

REVIEW ARTICLE: UTILIZATION OF INDONESIA' NATURAL RESOURCES AS RAW MATERIALS IN PHARMACEUTICAL INDUSTRIES FOR THE TREATMENT OF DEGENERATIVE DISEASES

Agi Meisarani, Amalia O. Permatasari, Gadis Fujiastuti, Gina Andriana, Liza F. Koeswandy, Rano K. Sinuraya

Pharmacist Professional Programme, Faculty of Pharmacy, Universitas Padjadjaran
Jalan Raya Bandung, Sumedang, Km. 21 Jatinangor 45363
agimeisarani17@gmail.com

ABSTRACT

In Indonesia, health problems such as treatment of degenerative diseases are still not be handled properly. The common degenerative diseases in Indonesia are diabetes mellitus and hypertension. Generating qualified medicines with lower cost for degenerative disease are still be a major problem because Indonesia has not been independent in pharmaceutical raw materials. Raw materials are important part in the production process of pharmaceutical preparations. Indonesia obtained raw materials by importing from various countries. By looking at the various potentials of natural resources that can be used as a source of raw material in pharmaceutical industries, both active pharmaceutical ingredients (API) and excipients, Indonesia will be able to independently produce the pharmaceutical raw materials. To achieve independency of pharmaceutical raw materials, the appropriate processing methods to produce quality raw materials is needed. Based on this issue, a review of various studies was performed including the processing of API and pharmaceutical excipients raw materials of plant and animal body parts. "Kayu Manis" (*Cinnamomum burmanii*) and "Brotowali" (*Tinospora cripa* L.) which can be utilized as raw material pharmaceutical ingredient for the treatment of diabetes mellitus and "Mengkudu" (*Morinda citrifolia* L.) which can be used for the treatment of hypertension disease. Meanwhile, some natural resources that can be used as excipients are gelatin from the skin and fish bones (as a binder in the preparation of tablets), carrageenan from seaweed (emulsifier and suspending agent) and the Mimosa "Putri Malu" (*Mimosa pudica* L.) mucilago seed (as an alternative to polymer as buchoadhesive agent, disintegrator and binder).

Keywords: Independency of pharmaceutical raw materials, natural resources of Indonesia, pharmaceutical industries independency, natural API for diabetes, natural API for hypertension, Indonesia' natural excipients

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1. Introduction

One of the important component in producing products in the pharmaceutical industry is the raw materials. Pharmaceutical raw materials are needed to produce different types of drugs. The raw materials

which are used in pharmaceutical industry are outlined into four types of raw materials. The first is active drugs raw materials (BBAO) which are chemically processed. The second is additional drugs raw materials (excipients), the third is active drugs raw

materials which are biotechnology-processed, and the last is active drugs raw materials derived from ingredients of the stem cell (cell stem) which is a new technology in the developing active ingredients of the drug.

The Indonesian pharmaceutical industry has not developed intermediate chemical industry (including agrochemicals), active pharmaceutical ingredients, and development research contracts (Sparinga, 2010). The Indonesian pharmaceutical industry is developing more industrial formulations, enhancing the final product by relying on its superiority or equality in bioavailability/bioequivalent (BA/BE).

Drug raw materials in Indonesia are still dependent on imports, both Active Pharmaceutical Ingredients (API) and supporting drug raw material (excipients). Both are as much as 90% , likewise raw materials for packaging also amounted to 50%, it is due to the qualified professional human resources as well as the state of infrastructure to produce raw materials of drugs are still very limited (Binfar Kemenkes RI, 2016; Limakrisna, et al., 2017). Domestic production for active ingredients of drugs (raw materials of drugs) is still very limited and not yet meaningful. Although Indonesia is able to produce it,

most of them cannot compete with imported products.

Pharmaceutical raw materials can be obtained from various natural and synthetic sources. Indonesia has a tropical climate and is well known as a country which is rich of biodiversity that can be used as a source of raw materials of drugs to overcome various diseases (Susiarti, 2015). The utilization and development of traditional medicine from natural materials in Indonesia has been done hereditary heritage based on experience/empirical (Kemenkes RI, 2013). Indonesia also exports some herbal medicine to various countries. The value of Indonesian herbal medicine exports in 2013 reached US \$ 23.44 million, while the export value in the period of January-June 2014 amounted to US \$ 29.13 million, an increase of 600% of the export value in the period from January to June 2013. The herbal medicine exported from Indonesia during the period of 2009-2013 increased by 6.49% per year. This proves that natural materials in Indonesia have a high potential to be developed into a source of pharmaceutical raw materials for the pharmaceutical industry.

According to WHO, countries in Africa, Asia and Latin America use herbal medicine as a complement to primary treatment. WHO recommends the use of traditional medicine for maintaining public health, preventing and

treating some diseases, especially for chronic diseases, degenerative diseases and cancer. WHO also supports some efforts to improve the safety and efficacy of traditional medicine (WHO, 2013). This can be the basis for the Indonesian state to develop the production of medicinal raw materials, especially herbal-based active ingredients.

Currently, degenerative diseases are one of the biggest causes of death in the world. According to WHO, about 17 million people die earlier each year due to the global epidemic of degenerative diseases. These degenerative diseases include cardiovascular disease (heart and blood vessels) including hypertension, diabetes mellitus and cancer (Brunner and Suddarth, 2002). One of the most common degenerative diseases which has a high mortality rate and affects the life and productivity of one person is hypertension and diabetes.

The prevalence of degenerative diseases in Indonesia has increased, especially hypertension and diabetes mellitus. Based on Riskesdas data in 2007, the prevalence of diabetes mellitus is 1.1% and hypertension 7.2%, while for the year 2013, diabetic prevalence increased to 2.1% and hypertension is to 9.4% (Rahajeng and Tuminah, 2009).

Hypertension or high blood pressure is one of the most deadly diseases in the world, according to WHO. Hypertension is a

condition in which consistent blood flow has high pressure on artery walls. Besides the hypertension, the disease that is still a problem for the population of Indonesia is diabetes. Diabetes Mellitus (DM) disease known as diabetes or blood sugar disease is a chronic disease class characterized by an increase in blood sugar levels exceeding 150 mg/dl, as a result of a metabolic system disorder in the body, where the pancreas organ is unable to produce hormones insulin according to body needs (Ernawati, 2013). Indonesia is the fourth most populous nation after the United States, China and India (Sari, 2013).

Degenerative diseases such as hypertension and diabetes mellitus require long-term treatment with medications that have minimal side effects. Synthetic drugs have greater side effects compared to drugs derived from natural ingredients. Therefore, it is necessary to develop drugs derived from natural materials.

2. Methods

References in this review were generated from online data basis, e.g. scientific journals, both national and international journals from database. Searchingsystem was done using keywords: antidiabetes from plants, medicinal plants of Indonesia used for diabetes, antihypertensive from plants, Indonesia' plants used in the treatment of

hypertension, natural excipients, Indonesia' pharmaceutical excipients, Indonesia' herbal excipients. Strategies in searching related articles as references was done using scientific database such as Google Scholar, PubMed, PLoS, science direct, and springer. It was obtained 30 original articles in this review.

3. Results and Discussion

One alternative that can be used in the development of new drugs is to utilize plants as a starting material. The summary of utilization of Indonesia' natural resources as a pharmaceutical raw material in pharmaceutical industries can be seen in **Table 1**. The potential of pharmaceutical industry raw materials derived from natural ingredients in the framework of development of new drugs that can be used including cinnamon (*Cinnamomum burmanii*) and

brotowali (*Tinospora cripa* L.) which can be utilized as raw material for diabetes mellitus medication, and noni is used for the treatment of hypertension disease (*Morinda citrifolia* L.) (Menkes RI, 2016).

3.1 Natural API as Pharmaceutical Raw Material Ingredients for the treatment of Diabetes Mellitus

As one of the alternatives that can be used in the development of new drugs for diabetes mellitus is to utilize the plant as a starting material. Diabetes mellitus can be overcome with plants that have flavonoid chemical compounds. Based on the results of research and has been scientifically proven that plants containing flavonoid compounds can lower blood glucose levels. One of the plant that containing flavonoids is cinnamon (*Cinnamomum burmanii*) (Alusinsing, et al., 2014).

Table 1. Utilization of Indonesia' Natural Resources as a Pharmaceutical Raw Material in Pharmaceutical Industries

Utilization	Natural source	Part of natural source	Activity	Research
Raw material ingredient as natural API	Cinnamon (<i>Cinnamomum burmanii</i>)	Folium, cortex	Anti-hyperglycemic	Djaya, N., et.al., in 2011; Kondoy, S., et.al., in 2013; Alusinsing, G., et.al., in 2014; Novianti, E., et.al., in 2016
	Brotowali (<i>Tinospora crispa</i>)	Radix, folium	Anti-hyperglycemic	Sangsuwan, C., et.al., in 2004; Klangjareonchai, T., et.al., in 2012; Mathew et. Al., in Kundicrao (2013); Jaya, L.R., in 2015
	Noni (<i>Morinda citrifolia</i> L.)	Folium	Anti-hypertensive	Wang, M.Y., et.al., in 2002; Yang, S.C., et.al., in 2007; Palu, A., et.al., in 2008; Ali, M., et.al., in 2016
Raw material ingredient as natural excipient	Mimosa mucilago (<i>Mimosa pudica</i> L.)	Seeds	Buchoadhesive agent, disintegrator, and binder	Ahuja, M., et.al., in 2010; Ahuja, M. et al., in 2013
	Lencam fish (<i>Lethrinus sp</i>); Tenggiri fish (<i>Scomberomorus commersonii</i>); Patin fish (<i>Pangasius pangasius</i>); Catfish (<i>Clarias gariepinus sp</i>); Tuna fish (<i>Thunus albacares</i>)	Gelatin from the skin fish; Gelatin from the fish bones	Binder	Adiningsih, Y., et.al., in 2015; Saputra, R., et.al., in 2015; Iqbal, M., et.al., in 2015; Agustin, A., et.al., in 2015; Imani, D., et.al., in 2016
	Seaweed (<i>Kappaphycus alvarezii</i>)	Carrageenan from Seaweed	Emulgator; Suspending agent	Harun, M., et.al., in 2013; Failu, I., et.al., in 2016; Erjana, S., et.al., in 2017

3.1.1 Cinnamon (*Cinnamomum burmanii*)

The mechanism action of cinnamon is increasing the sensitivity of the insulin receptor, which activates the PI 3-kinase receptor and inhibits tyrosine phosphatase to increases the concentration of the phosphorylated IRS-1 substrate and binds to PI 3-kinase, activates glycogen synthase, stimulates glucose uptake, and activates kinase from the receptor insulin (Djaya, et al., 2011).

A research on potency of ethanol extract of cinnamon leaf decreasing blood glucose level was done by Kondoy, S., Wullur A. and Bodhi, W., in 2013 which was conducted on male white rat that induced by sucrose. The ethanol extract of cinnamon leaf was obtained from the extraction process by maceration method using 95% ethanol. In this study, the test was performed by male white rat which has been divided into 5 groups, group A (negative diabetes), group B (positive diabetes and previously induced by sucrose), group C (dose of leaf extract cinnamon 5% ie 0.125 g extract/2.5 ml aquades), group D (10% cinnamon leaf dose ie 0.25 g extract/2.5 ml aquades), and group E (dose of cinnamon leaf extract 20% ie 0.5 g of extract/2.5 ml of aquadest). In this study, the results of the group of rats has proven that cinnamon leaf extract decreased blood glucose levels (Kondoy, et al., 2013).

Other research is done by Novianti, E., Irawan, N., Hertati, A., and Tisnadajaja in 2016 was to make a chewable lozenges formulation of cinnamon extract (*Cinnamomum burmanii*) as an alternative to type 2 DM therapy. The formulation of chewable lozenges extract cinnamon made because to overcome the patients boredom in taking antidiabetic medicines. In this study, extraction of cinnamon bark (*Cinnamomum burmanii*) was the first and until the extract of dried cinnamon bark was extracted.

After that a chewable lozenges formulation was prepared into 3 formulations with different gelatin and sorbitol compositions, ie formula I (Gelatin 22.5 g and Sorbitol 20 ml), Formula II (Gelatin 20 g and Sorbitol 17.5 ml), and the formula III (Gelatin 17,5 mg and 15 ml). Made a chewable lozenges base by adding gelatin with liquid sorbitol into water and then heated to homogeneous and cooled. Then added another composition of sodium propionate, dried cinnamon bark extract, chocolate essence and aspartame. Then, added aquades and poured in, then put into the refrigerator (Novianti, et al., 2016).

After the preparation hardens remove it from the mold and insert it into a tightly sealed container. To prevent each preparation stick together then added starch. The resulting chewable lozenges are then evaluated physically and chemically. The results of the test on chewable lozenges

formula of cinnamon extract which has the best quality and level of elasticity is the formula III with the composition of 17.5% gelatin and 15% sorbitol, but need to improve the formula in order to cover the bitterness caused by cinnamon extract. From some of these studies, it can be seen that cinnamon leaf extract has the potential to lower blood glucose levels (Novianti, et al., 2016).

3.1.2 Brotowali (*Tinospora crispa*)

Besides cinnamon, other plants that have the potential to be used as starting materials for diabetes drug is brotowali (*Tinospora crispa*). Brotowali contains bitter substances tinokriposid, soft resin, starch, glycosides, pikroretosid, harsa, kolumbin, kaokulin or pikrotoksin, and some alkaloids such as aporfin, beberin, and palmatin. Brotowali also contains flavonoid compounds, phenylpropane, acetogenin, saponins and tannins. The most important compounds found in brotowali stems are suspected to be tinokrisposid compounds that have activity as antimalarial, antiinflammatory, and antidiabetic (Dalimartha, 2008).

Various studies have shown that brotowali has the potential to lower blood glucose levels. *Tinospora crispa* was found to have an anti-hyperglycemic effect in animals. The hypoglycemic effect of *Tinospora crispa* is mediated by increasing

insulin secretion from isolated rat and human islets of Langerhans (Sangsuwun, et al., 2004).

Research done by Matthew et.al. in Kundlicrao (2013) showed that oral administration of an aqueous *T. Cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant anti-hyperglycemic effect in different animal models, its effect was equivalent to only one unit/kf of insulin (Kundlicrao, 2013).

Research conducted by Jaya (2015) using a brotowali plant to be consumed by humans with brotowali tea manufacturing. Processing by cutting leaves brotowali, then dried until dry then pounded. After that, put into the tea pack, with concentrations of 10 - 20% per pack. Brotowali tea is very useful to lower blood sugar levels of people with type II diabetes. With a concentration of 10-20% on a glass of tea and drunk twice a day, will help lower sugar levels in people with type II diabetes. This study proves that borapetoside C can increase the benefits of glucose, slows insulin growth and increases insulin sensitivity (Jaya, 2015).

Another study done by Klangjareonchai and Chulaporn (2012), was performed from 10 healthy subjects and 10 diabetic type 2 participants, who had fasted overnight, were obtained every 30-60 minutes during the 3

hours of continued fasting and during the 3 hours after ingestion of 75 g of glucose with or without ingestion of 125 or 250 g of *Tinospora crispa* dry powder capsule. Coarse powder of *T.crispa* stem was defatted with petroleum ether (60–80°C) and dried material was extracted with 70% ethanol using soxhlet apparatus at 65–70°C for 7 days. The extract was dried under vacuum in a rotary evaporator. Powder was used microcrystalline cellulose at 7% of powder weight and using dry granulation technique. Powder of 125 and 250 mg *T.crispa* stem was prepared in form of capsule (Klangjareonchai and Chulaporn, 2012).

Glucose and Insulin levels were analyzed and the areas under the curve for mean serum glucose and insulin levels were calculated. The result is demonstrated that *T.crispa* cannot significantly reduce mean serum glucose AUC in diabetic patient but can show a trend to reduce mean glucose AUC 478 to 444 mg mL/min. 250 mg of *T.crispa* may not be adequate dosage to reduce serum glucose and stimulate insulin and another reason is that it may not last long enough to show the effect of treatment (Klangjareonchai and Chulaporn, 2012).

In Indonesia, brotowali and cinnamon are almost spread throughout the region. The cinnamon plant itself has long been

developed in Indonesia and is one of the commodity spices that became the main merchandise since the colonial era. This plant is a prime commodity, especially in the area of West Sumatra and Kerinci regency, as the center of cinnamon production in Indonesia. Brotowali itself is found in Java islands, Bali and Ambon (Hidayat, 2011).

3.2 Natural API as Pharmaceutical Raw Material Ingredients for the Treatment of Hypertension

In addition to diabetes mellitus, one of the many diseases suffered in Indonesia is hypertension. Hypertension is the most common cardiovascular disease and can lead to complications of heart failure, coronary heart disease, kidney failure, and stroke. Antihypertensive drugs currently used include diuretic class drugs, β -blockers, ACE inhibitors, calcium antagonists, α blockers, and vasodilators. However, the procurement of these drugs can not be reached by the public because the price is quite expensive. Therefore, currently developed natural medicine (back to nature) that is more affordable by the community. One natural remedy widely used public is noni (*Morinda citrifolia* L.)

3.2.1 Noni (*Morinda citrifolia* L.)

Noni (*Morinda citrifolia* L.) is a tropical plant that has been used as food and herbal medicine. Noni has many benefits for health such as antithrombolytic, antioxidant,

analgesic, anti-inflammatory, antidiabetes, anticancer, improve the immune system and antihypertensives (Ali, et al., 2016). Noni (*Morinda citrifolia* L.) contains several main active substances, such as scopoletin, octoanoic acid, potassium, vitamin C, alkaloids, anthraquinone, b-sitosterol carotene, vitamin A, flavone glycosides, linoleic acid, alizarin, amino acid, acubin, L-asperuloside, caproic acid, caprylic acid, ursolat acid, routine, proxeronine and terpenoids (Wang, et al., 2002). One of the active compounds was act as antihypertensive is scopoletin. Scopoletin has hypotension activity by vasodilatation mechanism through its smooth muscle relaxant activity, acting as a nonspecific spasmolytic agent, and might have an ACE inhibitory effect (Ojewole and Adesina, 1983).

According to Yang et. al. (2007) on their research "Chang in phenolic compounds content, free radical and superoxide anion radical scavenging activities were determined in two noni juices with different extent of maturity from traditional fermentation process" showed that fermented noni juice obtained from ripe fruit is better yield than unripe fruit and also contains higher quantities on total phenolic compounds, flavonoids, condensed tannin and scopoletin, thus exhibiting higher

reductive activity, better superoxide anion and H₂O₂ scavenging activities, and better ACE inhibitory activities (Yang, et al., 2007).

The second research by Palu et al. (2008) conducted on human subjects aged 28-56 years are all diagnosed by the primary care physician to have high blood pressure, not taking prescription drugs and was a volunteer participants. Only those with an average systolic pressure ≥ 130 mmHg and at least 1 diastolic pressure ≥ 80 mmHg were included in this study. The research focus is on the possible mechanisms involved in vitro, while not taking prescribed blood-pressure medications. The test group consisted of 10 subjects (7 males, 3 females, ages 28-56 years) who were medically diagnosed with high blood pressure, but currently not taking any prescribed medications. Each subject consumed 2 ounces of TNJ twice a day, for 1 month. The result has shown that *Morindacitrifolia* L noni products can inhibit ACE enzyme and angiotensin receptors AT1 and AT2.

The third research by Indiriawati et al., where they conducted research on the influence of Noni (*Morindacitrifolia*) against Hypertension in the Elderly Group. This research is an experimental research with pre-test-post randomized control group design design with 30 subjects. Each respondent was required to drink capsule 2x

per day for 15 days on a regular basis. Each capsule contains pure *M. citrifolia* extract of 450 mg. Results from the study showed that there is a decrease in systolic and diastolic blood pressure were statistically significant in the elderly who consume *M. citrifolia* extract capsules regularly. From all these studies it can be concluded that *Morindacitrifolia* L. has a strong enough effect as antihypertensive (Palu, et al., 2008).

Noni (*Morindacitrifolia* L.) was one of the 13 commodities featured medicinal plants established by the government through the Directorate General of POM as one of the government's efforts in supporting the development of Agroindustry in Indonesia. The consideration that noni become one of the featured medicinal plants, because noni have high economic value, a market opportunity and high production potential, and opportunity in the technology development (Sumarno, 2002).

The composition of biopharmaceutical production in Indonesia especially noni (*Morindacitrifolia* L.) increased in 2014 compared to the year 2013 which is 8.432.119 kg to 8.577.347 kg [28]. In addition, the noni plant has also become one of the plants cultivated in the center of medicinal plants, which are spread in 15 provinces in Indonesia, such as North Sumatra, Riau, Jambi, DKI Jakarta, West

Java, Central Java, Yogyakarta, East Java, Banten, Bali, West Kalimantan, East Kalimantan, North Sulawesi, South Sulawesi, and Gorontalo (BPS, 2003).

Cinnamon, brotowali and noni has been produced into traditional medicines such as herbal medicine and traditional medicine industry. In addition, because of the large population of these plants in Indonesia, then all these plants have the potential to be developed into a drug active raw materials in order to attempt independence of medicinal raw materials companies in Indonesia.

3.3. Indonesia's Natural Ingredients Potency as Pharmaceutical Excipients Raw Material

In addition to the Active Pharmaceutical Ingredients (API), another important component in the manufacture of pharmaceutical products is excipients. Pharmaceutical excipients are defined as non-active ingredients mixed with therapeutically active compounds to form a medicine (Singh, et al., 2016). Some natural sources can also be used as excipients. For example, gelatin from skin and fish bone can be used as a binder in tablet preparations, carrageenan from seaweed can be used as emulsifier and suspending agent, and Mimosa (*Mimosa pudica* L.) known by name "Putri Malu" in Indonesia, and especially the

Mimosa mucilago seed can be used as an alternative to polymer as bucoadhesive agent, disintegrator and binder.

Advantages of pharmaceutical excipients from natural resources are: (1) Easily degraded, naturally forming polymers produced by all living organisms; (2) Biocompatible and non toxic; (3) Lower cost; (4) Safe and minor side effects; (5) Easy and large availability (Singh, et al., 2016). While the disadvantages of using natural excipients are: (1) Vulnerable microbial contamination; (2) The production of natural polymers depends on the environment and variation of physical factors; (3) Uncontrolled level of hydration; (4) The process is quite slow in producing of natural polymers; (4) Contamination of heavy metals (Singh, et al., 2016).

3.3.1 Indonesia' Plant as Pharmaceutical Raw Material Ingredients Excipients

a. Mimosa mucilago seeds as Bucoadhesive Agent, Disintegrator, and Binder

One of the plant that through several studies has shown its benefits as a pharmaceutical excipient is Mimosa (*Mimosa pudica* L.) known by name "Putri Malu" in Indonesia. Based on several studies, the seed of this plant can be used as an alternative to polymer (Choudary and Pawar, 2014). Mimosa seed are used as pharmaceutical excipients because one of its

natural polymers, mucilago, has been studied as having potential as a bucoadhesive polymer in buccal tablet dosage, as well as disintegrator and binder in tablet dosage. The *mucilago seed* consists of D-xylose and D-glucuronic acid (Ahuja, et al., 2013).

Based on a study that conducted by Ahuja, et al., (2010) aiming to evaluate Mimosa seeds mucilago as a bucoadhesive polymer with buccal tablet dosage of fluconazole as a model drug. The buccal fluconazole dosage, Mimosa seeds mucilago, and lactose as excipients are directly compressed to form a tablet dosage, the result tablet used to be tested later. In this study, the process for extracting *M. pudica* seeds were to soak them in sufficient amount of water for 10 hours, the mucilago will be hydrated along the seeds and then spread on the stainless steel tray which are dried in the oven at 50°C for 4-5 h. The dried mucilago is then separated from the seeds by passing it through the mess No. 18, which purified further through the winnowing to separate the seed husk (Ahuja, et al., 2010).

The research conducted by Ahuja, et al., (2010) is an experimental design of central composite, in which the ratio of mucilago/lactose, drug concentration and compression force is observed as a dependent variable for optimization studies by evaluating *ex vivo* bioadhesion time and percentage of drug release. The evaluation

result of the bioadhesive time parameter shows that the combination effect of mucilago/lactose ratio has a better effect compared to the compression force. While the observation result's of the percentage of drug release also showed the mucilago/lactose combination ratio has more prominent effect than the compression force, where the formation of a thicker gel layer with a longer diffusion path, resulting in a reduction in the drug diffusion coefficient, thus the rate of drug release with the increasing of relative amount of the mucilago on the buccal disc becomes lower (Ahuja, et al., 2010).

This means that mucilago as bucoadhesive agent is can be used in buccal dosage formulations, as it can make sufficient contact time with the oral mucosa, so that the absorbed drug is also in the appropriate amount. From these results, the Mimosa seeds mucilago can be used as a reference to natural materials that have the potential to be used as mucoadhesive polymers in buccal tablet dosage, although further *in vivo* studies are still needed (Ahuja, et al., 2010).

Mucilago mimosa seeds used as binders and disintegrator by using different concentrations, and the use of hydrochlorothiazide and paracetamol as drug models, which are further compared to the

prepared tablet using the standard binder and disintegrator have also been evaluated through a study conducted by Ahuja et al., (2013). Mucilago mimosa seeds extraction used the same method as the previous study by Ahuja, et al., (2010). Hydrochlorothiazide tablets with the direct compression method using mucilago as disintegrator and paracetamol tablet with the wet granulation method using mucilago as binder are used as model drug being evaluated. The evaluation result's on Hydrochlorothiazide tablets with Mimosa seed mucilago showed that increasing concentration of mucilago from 1% w/w to 3% w/w in the tablet, resulting the significantly lower disintegration time from 114 seconds to 31 seconds. However, a further increasing in mucilago concentration on tablets from 3% to 5%, 7,5% and 10% w/w, indicates the disintegration time of 185, 221 and 415 s. There was also an increase in the hardness of the tablet by increasing the concentration of mucilago 3% to 10% (Ahuja, et al., 2013).

The efficient disintegration of tablets by various disintegrators depends on their water absorption properties (Ahuja, et al., 2013). The results of the study on increasing mucilago concentration from 1% to 3% w/w showed an increase in the rate and extent of water absorption by tablet, where the mucilago disintegration time of

3% w/w showed a shorter time than tablet with 1% w/w mucilago concentration. However, with the increasing of mucilago concentration by 5%, 7,5% and 10% w/w, there was a decrease in absorption rate due to the higher viscosity of the mucilago, and also gel formation occurs, but with this increasing concentration makes the water absorption increased due to the higher amount of the mucilago. Tablets containing high concentrations of mucilago can make a soft tablet mass on the surface yet hard inside, causing the mucilago to rapidly expand but not quickly disintegrate. Mucilago concentrations of 3% w/w is chosen as the most suitable disintegrating concentrations for the direct compressed hydrocholorthiazide tablets (Ahuja, et al., 2013).

Evaluation of paracetamol granules was performed on tablets with 6%, 8% and 10% w/w variations concentrations of mucilago compared to paracetamol tablets using 1,7% PVP-K25 as binder and also tablet with 6.8% acacia as binder. The results showed that the disintegration time of paracetamol tablet with PVP-K25>mucilago (6%)>mucilago (8%)>mucilago (10%)>acacia gum. The increasing concentrations of mucilago are responsible for decreasing dissolution rate. Tablet with 6% and 8% w/w mucilago concentrations did not have sufficient hardness and were very

fragile, whereas tablets with mucilago concentration of 10% had hardness and friability that passed the test (adequate), so the concentration of mucilago 10% w/w became the suitable concentration for tablet preparation. Through these results, it can be concluded that mucilago seeds *M. pudica* has the potential to be used as a disintegrator and binder in tablet formulations (Ahuja, et al., 2013).

Evaluating the results of research conducted on mucilago Mimosa seeds, it is concluded that *M. pudica* seeds have the potential as a natural excipient in the formulation of tablets. The extracting process of mucilago Mimosa seeds which can be done easily and quickly becomes one of the advantages in making the initial raw material from the source of natural materials used as excipients. In addition, the availability of Mimosa seeds which are widely available in Indonesia also becomes an advantage to make them as natural excipients that can be used in formulations as bucoadhesive polymers on buccal tablet dosage, as well as disintegrator and binder on tablet formulation.

3.3.2 Natural Marine Ingredients's Potency as Pharmaceutical Raw Materials

Apart from plants, Indonesia has natural resources from the sea which is also very potential to be utilized as a source of

excipient raw materials for pharmaceutical preparations such as gelatin from the skin and fish bones that can be used as a binder in the preparation of tablets and carrageenan from seaweed which can be used as emulsifier and suspending agent.

a. Gelatin from the Skin and Fish Bones as a Binder

Research on the manufacture of gelatin from the skin and fish bones has been widely practiced in Indonesia. Research conducted by Dian Inamhi and Yunianta (2016) is gelatin extraction from skin of Lencam fish (*Lethrinus sp*). In this research, demineralization of skin pieces of the fish is used in 6% concentration of acetic acid solution for 24 hours and then extraction by soaking the fish skin using aquades with ratio 1: 2. From the result of this research, gelatin produced has fulfilled SNI and FTIR gelatin from skin of Lencam fish compared with commercial gelatin, the spectrum of functional groups is almost the same between the two [34]. Research conducted by Yudi and Tatik (2015) is characterization of gelatin quality from bone of *Tenggiri fish* (*Scomberomorus commersonii*) with soaking using citric acid and sulfuric acid. The results showed the best characteristic quality of gelatin from *Tenggiri* fishbones using citric acid concentration of 6%. The gelatin produced from the study has fulfilled SNI

06-3735-1995 (Adiningsih and Purwanti, 2015).

Research conducted Reza Hekta, et al (2015) that is physical and chemical characteristics of gelatin skin of Patin fish (*Pangasius pangasius*) with combination of various acid and temperature. The ratio of fish skin to the solution is 1:10 (w/v). The skin of catfish was soaked in each acid treatment solution (acetate, citrate, and chloride) with 1% concentration for 2 h, then extracted in warm water solution with treatment temperature (45°C and 55°C) for 12 h. The strength value of gelatin extracted from various types of acid and the temperature of the treatment is still in the gel girth range according to Indonesian National Standard (SNI) No. 3735 year 1995, for gelatin product that is 50-300 Bloom. From the results of this study it is known that the use of temperature significantly affect the value of gelatin yield while the acid type treatment has no significant effect. The highest yield was obtained from the treatment of hydrochloric acid at 45°C. The physical characteristics, especially the viscosity and the strength of the gelatin gel produced are influenced by the temperature of the extraction. It is recommended to use 45°C for extracting. Chemical characteristics of gelatin such as the degree of acidity and

fat content are influenced by acid factors (Saputra, et al., 2015).

Research conducted by Muhammad Iqbal, et al (2015) is the optimization of the yield and gelatin gel strength of big catfish extract (*Clarias gariepinus* sp). In this research, the optimum yield of gelatin from bone of big catfish is 2,9080% obtained by addition of protease enzyme 0,084%, citric acid concentration 5,875% and immersion time 41,464 h. Optimum gel strength of gelatin extract of big catfish was 2,9644 g/mm² or 136,439 g bloom obtained with 0.0664% protease enzyme treatment, 4.4224% citric acid concentration and 34,0224 hours of soaking time. Gelatin extract from bone of big catfish proved to have characteristics that are comparable to the gelatin on the market (Iqbal, et al., 2015).

Research conducted by Agnes and Meity (2015) is a study of gelatin from skin of Tuna fish (*Thunnus albacares*) processed using acetic acid. In the study the skin of tuna fish was immersed in water temperature 50°C for 30 minutes. After the immersion process is complete, the skin is washed with running water repeated three times until the pH is neutral. The washed skin is further extracted in a 55°C temperature waterbath for 5 h and then concentrating and cooling. The results of the research are gelatin from skin of tuna fish produced using acetic acid solution 3%, 6% and 9% yield gelatin

characteristics with good quality and in accordance with SN (Agustinand Sompie, 2015).

b. Carrageenan from Seaweed as Emulsifier and Suspending Agent

Research on the manufacture of carrageenan from seaweed has also been done in Indonesia. Research conducted by Ardiawan Pandu, et al (2013) is the influence of different types and concentration of alkaline solution to gel strength and viscosity of carrageenan from *Kappaphycus alvarezii*. In the study the seaweed washed was heated in an alkaline solution ie, KOH 4%, 6%, 8% and NaOH 4%, 6%, 8% at 60-70°C for 1 hour. After heating and then filtered and washed with water until pH 9. From the research it is known that the type and concentration of alkali effect on gel strength and viscosity of carrageenan. The 6% KOH solution gives the highest effect on gel strength of 630.71 ± 10.32 g/m² when compared with other types and concentrations, whereas for the viscosity having the highest effect occurs on 8% NaOH with 25.07 ± 0.17 cPs (Romenda, et al., 2013).

Research conducted by Maya Harun, et al (2013) that is characteristic of chemical physics carrageenan from *Kappaphycus alvarezii* seaweed at the different harvest age in the waters of Tihengo Village, North Gorontalo regency. In the study,

Kappaphycus alvarezii seaweed samples were harvested in six harvest age levels, 0 days, 10 days, 20 days, 30 days, 40 days and 50 days. Each sample is treated equally from harvest, soaking, and washing. The extraction process is done by soaking the seaweed with aquades and adding 1% NaOH solution while heated with a temperature of 70°-90°C and setting the pH about 8,5-9 before heating. The results of the study showed that carrageenan has the best physical and chemical characteristics of carrageenan from seaweed age 30 days upwards. Content of highest yield was obtained on the 40th day that is 30,63%, the lowest of water content was obtained on 30th day is 17.72%, the highest viscosity value on 30th day was 85 cp, and the highest gel strength was obtained on the 50th day (80,31 g/cm²) (Harun, et al., 2013).

The research conducted by Ismail Failu, et al (2016) is improving the carrageenan quality from seaweed of *Kappaphycus alvarezii* with the method of basket culture cultivation. In the study, the procedure of seaweed planting in each treatment of net basket is the same on the long line method is seaweed tied to the ris rope and given a container of basket nets to protect the seaweed. Each treatment of *K. alvarezii* seaweed planting is given a spacing of 25 cm. Every two times a week controlled

seaweed. From the research, the water content of carrageenan in each treatment was not significantly different from 17,20-17,39%. The viscosity of carrageenan treatment method of the lantern netting basket (179.40 cPs) was higher than other treatments. The gel strength of the carrageenan treatment method of the lantern nap basket (702.53 g/cm²) is higher than other treatments (Failu, et al., 2016).

Research conducted by Sopinia Erjanan, et al (2017) is the quality of carrageen and the strength of the gel from red seaweed *Kappaphycus alvarezii*. In the study, as much as 250 grams of seaweed soaked with KOH with some variation of concentration, then washed with water until neutral pH. Seaweed extracted for 2 hours with seaweed and water ratio of 1 kg: 20 liters and 1 kg: 30 liters. The extracted filtrate was mixed with KCl according to the treatment, and was allowed to stand for 30 minutes. The results showed that the best treatment in this study was F treatment (Comparison of water with 20 liters sample, cooking time of 2 hours, KOH 0.15%+KCl 1.25%) due to the highest gel strength, neutral pH, ash content according to the standard, and the lowest water content (Erjanan, et al., 2017).

From these studies, it can be seen that to produce a raw material required an appropriate stage of the cultivation of

sources of raw materials and processes used during the manufacture of raw materials. Appropriate processing methods such as temperature, duration of immersion, and appropriate reagents are key to producing good quality raw materials. In addition, the use of natural resources as natural excipients can be an advantage because these natural materials can be renewed and processed or harvested in a sustainable way, so that the availability of raw materials derived from natural resources is constant and its potential as a raw material for excipients is considerable.

4. Conclusion

One of the important component in producing products in the pharmaceutical industry is the raw materials. Pharmaceutical raw materials are needed to produce different types of drugs. The utilization and development of traditional medicine from natural resources in Indonesia has been done hereditary heritage based on experience/empirical. This proves that natural resources in Indonesia have a high potential to be developed into a source of pharmaceutical raw materials for the pharmaceutical industry. The potential of pharmaceutical industry raw materials derived from natural resources in the framework of development of new drugs that can be used include cinnamon (*Cinnamomum burmanii*) and brotowali

(*Tinospora cripa* L.) which can be utilized as raw material for the treatment of diabetes mellitus. and noni is used for the treatment of hypertension disease (*Morinda citrifolia* L.). Meanwhile, in addition to API, another important component in the manufacture of pharmaceutical products is excipients. Some natural resources can also be used as excipients. The potential resources are gelatin from skin and fish bone that can be used as a binder in tablet preparations, carrageenan from seaweed can be used as emulsifier and suspending agent, and Mimosa (*Mimosa pudica* L.) mucilago seeds that can be used as an alternative to polymer as buchoadhesive agent, disintegrator and binder. By looking at the various potentials of natural resources that can be used as a source of raw material pharmaceutical both active pharmaceutical ingredients (API) and excipients, Indonesia will be able to independently produce the pharmaceutical raw materials.

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Conflict Of Interest

All authors expressed no potential conflict of interest with research, authorship, and/or publication of this article.

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