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Potency of Pulai (*Alstonia Scholaris*) As an Immunostimulant

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ABSTRACT

South Sumatera is one of provinces in Indonesia with broad peat soil ecosystem. Pulai or Alstonia scholaris is an evergreen plant commonly grow in peat soil ecosystem dan can be found in numerous areas in South Sumatera. Pulai has been globally used as traditional medicine to treat various kinds of disease ranging from gastrointestinal disorder, skin diseases, to anti-cancer. Therefore, researchers have been intrigued to analyze pharmacological aspect of Pulai. Several prior studies have found a large number of compounds within Pulai and a handful of them have been proved to function as anti-oxidant, anti-inflammation, anti-malaria, and even as immunomodulator. The present article is aimed to give preferences around the potential of Pulai or Alstonia scholaris as immunostimulant.

1. Introduction

Pulai or also known as Alstonia scholaris is an evergreen tropical plant with high economic value that can thrive in various soil conditions, especially in peatlands. Furthermore, one of the largest peat ecosystem in Indonesia located in South Sumatera spanning 1,4 million ha (16,3%) spread across 5 regencies. Therefore, Pulai may be found all around South Sumatera including in Padiampe forest of Pagar Alam, Kebun Raya Sriwijaya of Indralaya, and Empat Lawang regency. In addition, South Sumatera has a monocultural community forest situated in Musi Rawas regency. Pulai trunks from this forest mostly utilized as the key material for pencil manufacturing industry.[1–3]

Along with that, Pulai also function as a shade tree and has been used in traditional medicine. Traditional medicine or ethnomedicine is an understanding or expertise in health services, disease prevention, and physical and mental health booster based on beliefs or experiences derived from different cultural origins and passed down from generation to generation. Ethnomedicine include Chinese traditional medicine, ayuverda from India, unani treatment from Arabia, traditional medicine from Egypt, Africa, America, Mediterranean as well as traditional medicine from various region of Indonesia. A handful citizens across the globe and Indonesia including South Sumatran natives believe that Pulai can treat syphilis, worms, diabetes, intestinal disorder, skin disorder, epilepsy, asthma, cough, as an anti-malaria, stops bleeding, and even prevent cancer.[2–5]

Immunomodulator is a biomolecule substance that can modulate, normalize, suppress, stimulate, nor modify different components of immune system. Generally, immunomodulator classified into three groups, such as immunosuppressant, immunostimulant, and immunoadjuvant. Bioactive substances from plants which have immunostimulant properties can improve immune system effectivity through different mechanism.[6]

This article aims to provide reference on bioactive compounds found in Pulai (Alstonia scholaris) that may have potency as an immunostimulant.

2. Method

The present article is a literature review executed by search of literature in English and Indonesian language from five databases, such as Google Scholar, ScienceDirect, EuropePMC, Proquest, and Wiley Online Library. Those articles that relevant and met the inclusion criteria were screened. The inclusion

criteria in this article include studies regarding the role of Pulai (Alstonia scholaris) as an immunostimulant either in computation, in vitro, in vivo, or in clinical test.

3. Result and Discussion

Characteristic of Pulai (Alstonia scholaris)

Alstonia scholaris comes from Apocynaceae family.[7] In 1767, Pulai was known as Echites scholaris. The name was later changed to Alstonia scholaris by Robert Brown in 1811 as an honour to Charles Alston, professor of the Materia Medica and Botany in the University of Edinburgh. Nevertheless, Alstonia scholaris also known as different names in different areas such as devil's tree, milk wood pines, mill wood, white cheese wood, blackboard tree, ditabark, saptaparna, chatian, paalimaaraa, and satvin.[8]

Pulai tree shaped like a pagoda with height ranging from 40-45 m and diameter of 40-60 cm. The trunk is straight, with slightly cracked bark, greyish brown or greyish white outer bark, and yellow to brown inner bark. The sap is milky white and can be obtained by cutting or scraping the bark. Pulai leaves are ellipse with size of 11-23 x 4-8 cm and 4-8 leaves whorls in one branch. It has dark green upper surface and paler lower surface. Flowers of Pulai are funnel shaped with length of 7-10 cm, white cream or green colour, densely clustered, and unique fragrant. Pulai blooms after dry season. Pulai has green-brown cylindrical fruits with length of 21-56 cm and diameter of 0,2-0,3 cm. The fruit contains a couple brown seeds inside.[7–11]

Pulai spreads around mixed forest ecosystem such as those in India, Sri Lanka, Indonesia, Malaysia, Myanmar, Nepal, Papua New Guinea, Filipina, Thailand, Vietnam, South China, Australia, and Solomon Island.[7,8] Pulai also can be found in tropical forest with red alluvial soil as well as rocky hillside at an altitude of 0-1000 m above sea level.[9,12] Pulai's taxonomy is as follows:[9,13,14]

Kingdom	: Plantae
Subkingdom	: Viridiplantae
Division	: Tracheophyta
Subdivision	: Spermatophytina
Class	: Magnoliopsida
Order	: Gentianales
Family	: Apocynaceae
Genus	: Alstonia
Species	: Alstonia Scholaris

Components of Pulai

Leaves

Leaves of Pulai contain substances such as triterpenoid, sterol, and alkaloid. Several indole alkaloids that have been identified from Pulai leaves like picrinine (5-methoxystrictamine, picralinal, and 5-methoxyaspidophylline), scholaricine, vallesamine, and 19-epischolaricine are believed to act as antitussive, anti-asthmatic, expectorant, analgetic, anti-inflammation, anti-allergic for asthma, and able to treat emphysema and pulmonary fibrosis.[16]

Bark

Substances found in Pulai bark are alkaloid, ditaine, echitenine, echitamine (ditamine), 17-O-acetylechitamine (echitamine derivate), echicaoutchin, echitamidine, echicherin, echitein, echiretin, triterpene β-amyrin, and lupeol.[7,17] The bark also known to hold hexane which has cytotoxic and antioxidant effect towards Dalton's Lymphoma Ascetic (DLA) cells.[16] Previous research also has been able to isolate N-Demethylechitamine, luperol acetate, stigmasterol, and α-sitosterol from root bark of Pulai.[8]

Flowers

The flowers enclose substances namely alkaloid, iridoid, triterpenoid, lupeol, β-amyrin, and ursolic acid.[7,8] Betulin and betulinic acid also identified from ethanol and aqueous extract of Pulai flowers. On top of that, a few triterpenes have been collected from ethanol extract of Pulai flowers including oleanane, alstoprenyol, (3-b-hydroxy-28-b-acetoxy-5-olea triterpene), 3,28-b-diacetoxy-5-olea-triterpene, and ursane like alstoprenylene (3-b-acetate-24-nor-urs-4,12,20-triene ester triterpene), 3b-acetate-24-nor-urs-4,12-diene ester triterpene, and 3b-hydroxy-24-nor-urs-4,12,28- triene triterpene.[8]

Figure 1. Pulai tree[12]

Figure 2. Leaves, flowers, and fruits of Pulai[11,15]

Fruits

Fruits of Pulai contain alkaloids as well. Those alkaloids are Q and R scholarisine with cytotoxic properties.[18] While alkaloids such as chlorogenic acid and small number of indole hallucinogen alkaloid (chlorogenine, alstovenine, reserpine, echitamine, ditamine, and venenatine) were found in Pulai seeds.[9]

Immunomodulator

Human immune system consists of non-specific (innate) and specific (adaptive) immune system. Innate immune system takes a role as first line defender against infection. This immune system response within minutes. Components of this immune system are external layer of epidermis (which contain keratinocytes), epithelial cells, effector cells such as granulocytes, macrophages, dendritic cells, natural killer cells, lymphoid cells, endothelial cells, antimicrobial peptides, and mediator cells. These innate cells able to recruit other immune cells to infection or inflammation sites through production of cytokine and chemokine. Some innate cells are phagocytic and capable in phagocytosis of microbe, pathogen, infected cells, and clearance of residual cells and foreign object in tissue, organ, blood, and lymphatic system.[19]

Specific or adaptive immune system act on specific pathogens. This immune system classified into cell mediated and humoral immune response. Main role of adaptive immune system is to differentiate "non-self" antigen with "self-antigen" and create immunological memory of those specific antigen in order to faster elimination in case of re-infection. Adaptive immune system comprises of antigen specific T cells which activated by interaction with Antigen Presenting Cells (APC) and B cells that will differentiate to plasma cells to produce antibody.[20]

Major Histocompatibility Complex (MHC) can be detected on the surface of APC. The interaction between T cells and antigen-MHC complex will stimulate T cells to differentiate into cytotoxic T cells (CD8+) and helper T cells (CD4+). Cytotoxic T cells deal with destruction of infected cells while helper T cells in charge of summoning cytotoxic and phagocytic immune cells as well as regulate the type of immune responses.[20]

An overreacting immune response is also called as hypersensitivity reaction. There are four hypersensitivity reactions, they are type I hypersensitivity (an allergic reaction due to provocation of repeated allergen exposure) marked by secretion of IgE by plasma cells, type II hypersensitivity, occurs when IgG and IgM antibody bind with cell surface antigens and complements causing agglutination of red blood cells (RBC), lysis, and cell death. Additionally, type III hypersensitivity arises when IgG and IgM antibody bind with protein and generate deposits in tissue causing activation of complement, inflammation, and mast cell degranulation. Moreover, type IV hypersensitivity develops over excessive stimulation of T cells and monocytes or macrophages prompting cytokine release and exciting inflammation, cell death, and tissue destruction.[19,20]

Immunomodulators are compounds that can affect immune system, either as stimulator, suppressor, or by influencing different aspects of immune response. Immunostimulators function to facilitate immune response in immunocompromised condition, such as in viral infection, cancer, and autoimmune disease patients. Immunosuppressors are given to autoimmune patients (for instance rheumatoid arthritis, lupus, Crohn disease) and individuals who received organ transplant to inhibit natural self-defence and to control immune response.[6,19]

Immunostimulant influence immune system by stimulating phagocytic cells, complement system, IgA antibody, encouraging release of α and γ interferon, T and B lymphocyte, and synthesis of cytokine, specific antibody, and lung surfactant. The efficiency of immunostimulant can be evaluated through in vivo and in vitro tests. In vitro test should be done before in vivo test to assess the basic mechanism. In vitro test should be accomplished using parameters such as lysozyme serum, complement, total leukocyte count, monocyte/lymphocyte/granulocyte count, antibody titer, phagocytosis activity, and leukocyte proliferation.

Plants Immunomodulator Screening Methods

The standard procedure used for screening is by substance extraction or fraction and biological activity examination of the substance pharmaceutically, via both in vitro and in vivo. In vivo method achieved by evaluation on organisms (experimental plants or animals). A number of screening techniques to assess immunomodulator

effect of a substance using in vivo approach are phagocytic activity test, leukocyte count, delayed type hypersensitivity test, nitroblue-tetrazolium reduction test, immunohistochemistry assay, haemagglutination antibody (HA) titer, splenocyte proliferation test, macrophage function test (production of NO), carbon clearance and Candida albicans clearance, and lymphocyte phenotype test. On the other hand, a couple screening methods using in vitro approach are chemiluminescene, nitroblue-tetrazolium assay, nitrous oxide assays, real-time polymerase chain reaction (PCR), western blot assay, enzyme-linked immunoassay (ELISA), plaque assay, and bead panel assay.[19]

Pulai as an Immunostimulant

Phytochemistry observation towards Pulai discover over 400 compounds including alkaloid (±169 alkaloids, e.g., alstonine, picrinine, akuamicine, echitamine), iridoid, coumarin, flavonoid, steroid, triterpenoid, and phenolic acid.[7–9,21] Flavonoids are known to stimulate immune system by enhancing macrophage and T cells activity as well as encourage mononuclear cells to release cytokines thus IL-1β, IFN-γ, and TNF-α. Likewise, terpenoids renowned to improve phagocytic activity of macrophage. In addition, alkaloids exhibit diverse chemistry configuration and provide pharmacological properties of a plant which play an important role in the development of novel medicines.[17]

Monoterpenoid Indole Alkaloids (MIAs) are the predominant secondary metabolite obtained from condensation of tryptamine and secologanin. This compound gives anti-inflammatory property through inhibition of IL-6 cytokine, supress production of TNF-α and IL-8 in lungs, and constrain COX-2 and/or 5-LOX (picralinal and tubotaiwine alkaloids, in particular).[8] Anti-inflammatory and anti-asthmatic property of Pulai attained by stimulation of β2 adrenergic receptor and impede expression of nuclear factor-κB (NF-κB).[16,22]

Combination of alkaloids and triterpenoids from Pulai leaves affirmed to escalate immunomodulator activity in mice (in vivo) and induction of A549 cell apoptosis (in vitro). This combination proven to induce A549 cell apoptosis by regulation of pro-casp8 and caspase-8.[16]

Earlier research using Pulai's bark extract administered to mice uncover numerous mice that received 100 mg/kgBW aqueous extract have an increase lytic activity of peritoneal exudate cells against Escherichia coli. At a dose of 50 mg/kgBW/day, the phagocytic activity of mice with immunodeficiency increased. While, a dose of 100 mg/kgBW able to supress type IV hypersensitivity reaction (delayed-type).[9,14,17,23,24] Other research examining methanol and chloroform from Alstonia scholaris discovered enhancement of delayed-type hypersensitivity reaction on albino wistar rats at a certain dosage. The research also found that methanol and chloroform extract at a dose of 400 mg/kgBW shown the highest phagocytic index. Whereas, the group of rats given dosages of 200 and 400 mg/kgBW manifest increased number of erythrocyte, leukocyte, and haemoglobin. Another study with animal trial that were given cyclophosphamide (compound with suppressor activity against specific and non-specific immune response) causing decreased of erythrocyte, leukocyte, lymphocyte, and platelet counts of the animals. Afterwards, those animals were given methanol and chloroform extract of Pulai consequently there are significant changes of erythrocyte, leukocyte, and haemoglobin quantity. Thus unveiled that components in Pulai extract are competent to prevent cyclophosphamide to interact with stem cells, hence synthesis of haemoglobin, leukocyte, and erythrocyte are uninterrupted.[19,25]

4. Conclusion

Pulai or Alstonia scholaris is a widespread plant in South Sumatera. This plant has been used as herbal medicine by society and has been studied by numerous researches. Alkaloid is one of the predominant bioactive compounds and proven to sustain pharmacological property in Pulai. Nevertheless, knowledge of Pulai's immunostimulant property is limited. Therefore, further study is required.

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