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Probability Induction of Kratom Plant Bioactive Components in Antidiabetic and Antiobesity Studies

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ABSTRACT

Background: Kratom (*Mitragyna speciosa* Korth.) is widely used by the surrounding community as a traditional antidiabetic and anti-obesity drug due to its high content of secondary metabolite compounds. The purpose of writing this review is to find out the bioinduction influence of *Bacillus thuringiensis* and *Pseudomonas fluorescens* and to find out the presence of an increase in secondary metabolites. **Method:** Writing and assessing source problems related to using literature study methods. **Results:** Kratom leaf methanol extract contains secondary metabolites of alkaloid groups, flavonoids, steroids/terpenoids, phenols and saponins. The main compound content of kratom leaves classified as alkaloids is mitragynine that has not been found in other plants. The administration of non-pathogenic bacteria such as *Bacillus thuringiensis* and *Pseudomonas fluorescens* can induce plant defences and accumulate phenol compounds and flavonoids in plants. **Conclusion:** Kratom can indeed function as an antidiabetic and anti-obesity, and induction of microbes, namely *Bacillus thuringiensis* and *Pseudomonas fluorescens* bacteria, can increase the content of secondary metabolites of plants. Through the increase in secondary metabolites, the efficacy of plants is higher to overcome health problems, namely antidiabetics and anti-obesity.

Probabilitas Induksi Komponen Bioaktif Tanaman Kratom pada Kajian Antidiabetes dan Antiobesitas

Kata kunci:
Bakteri non patogenik;
Bioinduksi;
Metabolit sekunder;

ABSTRAK

Background: Kratom (*Mitragyna speciosa* Korth.) banyak digunakan masyarakat sekitar sebagai obat tradisional antidiabetes dan antiobesitas karena kandungan senyawa metabolit sekundernya yang tinggi. Tujuan penulisan review ini yaitu mengetahui pengaruh bioinduksi *Bacillus thuringiensis* dan *Pseudomonas fluorescens* serta untuk mengetahui adanya peningkatan metabolit sekunder. **Metode:** Penulisan dan pengkajian masalah sumber terkait dengan menggunakan metode studi literatur**. Hasil:** Ekstrak metanol daun kratom mengandung metabolit sekunder golongan alkaloid, flavonoid, stereoid/terpenoid, fenol dan saponin. Kandungan senyawa utama dari daun kratom yang tergolong alkaloid adalah mitragynine yang belum ditemukan dalam tanaman lain. Pemberian bakteri non patogenik berupa *Bacillus thuringiensis* dan *Pseudomonas fluorescens* dapat menginduksi pertahanan tanaman dan mampu mengakumulasi produksi senyawa fenol dan flavonoid pada tanaman. **Kesimpulan:** Berdasarkan hasil pencarian literatur membuktikan bahwa kratom memang dapat berfungsi sebagai antidiabetes dan antiobesitas dan induksi mikroba yaitu bakteri *Bacillus thuringiensis* dan *Pseudomonas fluorescens* dapat meningkatkan kandungan metabolit sekunder tanaman. Melalui peningkatan metabolit sekunder maka keampuhan tanaman semakin tinggi untuk mengatasi masalah kesehatan yakni antidiabetes dan antiobesitas.

Introduction

Kratom (*Mitragyna speciosa* Korth.) is a Rubiacea family plant native to Southeast Asian countries, especially in Thailand, Malaysia and Indonesia (Hassan *et al.*, 2013). Kratom in Indonesia is found in Putussibau Kapuas Hulu Regency, West Kalimantan. Kratom leaves have long been used traditionally as herbal medicine in some Southeast Asian countries (e.g. Malaysia and Myanmar). The traditional use of kratom leaves is generally by chewing fresh leaves as technology develops, the way of use changes such as leaves the first ground, fresh leaves or dried leaves are added in cooking and made into a tea (Assanangkornchai *et al.*, 2007). Kratom was first used traditionally as a substitute for opium by native Malaysians and as a wound Poulter, remedy for fever, and suppressant opiate-piercing syndrome (Jansen & Prast, 1988). In 1975, the effects of kratom were first reported in Thailand as mind-sedative, improving the work outcomes and use of culturally bound and ritualistic in the countryside (Suwanlert, 2012). In the 1990s, along with the increasing migration of the population from Southeast Asia to Europe and the United States (US), kratom consumption as a natural remedy also increased through internet marketing. In 2016 in the U.S., it is estimated that there were several million consumers who bought more than ten products.000 retail outlets with an annual market forecast of $207 million (Henningfield *et al*., 2018).

Figure 1. Kratom plant (*Mitragyna speciosa* Korth.) (Source: Personal Documentation).

Kratom leaves contain alkaloids, glycosides, terpenoids, flavonoids, and saponins. Alkaloids become the main compound found in kratom leaves. The main content of this leaf is the alkaloid indol, which is mitragynine (66.2%) and 7-hydroximitraginin (2.0%). Several studies on the pharmacological effects of kratom leaves have been studied such as analgesic activity, stimulants, antidepressants, anti-inflammatory, antinosiseptif, antioxidants, and antibacterials. Alkaloid extract from *Mitragyna speciosa* leaves is known to show antidepressant effects and reduce the impact of alcohol dependence (Cheaha *et al.*, 2015). Kratom methanol extract showed antidiarrheal effects on the digestive tract of mice (Chittrakarn et al., 2008). In addition, Kratom has been used traditionally as a medicine to treat diabetes, especially in Thailand, without much scientific evidence of its usefulness.

Compounds in kratom leaves underlie the need for an in-depth study of the health potential of kratom leaves, especially for the control of diabetes and obesity. Diabetes mellitus is a group of metabolic diseases with hyperglycemia symptoms (high blood sugar levels). This is due to damage to insulin secretion, insulin work, or both (Boulton *et al.*, 2005). Obesity, according to the World Health Organization (WHO), is a state of abnormal or excessive accumulation of fat that is detrimental to human health (Sahib et al., 2012). The healing process of diabetics is done by inhibiting the enzyme α-glucosidase (Hogan *et al.*, 2010). The enzyme inhibition process can be done by using compounds that are α-glucosidase inhibitors to reduce postprandial hyperglycemia (Patel, 2015). In obesity therapy, kratom leaves play a role in inhibiting the work of pancreatic lipase enzymes (PL). The benefits of kratom leaves can be increased in efficacy through increased production of secondary metabolite compounds. Types of bacteria selected for bioinduction include *Bacillus thuringiensis* and *Pseudomonas fluorescens* which are suitable for plant growth. One way to increase the efficacy of kratom in controlling diabetes and obesity is by using microorganism induction in plant roots.

This review aims to provide information about the effect of bioinduction of *Bacillus thuringiensis* and *Pseudomonas fluorescens* and determine the increase in secondary metabolites.

Methods

The writing procedure carried out in the preparation of this review is to look for various literature studies electronically, namely by accessing International and National article searches through databases such as PubMed, *ScienceDirect*, and Google Scholar using the keywords "kratom", "secondary metabolites", "diabetes", and "obesity". One hundred eight papers were downloaded through search results. All articles are selected and accepted based on the 2010-2020 issue. A total of 38 selected articles are discussed in this review. Then synthesis is done using a narrative method that groups articles that are willing to the topic. The data that has been collected is then searched for similarities and differences and then discussed to get conclusions. The topics discussed are chronologically organized into specific themes or sub-chapters, then made into a writing framework and developed to become a review paper. Through the 38 articles used, there are proceedings and research articles with a total of 1 proceeding and 37 research articles.

Results and Discussion

Based on the results of various literature searches on kratom, diabetes, obesity, and the influence of bioinduction on plants. Here is the information we have summarized.

Kratom (Mitragyna speciosa Korth.) and Its Potential Bioactive Compounds in Health

Kratom belongs to *Mitragyna speciosa* Korth, Family Rubiaceae and Genus Mitragyna. This plant is one of the herbs widely grown in Thailand, Myanmar, Malaysia, the Philippines, and Indonesia (Hassan *et al*., 2013). Kratom is also a typical plant and is widely grown in the Puttusibau area of West Kalimantan. Kratom leaves have different designations by region, such as in Indonesia kratom is known as "*Purik Leaf*", in Malaysia as "*Biak-biak*", and in Thailand as "*Ithang*" (Elsa, 2016).

Phytochemical screening results showed that kratom leaf methanol extract contained secondary metabolites of alkaloids, flavonoids, steroids/terpenoids, phenols and saponins. One of the main compounds of kratom leaves classified as alkaloids is mitragynine that has not been found in plants other than kratom (Luliana & Islamy, 2018).

Flavonoids are phenol compounds among the secondary metabolites in plants that function as antioxidants (Zuraida *et al*., 2017). The administration of antioxidants and components of polyphenol compounds can reduce oxidative stress. Suppression of oxidative stress plays an important role in reducing diabetes complications by administering phytochemical compounds (Widowati, 2008). Thus, the content of secondary metabolites of flavonoids is thought to have the potential as anti-obesity (Fauzi *et al*., 2019). Flavonoids are protective against cell damage β as insulin producers and can improve insulin sensitivity. Flavonoids can also inhibit phosphodiesterase, thereby increasing cAMP in pancreatic beta cells (Puspati et al., 2013). Increased cAMP will stimulate the production of protein kinase A (PKA) which stimulates increased insulin secretion.

Secondary metabolites in the form of alkaloids also act as anti-obesity (Tsuchiya *et al*., 2002). The primary alkaloid in kratom is mitragynine (Sabetghadam *et al*., 2013), and it is thought that side effects such as weight loss are also caused by mitragynine (Tsuchiya *et al*., 2002). It is proven that in tests conducted on mice, it is known that mitragynine content is able to reduce appetite (Fluyau & Revadigar, 2017). In addition, the group of compounds that are also contained in kratom is phenols that have antioxidant activity. The higher the content of phenols in an ingredient such as in leaves, the higher the antioxidant activity (Ricki Hardiana & Rudiyansyah, 2012).

Diabetes and the Mechanism of Inhibition

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (high blood sugar levels) due to damage to insulin secretion, insulin work, or both. Chronic hyperglycemia in diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (Boulton *et al*., 2005). Diabetes mellitus is divided into two, namely, type 1 diabetes mellitus and type 2 diabetes mellitus. Type 1 DM occurs because the pancreas cannot produce insulin. In this type of DM, there is little or no secretion (Suryani *et al*., 2016). This is caused by an autoimmune process that damages β-pancreatic cells to reduce and even stop insulin production. Sufferers will need exogenous insulin intake (Afdal & Rini, 2012). Patients who have type 2 diabetes is if the body can still produce insulin, but the insulin produced is not enough or the body's fat and muscle cells become resistant to insulin (Suryani *et al*., 2016). It is characterized by insulin deficiency caused by β-pancreatic cell dysfunction and insulin resistance in the target organ. Type 2 diabetes accounts for more than 90% of patients with diabetes (Chatterjee *et al*., 2017).

It is well known that more than 1200 plant species are reported to be diabetes cures, so it is an essential and promising source for the identification of new antidiabetic compounds (Lankatillake *et al.,* 2019) because the kratom plant itself has been used by the community, especially in Thailand as a traditional medicine for diabetes.

Diabetes treatment can be achieved in the presence of inhibition of the enzyme α-glucosidase (Hogan et al., 2010). A-glucosidase inhibitors can reduce postprandial hyperglycemia (Patel, 2015). Currently, drugs that can function as alpha-glucosidase inhibitors are acarbose, miglitol, and voglibose (Van de Laar *et al*., 2005). It is known that the way alpha-glucosidase inhibitors work in the body is by extending the process along the intestines, extending the duration of carbohydrate absorption, and flattening blood glucose concentrations over time. There is a decrease in the concentration of glucose in the blood. A stable blood glucose concentration is important for diabetic patients because it can prevent hyperglycemia and other complications related to diabetes (Ye *et al*., 2002).

Kratom is known to treat diabetes (Chawla & Kunnen, 2005). Kratom water extract can stimulate glucose transport very similar to that carried out by insulin in the body (Purintrapiban *et al*., 2011). Insulin is known to cause GLUT (Glucose Transport) contained in muscle cells to move out (Slot *et al*., 1990). Glucose transport absorbs glucose from the blood circulation and directs glucose into muscle cells (Watson & Pessin, 2001). The results showed that the rough water, methanol, and alkaloidal extracts of kratom leaves in test samples significantly led to an increase in glucose uptake rate and glucose transport activity. This study shows that the effects of M consumption. Speciose in stimulating glucose transport in muscle cells, potentially to treat diabetes (Purintrapiban *et al.*, 2011).

Obesity Suppression with Lipase Inhibitors

Most dietary fats (90%) are mixed triglycerides (TGs) and need to be hydrolyzed for absorption. Of the various lipases, PL is a principle lipolytic enzyme that calculates hydrolysis of 50-70% of dietary fat into fatty acids (FA) and monoglycerides (MGs), respectively. Free MGs and FAs, released by lipid hydrolysis, form a mixed micelle with bile salts, cholesterol and liphosphophosphide acid (LPA) and are absorbed into enterocytes where TG synthesis takes place. TG is stored in adipocytes as its primary energy source (Birari & Bhutani, 2007).

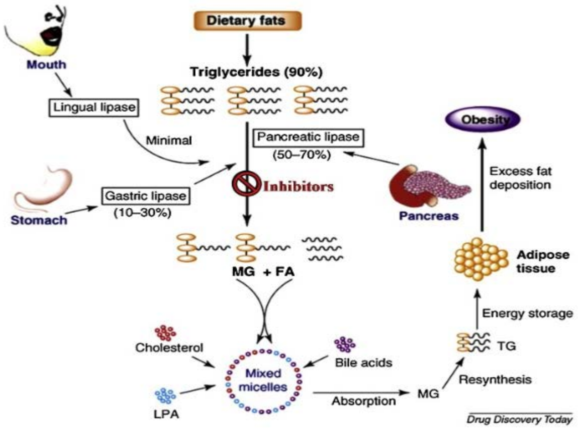

Figure 2. Lipid metabolic pathways in the body (Birari & Bhutani, 2007).

Pancreatic lipase (PL) is the primary enzyme responsible for digesting 50-70% of food triglycerides into *monoglycerides* and free fatty acids, both of which are absorbed by enterocytes. So inhibition of PL can result in reduced absorption of fat where energy absorption is one of the main targets responsible for obesity (Chakrabarti, 2009).

Research on the effects of CT-II (a fraction of ethanol extract containing tannins) from *Cassia nomame* herb extract can inhibit PL in pigs in vitro depending on the dose given, i.e. at deficient concentrations of extract 0.1 mg/mL resulting in 50% inhibition of lipase activity. So it has been tested to give CT-II extract can inhibit weight gain and plasma triglyceride levels in mice without affecting food intake. Ct-II can therefore be a potent lipase inhibitor (Yamamoto *et al.*, 2000).

Phenolic compounds also affect the prevention of obesity (Birari & Bhutani, 2007; Hsu & Yen, 2008). Polyphenol-rich extracts from herbal teas and fruit sources, such as berries, apples, melinjo or grape seeds, black or green oolong tea of different varieties, contain tannins reported as PL inhibitors during in vitro experiments (Sergent *et al.*, 2012). Polyphenols from plants are associated with proteins primarily through hydrophobic and hydrogen bonds. In addition, some microbes can also produce secondary metabolites as lipase inhibitors so that they could potentially be used as anti-obesity drugs. *Streptomyces sp.* water extract. AEBg12 derived from the bangle plant contains flavonoids, saponins and steroids that act as pancreatic lipase inhibitors. Saponins have also been shown to inhibit lipase activity both in vitro and in vivo, so saponin compounds, steroids and flavonoids contained in kratom leaves are also thought to have the potential to be lipase inhibitors and play a role in the treatment of obesity (Fitri *et al.*, 2017).

Induction of Accumulation of Secondary Metabolites of Plants by Microorganisms

Plants have self-defence mechanisms that can be activated in response to pressures like microscopic viruses to phytophage insects (Choudhary *et al.*, 2007). Generally, both biotic and abiotic in plants tend to increase the production of secondary metabolite compounds (Einhellig, 1996). In this case, microbes can also function as pathogen-controlling agents through competition mechanisms, antibiosis, parasitism or induced resistance. The use of bacteria is also known to be helpful to increase crop yields and protect plants from plant disrupting organisms (OPT) (Kuswinanti *et al.*, 2014).

Kratom plants contain secondary metabolites in alkaloids, saponins, tannins, phenolics, steroids, and triterpenoids. This compound is proven to be an antibacterial *Aeromonas hydrophilla* characterized by a dead zone around the paper disc (Juanda et al., 2019). Some bacterial microorganisms have good associative abilities with plants and play an essential role in supporting plant resilience. One of them is *Pseudomonas fluorescens* bacteria which are antagonistic microorganisms widely used in biological control by increasing the production of secondary metabolites in plants. In addition, the importance of the role of microorganisms in increasing plant growth and resilience is also proven in *Withania somnifera* (Ashwagandha) which is inoculated by Plant Growth Promoting Rhizobacteria (PGPR) bacteria such as *Azospirillum, Azotobacter, Pseudomonas* and *Basil*. The results showed a significant increase in plant height (45.80%) in root length (58.05%) and alkaloid content (189.45%) in ashwagandha plants (Rajasekar & Elango, 2011).

Pseudomonas fluorescens bacteria can play a role in supporting plant resistance and increasing secondary metabolites of plants, so that if the bacteria are induced into kratom plants, then it is suspected that these microorganisms will increase secondary metabolite compounds in kratom plants. Several plants have been studied with the induction of these bacteria and resulted in increased secondary metabolites in plants. Blackberries inoculated with Pseudomonas fluorescens bacteria showed a significant increase up to 3° Brix, total phenolics up to

18%, and flavonoids up to 22%. So that from existing trials can be concluded *P. fluorescens* N21.4 improves plant defense and fruit quality (García-Seco *et al*., 2013).

Giving bacteria directly to plants has a fundamental influence; namely, plants providing compounds that can be synthesized by bacteria such as phytohormones or bacteria can help the absorption of certain nutrients from the environment so that nutrient absorption can be done optimally through the help of bacteria. The administration of non-pathogenic bacteria such as *Bacillus thuringiensis* and *Pseudomonas fluorescens* will induce plant defences. Plant response is shown through genes that play a role in plant resistance to certain compounds, one of which is phenols. In addition to producing phenols, the activation of defence compounds is indicated by producing jasmonic acid and ethylene compounds (Wijayanti *et al*., 2018). The administration of non-pathogenic bacteria *pseudomonas fluorescens* has proven capable of accumulating the output of phenol compounds in plants (Anita *et al*., 2004).

Conclusion

Based on the literature search results, it is proven that kratom leaves contain secondary metabolite compounds in the form of alkaloids, saponins, tannins, phenolics, steroids, and triterpenoids. Traditionally this plant is used to cure diabetes and obesity, although there have been no scientific studies. Then, the kratom plant itself is thought to increase its secondary metabolites by inducing some microbe. It has been scientifically proven that the induction of microbes *Bacillus thuringiensis* and *Pseudomonas fluorescens* can increase the content of secondary metabolites in some plants. Through the increase in secondary metabolites, the efficacy of plants is higher to overcome health problems, namely antidiabetics and anti-obesity.

Declaration statement

The authors reported no potential conflict of interest.

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