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THE POTENTIAL OF INDONESIAN TRADITIONAL HERBAL MEDICINE AS IMMUNOMODULATORY AGENTS: A REVIEW

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ABSTRACT: The prevalence of infectious diseases in the world, including in Indonesia, has increased significantly. One of the factors of death due to infectious disease is decreasing the human body's immune system. Therefore, studies on immunomodulatory agents need further investigation. Many studies have shown that secondary metabolite compounds contained in plants have immunomodulatory properties. These compounds are flavonoids, alkaloids, polysaccharides, phenols, terpenoids, tannins, glycosides, saponins, and sterols. In Indonesia, there are many types of medicinal plants containing secondary metabolite compounds. Besides, Indonesian people usually consume Jamu for immune-boosting. Jamu is made from Indonesian traditional herbal medicine such as ginger, turmeric, galangal, Curcuma, cinnamon, sand ginger, lemongrass, cardamom, tamarind, lime and cloves. The most frequently used Indonesian traditional herbal medicine investigated regarding their constituents and immunomodulatory effect should be explored. Although, more research is needed to prove efficacy and assure safety scientifically. This paper aims to give comprehensive views useful for future development and further improve its utility as immunomodulatory agents.

INTRODUCTION: Immunomodulators are substances that can stimulate or suppress the immune system, both the adaptive and innate immune systems. Nowadays, immunomodulators are very important to study because of the increasing prevalence of infectious diseases worldwide, including in Indonesia. Some infectious diseases are HIV/AIDS, sexually transmitted diseases, diarrhea and other abdominal infections, acute respiratory infections, leprosy, frambusia, hepatitis, meningitis, herpes, HPV, tuberculosis, malaria [1].

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In 2019, malaria, tuberculosis, and HIV/AIDS all remained in the top 10 leading causes of death in low-income countries in the world. HIV, TB and malaria accounted for 0.8, 1.2 and 0.4 million deaths, respectively, in 2018 [2].

In 2016, there were 28 million cases of malaria in Southeast Asia, with 38 thousand deaths [3]. Besides that, infectious diseases also killed 3, 5 million peoples in developing countries like Indonesia. In 2018, Indonesia had several cases, such as AIDS with 641.675 patients and tuberculosis with 316 cases per 100.000 populations. The prevalence of tuberculosis in Indonesia is the second-largest in the world [4]. Decreasing of immune system response is usually associated with the number of death due to infectious diseases. The immune system is essential to protect the human body against pathogens.

When the immune system decrease, pathogens will attack our body quickly and our health becomes worse. One of the preventive efforts to increase the immune system is using herbal concoctions or traditional medicines, especially those with an immunomodulatory effect.

Many immunomodulators study had been done. Some researchers explained that the active secondary metabolites compounds containing in herbal plants have an immunomodulatory effect. These compounds are flavonoids, phenols, alkaloids, terpenoids, polysaccharides, glycosides, saponins, tannins, and sterols [5, 6].

According to WHO, 88% of the world's population uses traditional medicine, and 90% of developing countries use traditional herbs as primary healthcare [7]. Indonesian people used to consume Indonesian traditional herbal medicines called "jamu", a hereditary alternative medicine. Jamu is still very popular for maintaining health and treating diseases. The Indonesian tropical climate also supports this, so it makes Indonesia rich in natural resources. More than 30.000 species of plants grow in Indonesia, and around 9.600 species are known to have pharmacological activities.

METHODS: This review article was conducted in 2021 by reviewing all full-text articles published in English and the Indonesian language. Articles were collected from international and national search websites of Google scholar, Pub Med, and Scopus. The search keywords are immunomodulatory activity, herbal medicines, jamu, Indonesian traditional herbal medicine, and immunomodulator.

RESULTS: Based on the results search, 130 articles were identifier. Sixty articles in Google Scholar, 43 articles in Pub Med, and 27 articles in Scopus. After removing the same articles, I finally reviewed 80 articles, such as 70 English-language articles and 10 Indonesian language articles.

Immunomodulatory Activity of Secondary Metabolites in Plants: Types of Immuno-modulators consist of three categories: immuno-adjuvants, immunostimulants and immuno-suppressants. Immunoadjuvants use for increasing the response to a vaccine while not having any specific antigenic effect. Immunostimulants are agents that increase the body's resistance against infections, can act by the stimulated nonspecific immune system. Then, immunosuppressant could be used to control the pathological immune response in autoimmune diseases, hypersensitivity, and immune pathology associated with infections [8].

Secondary metabolite compounds with immuno-modulatory activities are alkaloids, flavonoids, glycosides, polysaccharides, polyphenols, tannins, terpenoids, saponins and sterols. The mode of action of these compounds had been studied in many research studies **Fig. 1**.

Flavonoids: Many types of flavonoids have immunomodulatory activity, such as centaurein, apigenin 7-o-β-Dneohesperidoside, orientin, Apigenin 7-O-β-D-galactoside, Vitexin, Silymarin, Naringenin, Dihydroquercetin, Genistein, and Hesperidin. The immunomodulatory effects of naringenin derived from citrus fruits due to down-regulated chemokine expression (CXCL1, CCL4, CCL5, CXCL5, CXCL10) and cytokines (IL-6, IL-10, IL-1β, IL-12p70, TNF, IL-1α) [9]. Flavonoids showed immunostimulants activity by stimulated mononuclear cells to secretion cytokine IL-1β, IFN-γ, and TNF-α [10].

Polyphenols: Some polyphenols impact immune cell populations, modulate cytokine production and pro-inflammatory gene expression. They inactivate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and modulate mitogen-activated protein Kinase (MAPk) and arachidonic acids pathways [11]. One example of polyphenols is curcumin, an active compound in Curcuma longa. Curcumin enhances bone marrow cellularity, α esterase positive cells, phagocytic activity. It inhibits IL-2 expression and NF-κB [12]. The extract of *Allium carolinianum* and *Pedicularis longiflora* significantly decreased TGF-β1, NF-κB, and TNF-αlevels [13].

Alkaloids: Alkaloids are the primary source of performance enhancement and improving immune functions. Some alkaloids that have been investigated due to their immunomodulatory activities are piperine, berberine, tetrandrine, sinomenine, punarnavine, papaverine [14]. Piperine analog augmented the levels of Th1 lymphocytes mediated TNF-α, IL-12, IL-1β and decreased the expressions of Th2 mediated IL-4, IL-10 and cell

viability in invitro study [15]. Papaverine modulated the activity of Th17 by reducing the expression of NF-κB, p38MAPK, RANKL, and IL-23 [16]. The tetrandrine in *Stephania tetrandra* can suppress antibody synthesis by B cells and the mitogen-induced lymphoproliferative response, inhibiting activation of human peripheral blood T-cells [17].

Terpenoids: The favourable effects of terpenoids on the immune system are mainly occurred either production of antibodies or improving T-cell response suppression [18]. An example of the terpenoids group is andrographolide, containing in *Andrographis paniculata*. It enhances the expression of IL-2, inhibits NO in endotoxin to stimulates macrophages. Boswelic acid containing in *Bowella serrata* can increase the number of peritoneal macrophages significantly [19]. Ursolic acid activates the phagocytosis process in human monocyte cells and THP-1 cells, suggesting the intracellular killing effect of macrophages during *Mycobacterium tuberculosis* infection [20].

Polysaccharide: The mechanism of poly-saccharides as immunomodulators is due to innate immunity modulation, especially in macrophage function. Generally, polysaccharide binds cell membrane receptors and stimulates immuno-modulator response in macrophage cells.

In one study, a polysaccharide from *Cipango paludina chinensis* could significantly increase the spleen and thymus signals and enhance the macrophage function [21].

Glycosides: Mangiferinis one of the examples of glycoside containing in *Mangifera indica* Linn. Mangiferin decreased the expression of Th2-mediated TNF-α, IL-3, IL-4, IL-5, IL-9, IL-13, IL-17 and concurrently enhanced the expression of Th1mediated IL-2, IL-12, IL-10, IL-γ in serum. Thus, mangiferin exerts potential immuno-regulatory activity by ameliorating the imbalance between the Th1/Th2 cytokines [22].

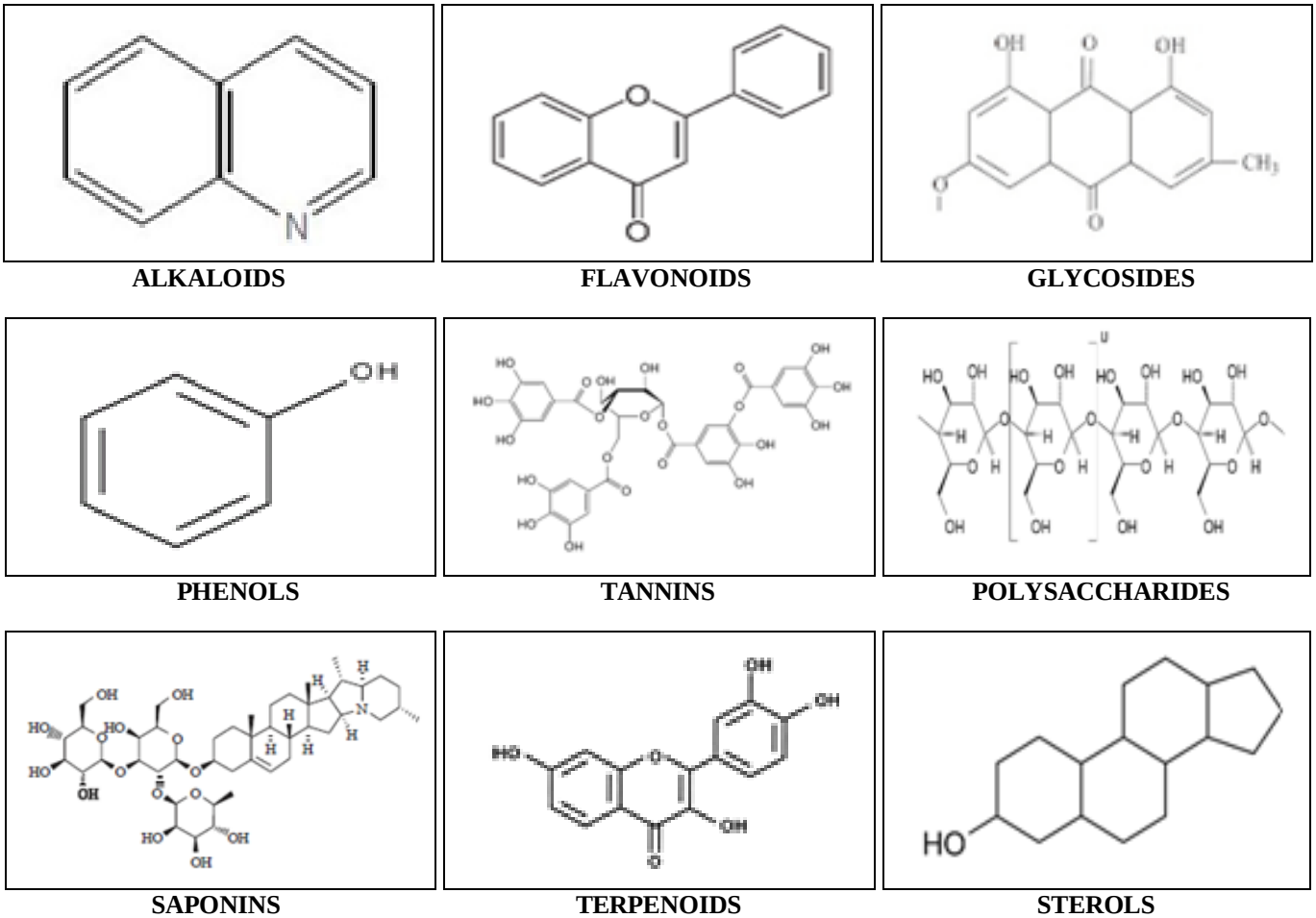

FIG. 1: CHEMICAL STRUCTURE OF SECONDARY METABOLITES SUBSTANCES THAT HAVE IMMUNO-MODULATORY EFFECT

Tannins: Tannins have some immunosuppressive activity such as suppressed the expression of IL-2, leukocyte reaction as well as CD^{3+} T cell infiltration, attenuated the expression of IL-2, TNFα and ROS production, inhibition of NF-κB activation, p38, JNK and ERK ½ phosphorylation, improve the WBC, platelets and DLC counts [14].

Corilagin, hypophyllanthin, geraniin, phyllanthin, which contain in *Phyllanthus amarus* extract, inhibit the production of NO and myeloperoxidase activity and improved both cellular and humoral immune responses [23].

Saponins: An experimental vaccine study has shown that *Quillaja brasiliensis* has immuno-stimulatory activity by improving the immune responses and protect lethal challenges in mice [24]. Ilexsaponin I derived from Ilex pubescen restricted PGE2 and NO formation by downregulating the expression of cyclooxygenase-2 and iNOS. Davidianoside F saponin also exhibits anti-inflammatory activity in human tumor cell lines by suppressing the IL-1β [25].

Sterols: The phytosterols (stigmasterol, shaftoside, β-sitosterol) extracted from *Clinacanthus nutans* significantly decreased the T-cell proliferation and improved the Th1 and Th2 mediated cytokines expression [26]. The β-sitosterol and daucosterol isolated from Dioscoreabatatas have immuno-modulatory effects. The β-sitosterol showed the immune-boosting effects by enhancing the expressions of iNOS and TNF-α and has immunosuppressive activity by lowering the expression of TNF-α. Besides, the daucosterol showed immunosuppressive effects by inhibiting the expressions of IL-6, iNOS, and TNF-α [27].

The Pharmacological Activity of Indonesian Plant Medicine as Immunomodulators: Several Indonesian plant medicine with their active compound and their modes of action as immuno-modulators showed in **Table 1**.

TABLE 1: LIST OF INDONESIAN PLANT MEDICINES HAVING IMMUNOMODULATORY ACTIVITIES

Plant name	Partsused	Active compounds	Immunomodulatory activities
Temulawak (*Curcuma xanthorriza Roxb.*)	Rhizome	Curcuminoid, volatile oil	As an immunostimulant by elevating B cells and T cells response for antibody production; It regulates the NF-κB pathwayof various immune cells such as dendritic cells, macrophages and NK cells [28]
Sambiloto (*Andrographis paniculata*)	Leaves	Terpenoid lactone such as deoxy-andrographolide, andrographolide, 14-deoxy-11, neoandrographolide, 12didehydroandrographolid, homoandrographolide, diterpenoid and flavonoids, alkaloids, steroids, glycoside and tannins	As an immunostimulator and immunosupressor [29]. Stabilize the number of lymphocytes, NK Cells, CD^{4+} expression and secretion of IFNγ [30, 31] increasing the levels of total leucocyte counts, along with the phagocytic index [32] Enhance the IgG [33] Andrographolide attenuate innate immune responses by through NF-κB signaling pathway [34]
Kayumanis (*Cinnamomum verum (L.*)	Stem	Polyphenols, alkaloids, triterpen, Cynamaldehide and volatile oil.	Volatile oil from Cinnamomum verum can enhance the immune response in Rheumatoid Arthritis (RA) Cynamaldehide also inhibits the proteinsin RA progression and potentiation [35]
Cengkeh (*Syzygium aromaticum*)	Flower	Eugenol, eugenol acetate, tannins, tymol and β-caryophyllene	The eugenol compound increases the release of IL-6 and TNF[36]
Sereh (*Cymbopogon flexuosus*)	Stem	Polysaccharides	Activates T and B lymphocytes and stimulates secretions from several cytokines. Polysaccharides can inhibit immunopotentiation such as increasing thymus and spleen, stimulating ConA- and inducing LSP splenocyte proliferation and increasing secretion of IL-2, IL-6, IL-12 and TNF-a in mice induced by tumors [37]
Jahe (*Zingiber officinale Roscoe*)	Rhizome	Gingerol, shogoal, volatile oil	Ginger inhibits lymphocyte proliferation, which is mediated by decreased IL-2 and IL-10 production. Ginger water extract significantly increases IL-1β, IL-6 and TNF-α production in rat macrophages and splenocyte proliferation and cytokine production [38]. Essential oils in ginger can increase the humoral immune response that involves the interaction between B cells and antigens resulting in proliferation and differentiation into plasma cells that secrete antibodies [39]

Kunyit (*Curcuma longa L.*)	Rhizome	Curcuminoid, volatile oil	Inhibits NO production to activate macrophages [40]. Increase white blood cell production and weight of lymphoid organs[41]increased serum levels of IgG and IgM [42], inhibits the immunostimulatory function of dendritic cells (DCs and interfere in the myeloid DC maturation [43]
Meniran (*Phyllanthus niruri*)	Roots and leaves	The flavonoid, consist of Phyllantine, hypophyllantine, quercetin, quercitrine, isoquercitrine, astragaline, tannin, damar, kalium, lignan	Water extract from *Phyllanthus niruri* leaves increases PBMC cell proliferation, improves phagocytic activity and increases the release of NO macrophages [44, 45]. As an immunostimulant by increasing neutrophil activity and antibody response significantly [46]
Jambubiji (*Psidium guajava L.)*	Leaves	Flavonoid, quercetin, guajaverine, gallocatechine, tannin elegat acidandguavin A, C and D, triterpene, volatile oil	Immunostimulant [47], stimulates humoral and cellular immunity in mice [48], increases the expression of IL8 gene, which shows potential defense in the immune system [49]
Kedondonglaut (*Polyscia sobtusa*)	Leaves	Saponins, tannins, flavonoids	*P. obtuse* inhibits the immunomodulating effect [50]. Simplesia leaves from *P. obtuse* have immunostimulants activity in *S. typhimurium* infections. The administration of *P. obtusa* leaves increases the levels of CD^{4+}, CD^{8+} and B220 + cells in *S. typhi* infection significantly [51, 52]
Kemukus (*Piper cubeba*)	Fruit	Piperine, piperidine, chavicine, protein, cineol, p-cymen, lignins, sesquiterpenespiperlotin, schimiditin andcarvon.	*P. cubeba* has immuno suppressants activity and decreases peripheral blood neutrophil levels. Another study show that *P. cubeba* effect on downregulation of cytokines, such as TNF-α and IL-6 so that can reduce the inflammatory reaction in experimental animals [53]
Kiseureuh (*Piper aduncum*),	Fruit	Piperine, piperidine, chavicine, protein, cineol, p-cymen, lignins, sesquiterpene, piperlotine, schimiditineandcarvon.	At low doses,*P.aduncum*acts as an immunosuppressant by reducing cell phagocytosis by 50% of the normal response. At high doses, hasimmunostimulants effect [53]
Cabejawa (*Piper retrofractum*)	Fruit	Piperine, piperidine, chavicine, protein, cineol, p-cymen, lignin, sesquiterpenes, piperlotine, schimiditineandcarvon.	*P. retrofractum* acts as an immunostimulant also increase peripheral blood neutrophil levels, which play essential role in the phagocytosis process [53]
Sirih (*Piper betle*)	Leaves	piperine, piperidine, chavicine, protein, cineol, p-cymen, lignin, sesquiterpenes, piperlotine, schimiditine and carvon.	Immunosuppressant, suppressing cellular and humoral immune activity, which indicates the potential of plants in autoimmune diseases [54]
Piper longum	Fruit and Leaves	piperine, piperidine, chavicine, protein, cineol, p-cymen, lignin, sesquiterpenes, piperlotin, schimiditine and carvon.	Immunostimulant, enhancestotal leukocytes by increasing stem cell proliferation in the hematopoiesis process in the bone marrow. Enhance antibody titers which play a role in humoral immunity [55, 56]
Bawang Dayak (*Eleutherine palmifolia* (L) Merr)	Leaves and roots	Alkaloids, glycosides, flavonoids, phenols, quinones, steroids, tannins, and essential oil.	Flavonoids stimulate the immune system by increasing the activity of macrophages and T lymphocytes. Ethanol extract have immunomodulators effect in mice and produce immunoglobulin G (IgG) and immunoglobulin M (IgM) [57]
Kelakai (*Stenochlaena palustris* (Burm.f) Bedd)		Quercetin, flavonoids alkaloids and steroids	Enhances the production of cytoticIL-10in *P. berghei infections*. IL-10 responds to T-helper cells in malaria to prevent the proliferation of Th1 cells, inhibitsthe production of IFN-γ, IL-6, TNF-α by T cells, by neutralizing the pathology of macrophages by inhibiting the secretion of IFN-γ and TNF-α in cerebral malaria [58]
Pasak Bumi (*Eurycoma longifolia*)	Roots	Quassinoids, flavonoids, and alkaloids (9-metoksisantin-6- alkaloidsandkantinon alkaloid).	Quassinoids increase *in-vitro* IL-12 secretion. IL-12 is an innate immune response booster that can activate macrophages against microbes by modulating the effector function of NK cells [59] Quassinoids enhance mRNA TNF-α expression, which is an inflammatory cytokine that can kill the Leishmania parasite [60]
Akar Kuning (*Fibraurea*	Stem roots and leaves	Alkaloids, terpenoids, berberine	Berberine has immunostimulant activity by increasing the ability of macrophages to kill bacteria in the body [61]. Berberine

chloroleuca)			can also increase the production of interleukin-12, which stimulates immunoregulatory activity by inhibiting T helper-2 cytokine cells in CD^{4+} cells [62]
Lidahbuaya *(Aloe vera)*	Leaves	carotenoids, steroids, terpenes and phytosterols	Stimulate T and B cell proliferation, promote the production of IL-1β, TNF-α, IL-2, IL-6 and IFN-γ [63, 64]
Mangga *(Mangifera indica L.)*	Fruits	Mangiferin	Increase in humoral antibody (HA) titer and DTH Modulating the humoral response. Inhibit reactive intermediate-induced oxidative stress in lymphocytes, neutrophils, and macrophages[65]
Jintanhitam *(Nigella sativa* L.)	Seeds	Nigellone, thymohydroquinone, and thymol	Release mediators (IL-2, IL-6, PGE2) from human immune cells (including T-lymphocytes and monocytes) [66].
Pepaya *(Carica papaya* L.)	Leaves, pulp and seeds	α-tocopherol, ascorbic acid, phenolic acids (trans-ferulic acid, para-coumaric acid, caffeic acid, vanillic acid), flavonoids (myricetin, kaempferol, quercetin), cyanogenic glycosides and glucosinolates	Decrease IgM and Nitric oxide levels. Increase IgG levels and phagocytosis. Decrease the proinflammatory cytokines (IL-10, IL-12, IL-1β, IL-6 and TGF-β1) [67]
Bawangputih *(Allium sativum)*	Fruits	Allicin, organosulfur	Enhancement in lymphocyte proliferation and cells account in the bone marrow. Allicin inhibits Th1 pro-inflammatory cytokines and activation of NF-Kb [68]. antibody secretion, phagocytosis promotion, and by creating a shift in cytokine production pattern from TH2 to TH1, leads to expansion of a strong cell-mediated immunity [69]
Pegagan (Centella asiatica (L.))	Leaves	Saponins, triterpenoids	It increases IgG levels and activation of macrophages [70]
Teh (Camellia sinensis (L.))	Leaves	epicatechin (EC), epigallocatechin (EGC), EC gallate and EGC gallate (EGCG)	increasing the expression of IL-8, IL-17A and HBD-2[71]
Mengkudu (Morinda citrifolia L)	Fruits	polysaccharide	increased the humoral and cell-mediated immune response [72]
Jeruknipis (Citrus aurantiifolia)	Fruit and leaves	Vitamin C	Inhibits proliferation of phytohaemaglutinin activated mononuclear cells[73]
Asamjawa (Tamarindus indica L.)	Fruits	polysaccharide	Enhancement of phagocytic, inhibition of cell proliferation and leukocyte migration inhibition [74, 75]
Brotowali (Tinospora cordifolia)	Stem and roots	alkaloids, steroids, glycosides, diterpenois lactones, sesquiterenoid and polysaccharides	Stimulate the macrophage activation, increase phagocytosis and antibody production, reduce eosinophil count [76]
Lengkuas (Alpinia galangal)	Rhizomes	Polysaccharide	It has a stimulating effect on reticulo-endothelial system (RES) and increased the number of peritoneal exudate cells and spleen cells of mice, which may relate to the immunomodulating effect [77]
Kencur (Kaemferia galangal)	Rhizomes	Polysaccharide	Effectively protect the thymus and spleen of tumor-bearing mice from solid tumors and enhance the immunoregulatory ability of CD4+ T cells, the cytotoxic effects of CD^{8+} T cells and NK cells [78]

The Immunomodulatory Effect of Jamu, Indonesian Traditional Herbal Medicine: Jamu, the famous traditional herbal elixir from Indonesia have been developed before the 18th century. Based on the results of Riset Kesehatan Dasar in 2018 showed that Indonesian people had used jamu for more than 50% [79]. Jamu is a traditional Indonesian medicine derived from ingredients or herb ingredients that are in the form of plant material, veterinary material, mineral material, Sarian preparations, or a mixture of such substances that are hereditary used for treatment and can be applied in accordance with the prevailing norms in the community [80]. The plant parts using for Jamu are roots, stems, leaves, fruit, flowers, seeds, rhizomes, or whole plant [81].

Nowadays, many jamu variants have been introduced to the Indonesian public. Each contains different ingredients due to the rich diversity of spices and herbs available in Indonesia that have many different benefits. Generally, jamu is used to maintain good health. It consists of turmeric, ginger, galangal, curcuma, cinnamon, lemongrass, cardamom, tamarind and cloves. Most of these ingredients work greatly for immune-boosting [82].

CONCLUSION: Based on the results of studies, some Indonesian traditional plant medicines including in Jamu can potentially be immunomodulatory agents. Because of their secondary metabolites content, which has pharmacological activities as immunoadjuvant, immunostimulants, and immunosuppressants?

The study of Indonesian herbal medicines needs further investigation to determine their specific mechanisms and prove efficacy and assure safety scientifically. The improvement of its utility as immunomodulatory agents should be developed in the future. Hopefully, Indonesian traditional herbal medicine will be used by Indonesian people to prevent various infectious diseases.

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