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PHALERIA MACROCARPA AND AVERRHOA BILIMBI L AS ALTERNATIVE MEDICINES IN THE TREATMENT OF PATIENTS WITH DIABETES MELLITUS TYPE 2

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ABSTRACT
DM is a metabolic disease characterized by blood glucose levels that closely related to oxidative stress and lipid abnormalities. There are side effects of the drugs, such as nausea, dizziness, and so other alternatives are needed with natural ingredients and lower side effects. One of them are Phaleria macrocarpa and Averrhoa bilimbi. The compounds can reduce GDP,MDA and improve lipid profile in DMT2. The aim is to determine Phaleria macrocarpa and Averrhoa bilimbi as alternative treatments. The method is a systematic review of 34 journals. Based on the analysis, Phaleria macrocarpa and Averrhoa bilimbi were shown to reduce GDP,MDA and improve lipid profile. The decrease GDP from saponin can reduce glucose absorption in the intestine and inhibit the glucose transporter GLUT-1, while the decrease MDA is due to flavonoids which play a role in suppressing free radicals production, inhibiting the production of inflammatory mediators, and increasing endogenous antioxidants. Improvement of lipid profile from niacin can reduce blood cholesterol levels by inhibiting VLDL secretion mechanism. It was concluded that Phaleria macrocarpa and Averrhoa bilimbi could be used as alternative drugs for the treatment of DMT2 by lowering GDP, MDA and improving lipid profile.

Keywords: phaleria macrocarpa; averrhoa bilimbi L; DMT2

INTRODUCTION
Diabetes Mellitus (DM) is a type of disease caused by a decrease in the hormone produced by the pancreas gland. This decrease in hormone causes the glucose consumed by the body cannot be processed perfectly, so glucose levels in the body increase. Insulin is a hormone that regulates blood glucose. Lack of insulin causes the glucose consumed cannot be processed by the body perfectly (Sumarmin et al., 2017). According to the American Diabetes Association (ADA), DM is a group of metabolic diseases characterized by high blood glucose levels (ADA. 2018). This can be caused by the failure of the pancreas to produce insulin or impaired insulin action/insulin resistance (Masaenah et al., 2019).

DM disease continues to increase every year, this is evidenced by the number of DM occurrences worldwide in 2019 as many as 463 million which will be predicted to increase by 24.83% in 2030, namely as many as 578 million people and will increase by 51.19% in 2045 with an incidence of 700 million people, while the incidence of DM in Southeast Asia in 2019 was 88 million and is predicted to increase further by 30.68% in 2030, which is 115 million, and will continue to increase by 73.86% in 2045, which is 153 million. (IDF, 2019). In Indonesia, the prevalence of DM based on blood tests in people aged less than or equal to 15 years in 2013 was 6.9% and in 2018 it was 8.5%. The prevalence of DM from 2013 to 2018 increased by 1.6% (Depkes RI, 2018). Diabetes mellitus with type 2 (DMT2) is the type of

diabetes that has the most frequency, which is about 90% of all cases of people with diabetes (Goyal, 2020; IDF, 2017).

The increasing DM disease can lead to several complications such as various cardiovascular diseases, dyslipidemia, nephropathy, retinopathy, and neuropathy with the worst possible cause of mortality. (Skyler, et al., 2017). In addition, the increase in cases of DM is influenced by several risk factors. Controllable risk factors, namely obesity, lack of physical activity, hypertension, dyslipidemia, smoking habits, and stress are risk factors that can be controlled while risk factors that cannot be controlled are age and family history (Utomo, AA., et al. 2018). The condition of insulin resistance can be assessed by a simple and validated method based on mathematical modeling using data on GDP and insulin, known as the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the Homeostatic Model Assessment for Beta Cell (HOMA-β) to assess pancreatic -cell function (Tjokroprawiro, 2017). In addition, oxidative stress also plays an important role in the onset and development of DMT2 disease due to the increased production of free radicals in the body (Burgos-Morón et al., 2019).

Free radicals, especially reactive oxygen species (ROS) in all tissues are formed as a result of hyperglycemia conditions that damage the natural enzymatic antioxidant defenses (He et al., 2017). Due to the high free radicals, lipid peroxidation also increases in cell membranes and produces the final product, namely *malondialdehyde* (MDA) (Moazen et al., 2013). Research by Sunita *et al*., (2020) revealed that DMT2 patients experienced a significant increase in MDA by 6.77 times compared to the control group (healthy people) and found a strong relationship between GDP and MDA levels (Sunita et al., 2020). MDA is a secondary product that is mutagenic and more stable than other aldehydes, so it is considered the best biomarker of oxidative stress on lipids. (Ayala et al., 2014).

Diabetes management uses a non-pharmacological approach in the form of providing education, meal planning/nutritional therapy, physical activity, and weight loss if you are overweight or obese. Nutrition therapy is part of diabetes management which can be the main key to lowering GDP levels in people with DMT2 (Prameswari & Widjanarko, 2014). In addition, pharmacological treatment is also carried out. Oral Anti-Diabetes Drugs that are often used by DMT2 patients in Indonesia are metformin and sulfonylureas (Tarigan et al., 2015). Although these drugs are often used, the use of these drugs has side effects such as hypoglycemia, nausea, dizziness, and constipation (Putra et al. 2017). Therefore, an alternative is needed to help overcome DMT2 with natural ingredients that are more effective, low in side effects, low in toxicity, and relatively cheaper. One of the natural ingredients that can be used as alternative medicine in the treatment of DMT2 sufferers are *Phaleria macrocarpa* and *Averrhoa bilimbi L*.

Phaleria macrocarpa is a plant native to Indonesia that is widely used in traditional medicine. *Phaleria macrocarpa* is a herbaceous plant. When it is young, the fruit is green, when it is old it becomes maroon. The flesh is white. So is the shell. The seeds are round, white, and very poisonous. So that only the leaves and fruit are used in medicine (Fiana & Oktaria, 2016). The parts that are often used are the fruit and leaves. According to Djamil and Winarti (2014), the results of phytochemical screening of *Phaleria macrocarpa* leaves showed the presence of alkaloids, flavonoids, saponins, tannins, triterpenoids, essential oils, and coumarins. According to Fiana and Oktaria (2016), saponins in *Phaleria macrocarpa* fruit work as inhibitors of the -glucosidase enzyme which can inhibit the breakdown of carbohydrates into glucose. In addition, the tannins contained in Phaleria macrocarpa meat also have an important role in reducing blood glucose levels. Tannins act as astringents that can precipitate intestinal mucous membrane

proteins and form a layer that protects the intestines, thereby inhibiting glucose absorption (Mulyaningsih. 2019). Alkaloids, which have detoxification properties that can neutralize toxins in the body, saponins which are useful as anti-bacterial and viral, reduce blood sugar levels, reduce blood clots, and flavonoids function as antioxidants, and polyphenols which function as antihistamines (Sumarmin et al., 2017).

Averrhoa bilimbi L is a plant that is grouped in the Oxalidaceae family. *Averrhoa bilimbi L* was introduced as a garden plant that can produce flowers throughout the year. (Liantari. 2014; Gendrowati, 2015). The fruit when young is greenish with the rest of the flower petals attached to the tip, while the ripe fruit has a pale yellow, juicy flesh and has a very sour taste. The active substances contained in *Averrhoa bilimbi L* are triterpenoids, tannins, flavonoids and saponins. The compounds contained in Averrhoa bilimbi L can be used for cough medicine, analgesics, rheumatism, hypertension, stroke, and also DM (Pendit et al., 2016). Based on the above background, it is hoped that the extracts of *Phaleria macrocarpa* and *Averrhoa bilimbi L* can be a new alternative in the treatment of people with DMT2.

METHOD

The method in this article is a systematic review of various journals, both international journals and national journals, which are then summarized into a topic of discussion. The journals used were 34 journals, both national and international journals and also supported by the results of research conducted by the authors at the Integrated Laboratory of Ahmad Dahlan University regarding antioxidant activity in Phaleria macrocarpa and Averrhoa bilimbi L, then the authors summarized all of these journals into an article. which is easy to understand. This systematic review presents material that has been previously published and will identify, assess, and interpret all findings on a research topic systematically to provide a summary in the form of comparisons between journals which are then presented in the form of articles.

RESULTS

Based on previous research, it is known that both *Phaleria macrocarpa* and *Averrhoa bilimbi L* have been shown to have very strong antioxidant activity. Antioxidant activity in *Phaleria macrocarpa* extract based on IC50 value of 6.43 ppm with linear regression equation y=5.5686x+14.213 while antioxidant activity in *Averrhoa bilimbi L* extract based on IC50 value of 8.29 ppm with linear regression equation y=6, 21x–1.5367. In addition, various previous studies have also proven that *Phaleria macrocarpa* and *Averrhoa bilimbi L* can reduce GDP levels, MDA levels and improve lipid profiles. Decreased GDP levels from saponin content that can reduce glucose absorption in the intestine, inhibit GLUT-1 glucose transporter, increase glucose utilization in peripheral tissues, and glycogen storage and increase insulin receptor sensitivity in tissues while decreasing MDA levels from flavonid content which plays a role in suppressing production free radicals, inhibit the production of inflammatory mediators, repair damaged molecules, initiate and increase endogenous antioxidants as the body's defense system. Improvement of lipid profile from niacin content can reduce blood cholesterol level by inhibiting VLDL secretion mechanism.

DISCUSSION

DM is a disease in which glucose levels in the blood are higher than normal, ranging from 60 to 120mg/dL. Meanwhile, the blood glucose level of diabetics when fasting is more than 126mg/dL, and when not fasting or normal is more than 200mg/dL. This is because the body cannot release or use the hormone insulin sufficiently (Mulyaningsih, 2019). The development of DMT2 disease will cause a decrease in the function of pancreatic beta cells to insulin secretion and the continuation of insulin resistance conditions that occur continuously (Declori,

2019). Continued hyperinsulinemia activates the mTOR/S6K1 protein kinase pathway leading to increased phosphorylation of IRS-1. In addition, activation of this pathway inhibits IRS-1 from activating phofatidylinositol 3-kinase (PI3K) and AKT, which are effectors of insulin metabolism. This results in insulin resistance and decreased insulin clearance. The mTOR activation pathway has a major role in skeletal muscle and adipocytes leading to decreased insulin clearance (Petersen and Shulman, 2018). Lipid profile abnormalities are also one of the causes of insulin resistance, which is characterized by increased levels of triglycerides, total cholesterol, and decreased LDL and HDL.

Phaleria macrocarpa and *Averrhoa bilimbi L* have very high antioxidant activity. This is evidenced by the results of research that the authors conducted at the Integrated Laboratory of Ahmad Dahlan University in 2021 which resulted in antioxidant activity in the Phaleria macrocarpa extract based on an IC50 value of 6.43 ppm with a linear regression equation y=5.5686x+14.213 while the antioxidant activity in the extract Averrhoa bilimbi L based on IC50 value of 8.29 ppm with linear regression equation y=6.21x–1.5367 (Sholehah et al., 2021). In general, *Phaleria macrocarpa* contains active substances in the form of alkaloids, flavonoids, saponins, tannins, triterpenoids, essential oils, and coumarins, while the active substances contained in *Averrhoa bilimbi L* are triterpenoids, tannins, flavonoids, and saponins. The ingredients contained in the two fruits can help people with DMT2 in their treatment. Saponins work as inhibitors of the -glucosidase enzyme which can inhibit the breakdown of carbohydrates into glucose. Saponins also reduce glucose absorption in the intestine, inhibit the glucose transporter GLUT-1, increase glucose utilization in peripheral tissues, and glycogen storage and increase insulin receptor sensitivity in tissues. (Dede et al., 2019). In addition, tannins also have an important role in reducing blood glucose levels. Tannins act as astringents that can precipitate intestinal mucous membrane proteins and form a layer that protects the intestines, thereby inhibiting glucose absorption (Mulyaningsih, 2019).
Based on previous research, it is known that *Phaleria macrocarpa* can reduce blood glucose levels in patients with DMT2. This is evidenced by a study conducted by Sumarmin, et al (2017) which stated that the extract of *Phaleria macrocarpa* could reduce blood glucose levels in male mice induced by sucrose. In addition, research conducted by Dede, et al (2019) also stated that *Phaleria macrocarpa* extract could significantly reduce blood glucose levels at doses of 250mg/kgBW and 500mg/kgBW after 7 days of extract administration. The effective dose that can reduce blood glucose levels in this study is 500mg/kgBW. Another study conducted by Sutrisna et al (2020) also stated *that Phaleria macrocarpa* extract could lower blood glucose and repair damage to the islets of Langerhans with the most effective dose being 300mg/200gBW rats.

Based on previous research, *Averrhoa bilimbi L* can also lower blood glucose levels. This is evidenced in a study conducted by Susanti et al (2017) which stated that administration of *Averrhoa bilimbi L* extract could reduce GDP levels in humans with a dose of 100 ml given for 14 days. In addition, research conducted by Maesanah et al (2019) stated that the administration of Averrhoa bilimbi L extract could reduce GDP levels in male mice modeled with DMT2, the effective dose in this study was 750mg/kgBW given for 7 days. Another study that also stated that *Averrhoa bilimbi L* extract could reduce blood glucose levels was a study conducted by Rofiah (2019). The effective dose used in this study was 750 mg/kgBW given for 30 days.

Oxidative stress is a condition caused by an imbalance between antioxidants and free radicals that leads to oxidative damage to proteins, fats, nucleic acids, and carbohydrates. This condition is known as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Adwas et al., 2019). Continuous fat oxidation reactions or hyperlipidemic conditions can cause excessive free

radical production which in turn can cause mitochondrial DNA damage and malfunction of pancreatic cells and produce end products, one of which is malondialdehyde (MDA) (Ayala et al. 2014). The flavonoids contained in *Phaleria macrocarpa* and *Averrhoa bilimbi L* act as antioxidants. Antioxidants can suppress the production of free radicals and their chain reactions by capturing oxidants, inhibiting the production of inflammatory mediators, repairing damaged molecules, initiating and increasing endogenous antioxidants as the body's defense system to reduce oxidation reactions and reduce MDA levels in people with DMT2 (Adwas et al., 2019). Based on previous research, it is known that *Phaleria macrocarpa* can reduce MDA levels in patients with DMT2. This is evidenced by research conducted by Edward and Yerizel (2009) which states that *Phaleria macrocarpa* extract can reduce serum MDA levels in alloxan-induced DMT2 mice. The effective dose used to reduce MDA levels is 500mg/kgBW. Another study conducted by Meiyanti et al. (2020) also showed that *Phaleria macrocarpa* extract could reduce MDA levels in humans with the most effective dose being 62.5 mg. In addition, *Averrhoa bilimbi L* can also reduce MDA levels in patients with DMT2. This is evidenced in a study conducted by Fajarini, et al. (2015) which stated that infusion of *Averrhoa bilimbi L* could reduce MDA levels in rats model DMT2. The effective dose in this study was 25.3g/kgBW given for 7 days.

In type II diabetes, high insulin levels and insulin resistance can affect fat metabolism. As a result of insulin resistance, hormone-sensitive lipase in adipose tissue increases, causing an increase in triglyceride lipolysis in adipose tissue. This situation causes the levels of free fatty acids to increase. These free fatty acids will be carried into the bloodstream as energy and carried in part in the liver as raw materials for the formation of triglycerides (Sunaryo et al., 2018). Excess fatty acids in plasma due to insulin deficiency trigger the conversion of fatty acids into phospholipids and cholesterol in the liver as a result of fat metabolism. Excess phospholipids, cholesterol, and triglycerides are formed at the same time in the liver which is then released into the blood in the form of lipoproteins. As a result, there is an increase in lipoproteins, which causes an increase in total plasma lipids and makes people with T2DM have abnormalities in their lipid profile. This increase in lipids, especially cholesterol, will trigger the development of atherosclerosis in the walls of blood vessels and will increase the risk of complications (Widiningrum. 2013). The content of niacin can reduce blood cholesterol levels by inhibiting VLDL secretion, while pectin can reduce blood cholesterol through two kinds of mechanisms, namely by inhibiting micellar formation and inhibiting the HMG CoA reductase enzyme. cholesterol in the blood decreases (Rosmalianti, 2012).
Based on previous research, it is known that *Phaleria macrocarpa* can improve lipid profile. This is evidenced by research conducted by Ubaidah (2012) which states that *Phaleria macrocarpa* extract can prevent an increase in LDL levels and a decrease in HDL levels in rats. Another study that proves that *Phaleria macrocarpa* can improve lipid profile is a study conducted by Julizar et al. (2012) who stated that infusion of *Phaleria macrocarpa* could inhibit the increase in total cholesterol in rats. In addition, *Averrhoa bilimbi L* can also improve lipid profiles, this is evidenced by research conducted by Nurbaiti et al. (2018) which states that *Averrhoa bilimbi L* extract has the effect of reducing total cholesterol, HDL, and LDL levels in hypercholesterolemic male white rats of the Sprague Dawley with an effective dose of 320mg/200gramBW. Another study that also showed improvements in lipid profiles was a study conducted by Rosmalianti (2012) which stated that *Averrhoa bilimbi L* extract could reduce LDL cholesterol levels in rats.

CONCLUSION

Based on the above study, it can be concluded that *Phaleria macrocarpa* and *Averrhoa bilimbi L* can be used as new alternative drugs for the treatment of DMT2 patients by lowering GDP

levels, MDA levels and improving their lipid profile.

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