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POTENCY OF PURPLE YAM (*Dioscorea alata L*) AS AN IMMUNOMODULATORY AGENT

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Abstract: Purple yam tuber (*Dioscorea alata L.*) is one of tubers that has not been used optimally. One of the nutrients contained in Dioscorea species is Saponin Steroid. This paper aims to examine the potential of Steroid Saponin in purple yam tuber (*Dioscorea alata L.*) as an immunomodulatory agent. The method is by reviewing from various literatures. This article found that Steroid Saponin in purple yam tuber (*Dioscorea alata L.*) had a potency as an immunomodulatory agent.

Keywords: Purple yam tuber (*Dioscorea alata L*), Steroid Saponin, Immunomodulatory

INTRODUCTION

Purple yam tuber (*Dioscorea alata L.*) is one of tubers that has not been used optimally. Some of the nutrients contained in Dioscorea species are carbohydrate, essential amino acid, mineral, polyphenol, mucin (Glycoproteins), purin derivatives (eg Alantoin) and steroid saponins.[1-10] *Dioscorea alata L.* contained diosgenin[11] which is the major aglycone of steroid saponin acting as an intermediate steroid in the pharmaceutical industry. Steroid saponin is the most important bioactive compound due to its several biological functions, such as anticarcinogenic, antithrombotic, antiviral, hemolytic, hypocholesterolemia, hypoglycemic, immunostimulatory, antitumorigenic, anti-mutagenic, immunomodulatory and anti-inflammatory depending on its structure.[6-9]

This article aims to find the potency of steroid saponin in purple yam tuber (*Dioscorea alata L.*) as an immunomodulatory agent.

DISCUSSION

Dioscorea genus is a member of the monocotyledon dioscoreaceae family and becomes staple food in West Africa, Southeast Asia, and the Caribbean.[12] Fresh cut tubers is widely used as a staple food in Taiwan and the dried pieces are used in traditional Chinese medicine.[13]

Dioscoreaceae family in Indonesia is *Dioscorea alata, Dioscorea hispida, Dioscorea pentaphylla, Dioscorea esculenta*, and *Dioscorea bulbifera*. The superiority of Dioscoreaceae family is its ability to grow under the tree in the forest. However, it is a substitution plant (not a staple food) because its utilization is still limited. Dioscoreaceae family is important because it also contains bioactive or functional compounds beside as staple food.[14,15]

Dioscorea alata L. is a relative of *gadung* and *gembili*. It is easily known from its rectangular trunk. Its tubers cannot be eaten raw because the juice causes itchy mouth. According to the shape, the tubers can be distinguished in several types. There are sharp spikes on the tubers that the wild boars scared of. That's why people often plant them around the yard to frighten these greedy animals.[16]

Dioscorea alata L. tubers have irregularly shape, brown soil color, and large size. The color of this tuber is purple and white. There are about 600 types of *Dioscorea* worldwide, but only about twenties have been cultivated and used for its tubers. Most of them are used for staple food. Several others are used for non-food purposes, for example traditional medicine, pesticides, and food colorings.[17]

Classification of *Dioscorea alata L.*:

Kingdom	: Plantae
Phylu	: Magnoliophyta
Class	: Liliopsida
Order	: Dioscoreales
Family	: Dioscoreaceae
Genus	: Dioscorea
Species	: *Dioscorea alata L.* [18].

Dioscorea alata L. has a high potency because of good nutritional content, good for diabetics because it is tasteless, good for gluten allergy sufferers, and contains natural purple dye. It is also used to make processed products of noodles, cakes, bread, ice cream and jam. Its nutrition contents are 89.73% water, 0.62% ash, 0,55% acid unsaturated-ash, 0,67% fiber content, 10,93% starch, 0,82% fat, and 1.36% protein.[19]

Figure I. Purple Yam (*Dioscorea alata L)*

The highest nutrient composition of *Dioscorea alata L.* is carbohydrate (73.27 - 92.37%) in the form of dry matter. Water and fat content changes especially in chips and flours of *Dioscorea alata L.* In chips, fat increases up to 2.314%, and water goes down to 56.61%. In flour, there was a decrease of water up to 88.93%. The highest phenolic compound in steamed *Dioscorea alata L.* is 265.49%, but there is a real difference between processing within phenolic content in *Dioscorea alata L.* The highest anthocyanin content in steamed *Dioscorea alata L.* which is 131.67%. It shows that there is a real difference between some processes with anthocyanin content. The largest antioxidant activity in steamed *Dioscorea alata L.* which is 64.97%. There is a real difference between the processing of *Dioscorea alata L.* with antioxidant activity. Steaming is the best process because it has the least effect on the reduction of nutrients, phenolic compounds, anthocyanin, and antioxidant activity.[20]

The results showed that Dioscoreaceae family contained bioactive compound, which were Dioscorin [21-23] and thick Musin in the form of Glycoprotein.[24] *Dioscorea alata L.* contained Diosgenin.[11]

Diosgenin is a steroidal saponin found abundantly in legumes and Dioscorea genus. Diosgenin is the basic ingredient of various synthetic steroid drugs that are widely used by the pharmaceutical industry. Over the past two decades, a series of preclinical and mechanistic tests have been performed to prove the benefits of Diosgenin against metabolic disease (hypercholesterolemia, dyslipidemia, diabetes, and obesity), inflammation and cancer.[25]

SAPONIN IN *Dioscorea alata L.*

Diosgenin is an aglycon steroidal saponin in the Dioscorea genus which being the raw material for steroid medicinal industry obtained after the hydrolysis of the genus Dioscorea saponin. Other saponins that have been identified in the Dioscorea genus are Dioscin, Gracilin, and Prosapogenin from Dioscin. Dioscin content is ± 2.7% (weight / weight). While Diosgenin content is ± 0.004% in cultivated Dioscorea and 0.12-0.48% in wild Dioscorea genus.[26,27]

Saponin is a steroid or triterpenoid glycoside found in wild plants or cultivated plants, low-grade marine animals, and some bacteria. Saponins contain steroid or triterpenoid aglicons bound to one or more sugar chains. Triterpenoid saponins are found widely in cultivated plants, whereas steroidal saponins are found in herbs. Steroidal saponins are found in whole grains, paprika, eggplant, tomato seeds, allium, asparagus, yam, klabet, yucca, and ginseng.[28]

Dioscorea species are characterized by Diosgenin, a steroidal saponin found in species from North America or Asia. Diosgenin is the main active compound in the Dioscorea genus and has similar structure to cholesterol.[29] Diosgenin levels vary among species.[30,31] Diosgenin contents and its benefit are based on species, growth technique, harvesting, processing, and storage conditions.[29]

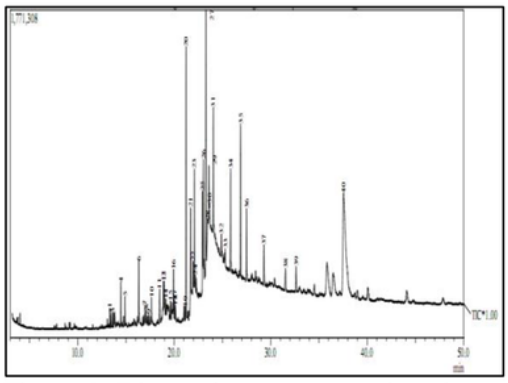

Figure 2. Diosgenin structure and analogues of protodioscin (a), steroidal saponin composed of hydrophilic sugars connected to hydrophobic steroid aglycon (b) [25].

Steroidal saponins found in Dioscorea sp. are Diosgenin and Dioscin. After oral administration, Diosgenin is metabolized in the liver and eliminated by bile. Diosgenin is synthesized and metabolized into steroids in the human body. Toxicology experimental studies have shown that Diosgenin with a concentration above 3.5% is safe, does not cause systemic toxicity, genotoxicity, and estrogenic activity.[25]

Gas Chromatography-Mass Spectrophotometry (GC-MS) test of *Dioscorea alata L.* tuber hexane extract contains steroidal saponin (Figure 3).

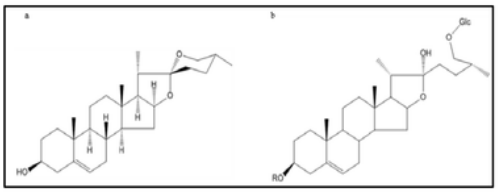

Figure 3. GC-MS spectrum of *Dioscorea alata L.* hexane tuber extract. Description: number 40 is steroidal saponin.

The results of GC-MS showed the presence of 11 compounds having the highest spectra peak. They were compound number 20, 21, 23, 25, 26, 27, 29, 31, 34, 35 and 40. The result of mass spectrophotometry of the compound was hexadecanoic acid methyl ester (methyl palmitate), hexadecanoic acid (palmitic acid), alpha octadene, hexadecadinoic acid (palmitolinoleic acid), octadecanoic acid (methyl ocadecec-14enoate, triglyceride), octadecanoic acid (oleic acid), methyl ester eicosadinoic acid, tricosanol (eikocene), tetradecanol , bensendicarbolic acid (ptalic acid), γ-sitosterol (fukosterol) (Steroidal Saponin).

The compounds are fatty acid groups. Alpha octadene is an anticancer, antioxidant, and antimicrobial agent.[32,33] Octadecanoic acid (oleic acid) is an unsaturated fatty acid that can decrease LDL (low density lipoprotein), increase HDL (high density lipoprotein), and it also has anticancer activity in breast cancer.

The result of Makiyah's study in 2016 proved that the isolates of steroidal saponin had potential as immunomodulators by decreasing the relative amount of CD4 + CD62L + T- lymphocytes and increasing CD4 + CD62L T-lymphocytes.[34]

Dioscorea sp. ethanol extract containing 28.34% of Diosgenin did not cause acute toxicity in mice at doses above 562.5 mg / kg / day significantly and did not cause toxicological parameters change at doses greater than 255 mg / kg / day (Qin et al., 2009). *Dioscorea villosa* extract at 0.79 g / kg / day did not cause toxicity on kidneys and liver, but administration for 28 days caused fibrosis of the kidney and inflammation of the liver. Therefore, the toxic effects occurred when taking this extract in the long term, especially in individual with impaired renal and hepatic function (Wojcikowski et al., 2008).[36]

EFFECTS OF SAPONINS ON THE IMMUNE SYSTEM

Saponin as adjuvant has a unique ability to improve immunity.[37] Adjuvant can improve the immune response to vaccine antigen several purposes, which are 1) increase immunogenicity of weak antigen, 2) increase the speed and duration of immune response, 3) modulate distribution of avidity, specificity, isotype or subclass of antibody; 4) stimulate immunity cell-mediated, 5) promotes mucosal immune induction, 6) improves immune response in immunologically immature individuals, 7) lowers antigen doses of vaccines to reduce costs, 8) helps to combat antigen competition in combination with vaccines.[38] Adjuvant was originally used as an agent to promote and maintain an antibody response. Adjuvant affects titer, duration, isotype, antibody avidity, and cell-mediated immunity.[39]

Saponin as an adjuvant has the ability to modulate the cell-mediated immune system and increase the production of antibodies. The benefit of this adjuvant activity is not only requires low dose.[40] Saponin induces a strong adjuvant effect to T cell dependent- antigen and T cell independent antigens. Saponins also induce a strong cytotoxic lymphocyte CD8 + response and respond to mucosal antigen.[41] Saponins not only have stimulatory effects on specific immune components, but also have non-specific immune reactions, e.g. inflammation[42,43] and lymphocyte proliferation.[44,45]

Diosgenin's suppressive effect on Th2 intestinal responses was associated with increased Treg cell immunity. Diosgenin administration reduced IL-4 and intestinal GATA-3 expression in ovalbumin sensitized Balb / C mice. This suggested that the Diosgenin's suppressive effect on Th2 intestinal response induced by allergens was closely related to upregulation of Treg cell immunity at the inflammation site.[46] Diosgenin had antiallergic activity in ovalbumin sensitized Balb / C mice which was indicated by suppression of IgE production, infiltration, and mast cell degranulation.[47]

The effect of Diosgenin on humoral immunity has been studied in ovalbumin sensitized Balb / C mice for 34 days. The result was increasing of production of serum IgG2a (Th1) specific to Ovalbumin significantly after Diosgenin administration. Ovalbumin induced IFN-γ secretion and mRNA expression characterized with the increase of splenocyte in Diosgenin treated mice. Tbet expression in splenocytes was up regulated by Diosgenin administration[48] but not in GATA. Study on the effects of 3 kinds of diosgenil saponins on immunostimulation effectiveness associated with phagocytosis, respiratory disturbance, and production of nitric oxide in macrophages cell of RAW 264.7 mice showed that Diosgenil saponins significantly increased the efficacy of phagocytosis as the saponin concentration increased to maximum. Then, it tended to decrease as concentration of saponin keep increasing.[49]

Antiallergic activity of Diosgenin was screened using RBL-3H3 cells, the aglycon group found to have higher activity than molecular glycosylated, in which substitution with rhamnoglucoside appeared to reduce antiallergic activity. Furthermore, Tewtrakul & Itharat in 2005 performed a study about the effects of antigen induced dioscorealide A, dioscorealide B, and dioscoreanone against IL-4 and TNF-α release in late-phase of allergic reactions.[50]

SAPONIN ACTION MECHANISM

The mechanism of action of saponins to stimulate the immune system has not been clearly understood. Saponins were reported to induce the production of cytokines, such as interleukins and interferon that would mediate their immunostimulatory effects.[41] It is possible that saponins interacted with Antigen-Presenting Cells to induce some of these responses. The combination of saponins into cells or endosomal membranes may expose antigen combinations with cytosolic proteases. Saponins joined with the cell membrane in the cholesterol section, forming small or porous holes. It is not known whether the adjuvant effects of saponins are associated with porous formation which will allow the antigen to reach the endogenous pathway of the antigen presentation and promote the cytotoxic T lymphocyte response.[51]

There is only a few review of immunostimulatory activity of saponins nor the mechanisms involved, both from the nutritional point of view and the relationship between the structure and its activity.[28] It has been shown that saponins improved the immune response by absorption of antigens from the gastrointestinal tract and other

membranes. Peroral administration of saponins from Panax ginseng, Quillaja saponin and butanol extract of *Lonicera japonica* have been shown to stimulate the in vivo mucosal immune response. Saponins also protect the antigen from breaking down in the digestive tract by forming a complex with the antigen. Saponin permeability is important when systemic response is induced in the intestinum. For example, Saponin-1 Deasilation is an effective intestinal agent which is able to increase the permeability with mild side effects on epithelial viability and barrier function.[52]

Saponin adjuvant activity may be associated with branching of the sugar chain, aldehyde group, or to the acyl bearing residue of aglycone.[41] Modification of the fire particles affects adjuvant activity but not its toxicity in vivo.[53]. Overall, juxtaposition of the hydrophilic and hydrophobic functional groups is preferable to the structure of the individual groups. This is an important element influencing the adjuvanity.[40]

The various actions of saponins show that the immunostimulatory effect of saponins is a result of a specific target of physiologic intermediates that is better than the result of the cell membrane permeability non-specific effects.[28]

CONCLUSIONS

Steroidal Saponin in purple yam tubers (*Dioscorea alata L.)* are potential as immunomodulatory agents.

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