, on human or non-human settings, exhibit pro or anti-inflammatory, phagocytosis activator and antibody stimulant effects (Table 3). As such, those three herbal plants could constitute a potential herbal mix immunomodulator supplement.

Several herbal plants were reported to have potencies of antiviral, antioxidant and immunomodulator. Therefore, they could be considered as adjuvant medicine to prevent or to cure human diseases [12]. The use of herbal products to strengthen immune system in COVID-19 pandemic is also acknowledged by the Indonesian Government [3,4]. Based on the available safety and efficacy data, they released an informatorium on herbal medicine, which suggested 14 standardized herbals that could be used as adjuvant therapy for COVID-19 mild symptoms and as immunosupplement for prevention [4]. Among those 14 herbs, meniran (*Phyllanthus niruri*) and sambiloto (*Andrographis paniculata*) were included. These are in line with our finding that meniran (*Phyllanthus niruri*) and sambiloto (*Andrographis paniculata*) are the most herbal plants studied as immunomodulator agents (Table 2). In case of black cumin and ginger, we found only few, and no studies could be graded as fair and good quality, respectively (Table 2). Nonetheless, through snowballing when we searched for ginger, we found red ginger (*Zingiber officinale* Roscoe var *Rubrum*) as another potential immunomodulator herbs. Indeed, red ginger is also included in the recommended herbal plant listed by the Indonesian government [4].

Our finding demonstrated that the immunomodulatory potencies of selection studies are mainly due to pro-inflammatory and phagocytic activator properties. The pro-inflammatory effect could be seen in the leucocyte count, lymphocyte profile [13-17], also cytokine [18,19] and antibody production [20,21], indicating the potential of those herbs in orchestrating both innate and adaptive immune response. In addition, almost all studies addressed phagocytic capacity effect. Phagocytosis is an important immune

mechanism whereby macrophage could quickly mobilize to injured site and destroy pathogens or could suppress inflammation, clear immune cells, and promote remodelling leading to tissue repair. Thus, phagocytic capacity indicates the potential of immunostimulant or immunosuppressant of those herbs, respectively, depending on the setting.

The immunomodulator potential of herbs found in this study was previously reported due to their bioactive compounds. Only one study of sambiloto, employed active fraction (Table 3). Sambiloto contains bioactive substance, namely andrographolide, an antioxidant which could also increase macrophage count and cytokine production. Other potent bioactive compounds found in Sambiloto were flavonoid and alkaloid [22]. Flavonoid was also found in Meniran. This compound could activate interferon production, activate macrophage and ultimately phagocytic capacity. This later effect in Meniran, is also due to another active substance, known as arabinogalactan [23]. For black cumin, the bioactive compound is found in their seeds oil, namely timoquinon. This substance could induce the release of enzyme Neu 4 xyalidase, which then activate macrophage [24].

The use of immunomodulator drugs derived from herbal plants should be addressed cautiously. As suggested by the Indonesian government, it is only for complementary purpose, not for standard therapy and not for emergency case. Also, their immunomodulatory effects and toxicity should be underline when they are used in COVID-19 patients. Sambiloto and black cumin may exacerbate cytokine storm due to their pro-cytokine properties, while both Sambiloto and Meniran exhibit toxic effects in high dosages [25-33].

Conclusion

To sum up, people generally search for supplements that could improve their immunity, particularly those derived from natural substances during COVID-19 pandemic. Here, we demonstrate that three herbs namely meniran (*Phyllanthus niruri*), sambiloto (*Andrographis paniculate*) and black cumin (*Nigella sativa*) could be further developed as one mix formula of immunomodulator herbal supplement. On the other hand, this study has also several limitations. First, the study focused on Indonesian herbal medicine so that the results could not reflect the most herbal studied for immunomodulator in worldwide settings. Also, we performed literature searching with only two

scholar databases. All in all, a larger study to identify the most herbal plants used for immunomodulators around the world, using several scholar databases, is recommended, not only to provide useful information but also to create potent herbal medicine for human immune system.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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