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COMBINING *AVERRHOA BILIMBI L* AND *PHALERIA MACROCARPA* ON FASTING BLOOD GLUCOSE LEVES IN A RAT MODEL OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: Around 90% of cases of diabetes mellitus that occur are type 2 diabetes mellitus. Traditional ingredients have been proven to contain several substances that can be used to prevent and treat diabetes. **Aims:** To analyze the effects of a combination of *Phaleria macrocarpa* and *Averrhoa bilimbi L* extracts on fasting blood glucose levels. **Methods:** A randomized post-test-controlled group design was used. Thirty-six Sprague-Dawley rats were fed a high-fat diet for two weeks in order to induce type 2 diabetes; streptozotocin and nicotinamide were then administered to induce type 2 Diabetes Mellitus. Six groups of rats were created: CN, C −, C+, T1, T2, and T3. The 21-day course of treatment included measurement of fasting blood glucose levels. The data were analyzed using one-way ANOVA and post-hoc Tukey's honest significant difference test. **Results:** The combination of Averrhoa bilimbi L extract and Phaleria macrocarpa effectively reduced fasting blood glucose levels over a 21-day period. The most effective treatment, T1, produced results comparable to those of the C+ group. Averrhoa bilimbi L at 375 mg/kg and Phaleria macroca at 750 mg/kg W/day were the combination that had the greatest impact on fasting blood glucose levels. **Conclusion:** The combination of the extracts from Averrhoa bilimbi and Phaleria macrocarpa shows promise as a natural blood glucose regulator. Further research is required to completely comprehend the underlying mechanisms and assess the long-term consequences of this combination therapy.

Keywords: *Averrhoa Bilimbi L, Phaleria Macrocarpa,* Diabetes Mellitus, Fasting Blood Glucose, Rat

INTRODUCTION

Global public health is of great concern in the context of diabetes mellitus. Approximately 573 million people worldwide, mostly in low- and middle-income nations, have diabetes. This highlights the urgent need for other nations must work with these to reduce the growing burden of diabetes in these regions. Additionally, 6.7 million deaths are directly associated with diabetes each year. Diabetes affects 90 million people in Southeast Asia worldwide. It is projected that this disease will claim 747,000 lives in 2025 (IDF, 2022). Diabetes, a chronic disease affecting blood sugar regulation, is a global public health concern, particularly in Southeast Asia, highlighting the need for preventive measures and improved healthcare infrastructure (Wu et al., 2014)(David, Singh and Ankar, 2023). In order to address this growing health crisis, more needs to be done to raise public awareness of diabetes prevention and management and to encourage healthy lifestyle choices (Sękowski et al., 2022). To effectively combat Southeast Asia's rising diabetes prevalence, cooperation between governments, healthcare providers, and communities is necessary (Te et al., 2023).

Diabetes incidence in Indonesia has risen from 6.9% in 2013 to 8.5% in 2018, according to blood tests conducted on individuals over 15 (Nuari et al., 2022)(Tanoey and Becher, 2021). Type 2

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diabetes mellitus is the most common type of diabetes and is characterized by reduced insulin production and insulin resistance. It is frequently associated with poor dietary habits and obesity (Galicia-Garcia et al., 2020). Dyslipidemia, nephropathy, retinopathy, neuropathy, cardiovascular disease, and even death are among the detrimental effects that this illness's rising prevalence may have (Skyler et al., 2017). Additionally, several risk factors affect the prevalence of diabetes. While being overweight or obese, not exercising, having dyslipidemia, and smoking are manageable risk factors, genetics is an inevitable cause of diabetes mellitus (Alam et al., 2021).

Diabetes increases the levels of low-density lipoproteins, cholesterol, triglycerides, blood glucose, and malondialdehyde. Therefore, managing risk factors and taking medications are necessary to avoid complications. Commonly used medications for patients with diabetes include glibenclamide, glipizide, gliclazide, and glimepiride (Tarigan et al., 2015). In addition to their benefits for patients with diabetes, these medications also have negative effects, such as vomiting, and hypoglycemia (Prasad-Reddy and Isaacs, 2015)(Anderson et al., 2014)(Padhi et al., 2020). Therefore, new drug therapies utilizing natural ingredients are required. These therapies should be more accessible, reasonably priced, effective, and have fewer side effects. Traditional remedies are often considered safe by the community because they are based on natural ingredients (Santanello and Carr, 2019)(van Wyk and Prinsloo, 2020). Natural ingredients used by the community to control blood sugar levels include *Averrhoa bilimbi* and *Phaleria macrocarpa*. Phaleria macrocarpa is frequently used in certain communities as an alternative to medications for lowering blood sugar levels in diabetic patients. The fruit extract of this plant possesses various important biological activities, including anti-inflammatory, antimicrobial, and antioxidant properties (Alara and Olalere, 2016). *Phaleria macrocarpa* contains many antioxidants including *flavonoids.* The benefits of flavonoids include anti-aging, anti-viral, anti-cancer, antidiabetic, anti-inflammatory, and cardioprotective effects (Marzouk, 2016)(Wang et al., 2016). The community also uses *Averrhoa bilimbi L* to treat conditions such as diabetes, rheumatism, and hypertension. Among Averrhoa bilimbi L.'s chemical constituents are tannins, triterpenoids, flavonoids, and saponins (Pendit, Zubaidah and Sriherfyna, 2016).

This study investigated the impact of plant extracts, particularly Averrhoa bilimbi L and Phaleria macrocarpa extracts, on blood glucose levels during fasting, with the aim of developing potential diabetes treatments. It is anticipated that the findings of this research will have a favorable influence on programs designed to improve the quality of life of those with diabetes.

METHODS

Preparation of Materials

The fruits of the Merapi plantation in Yogyakarta, specifically the Phaleria macrocarpa (Specimen Number: KLU 58034) and Averrhoa bilimbi (Specimen Number: KLU 58035) plants. The samples were standardized before processing to include fruits with smooth surfaces that were non-fragile and free of bacteria, fungi, and smells. Averrhoa bilimbi L had an elongated shape, a light green tint, and a sour flavour, while Phaleria macrocarpa had a round shape, a light brown hue, and an unpleasant taste. Powder was prepared from both samples. Triglycerides, cholesterol reagent, 2,2-diphenyl-1-picrylhydrazyl, 0.15 mm, and a combination of 4000 ul cholesterol reagent (4 parts) and 1000 ul (1 part) pure water are among the reagents used.

Extraction

Sample extraction with 1:10 simplistic flour. Both samples were extracted with 96% ethanol for 24 h using

the maceration and re-maceration (Simplisia) method, which was repeated twice. Following its passage through Whatman filter paper, the No. 40, To obtain a concentrated extract, the maceration extract was evaporated using a rotary evaporator for 18 h at 60°C. The extracted samples were stored in direct sunlight and refrigerated at ±4°C in bottles for testing purposes.

Creation of T2DM Animal Model

Six groups of thirty-six male rats of the Sprague Dawley breed, weighing 150–200 g at 8 to 10 weeks of age, were randomly assigned after seven days of preparation and housing. The rats were kept in cages with a 12-hour light-dark cycle, temperature range, humidity, and diet. The treatment group received a high-fat diet, whereas the control group received a Comfeed AD II diet. Water was available ad libitum or in accordance with animal demands. After the second week, rats with type 2 diabetes were administered 2 mL/200 g of saline along with 110 mg/kg BW of nicotinamide (NA) to induce diabetes. The rats were administered 45 mg/kg BW of streptozotocin (STZ) in 2 mL/200 g of cold citrate buffer 15 min later. The rats experienced hyperglycemia after three days of induction. Fasting blood glucose levels ranged from 267.97 to 271.49 mg/dL. This study was approved by the Ethics Committee of Universitas Sebelas Maret's Faculty of Medicine (approval number: 32/UN27.06.11/KEP/EC/2024).

Group samples

Rats with T2DM were administered a combination of Phaleria macrocarpa and Averrhoa bilimbi L extracts via gastric gavage for 21 days. Six groups of 36 rats each were created. There were six groups for the intervention: 1.CN (control normal), 2.C- (control negatif), 3.C+ (control positif/ glibenklamid 0,45 mg/kgBW), 4. T1 (EM 750 mg/kg + EB 375 mg/kg), and 5. T2 (EM 500 mg/kg + EB 750 mg/kg), and 6. T3 (EM 250 mg/kgBW + EB 1125 mg/kgBW).

Blood Sampling and Examination

Blood samples were collected at two time points: after STZ + NA induction and after 21 days of treatment. During blood collection, rats were fasted for at least eight hours. Blood was collected from the orbital vein (sinus orbitalis) using a 1 mL syringe with the retro-orbital plexus method. One milliliter of blood was collected and placed in an Eppendorf tube. Serum was extracted from blood by centrifugation it for ten minutes at 3000 rpm.

Quantitative measurement of blood glucose levels was performed using the enzymatic colorimetric "GOD-PAP" method, both pre-(before treatment) and post-test (after 21 days of intervention). A total of 10 µL of serum was mixed with 1000 µL of glucose standard and for ten minutes at 37°C.

$$\text{Blood glucose levels} = \frac{sample\ absorbance}{standard\ absorbance}\ x\ standard\ glucose\ concentration\ (\frac{md}{dL})$$

Analysis

The mean, median, minimum, maximum, and standard deviation are the formats in which processed data are displayed. These statistical measures provide a comprehensive overview of the data distribution and help to identify outliers or trends within the dataset. To test data normality, we used the Shapiro-Wilk test. Based on the test results, the data are normally distributed and homogeneous. Next, to test the effect of the dose and duration of the combination therapy, we used an ANOVA test.

RESULT

Maceration of Phaleria macrocarpa and Averrhoa bilimbi L for 48 h yielded extracts with characteristics such as color, texture, flavonoid, and saponin levels. These properties can determine the extract quality and potency, potentially benefiting the pharmaceutical and cosmetic industries. For more details, see Table 1.

Table 1. The features and phytochemical content of *Averrhoa bilimbi L.* and *Phaleria macrocarpa*

No	Characteristics	*Phaleria macrocarpa*	*Averrhoa bilimbi L*
1	Yield	11.30%	10.67%
2	Color	Black Brown	Black Brown
3	Texture	Thick	Thick
4	Saponin	3.582 ± 0.010 mg/g	3.582 ± 0.011 mg/g
5	Flavonoid levels	4.83 ± 0.010 mg/g	2.32 ± 0.011 mg/g

Based on Table 2, it is known that all treatment groups experienced an increase in body weight. This is because not all mice with diabetes were given treatment either through the two plants used or the drug gilbenclamide.

Tabel 2. Effect of Averrhoa bilimbi L and Phaleria macrocarpa extract on the body weight of rats with Type 2 diabetes

Group	*Mean* ± *SD* (effect of combination extract administration on Body weight) (Gram)			Mean difference ± Average (Gram)	Percentage Change (%)
	Day-0	Day-7	Day-21		
CN	204.83 ± 2.79	211.00 ± 2.61	226.83 ± 5.12	22.00 ± 2.33^{b}	10.74
C-	211.17 ± 3.55	206.00 ± 4.09	195.50 ± 3.21	-15.67 ± -0.34^{c}	7.42
C+	210.50 ± 2.59	215.50 ± 3.62	229.00 ± 3.35	18.50 ± 0.76^{a,b}	8.79
T1	211.33 ± 2.81	215.53 ± 3.44	229.33 ± 3.27	18.00 ± 0.46^{a}	8.52
T2	211.00 ± 3.58	216.00 ± 3.79	227.50 ± 3.84	16.50 ± 0.26^{a}	7.82
T3	208.33 ± 3.93	213.50 ± 3.27	223.33 ± 2.58	15.00 ± -1,35^{a}	7.20
Average	209.53 ± 3.21	212.92 ± 3.47	221.92 ± 3.56		

Information: CN (control normal), C- (conrol negatif), C+ (control positif/ glibenklamid 0,45 mg/kgBW), T1 (EM 750 mg/kgBW + EB 375 mg/kgBW), T2 (EM 500 mg/kgBW + EB 750 mg/kgBW), T3 (EM 250 mg/kgBW + EB 1125 mg/kgBW).

^{a,b,c}) Numbers followed by the same letter indicate no significant difference (post-hoc Tukey HSD test, α=95%).

All groups experienced a decrease in FBG levels, except for the negative control group and the normal control group. Neither the normal control group nor the negative control group showed any significant changes in their fasting blood glucose levels over the study period. This is because glibenclamide or an extract mixture of Phaleria macrocarpa and Averrhoa bilimbi L were not administered to mice in the normal control group. Moreover, it did not induce diabetes. One study found that mice with type 2 diabetes developed stable fasting blood glucose levels without medical intervention. Glibenclamide and a fruit extract mixture were administered to different mice, resulting in lower blood glucose levels after fasting. This suggests that glibenclamide and fruit extract can reduce fasting blood glucose levels in rats with type 2 diabetes, suggesting a potential combination therapy for managing blood glucose levels.

Table 3. Effect of Combination Doses of Phaleria macrocarpa and Averrhoa bilimbi L Extract on FBGse Levels in Type 2 Diabetes Rats

Group	***Mean* ± *SD* (Effect of extract combinationon FBGL) (mg/dL)**		Mean difference ± Average (mg/dL)	Percentage Change (%)
	Before intervention (H0)	After intevention (H21)		
CN	72.31 ± 1.89	73.99 ± 1.29	1.68 ± -3.6^{b}	2.32
C-	269.64 ± 4.89	271.77 ± 4.19	2.13 ± -0.7^{c}	0.79
C+	270.45 ± 3.02	103.57 ± 3.49	-166.88 ± -1.76^{a}	61.70
T1	271.49 ± 5.25	99.94 ± 5.23	-171.55 ± -0.02^{a}	63.19
T2	269.15 ± 5.33	123.00 ± 2.02	-146.15 ± -0.53^{d}	54.30
T3	267.97 ± 2.55	142.37 ± 3.09	-125.60 ± 0.54^{e}	46.87
Average	236.84 ± 3,82	135.77 ± 3.22		

Information: CN (control normal), C- (conrol negatif), C+ (control positif/ glibenklamid 0,45 mg/kgBW), T1 (EM 750 mg/kgBW + EB 375 mg/kgBW), T2 (EM 500 mg/kgBW + EB 750 mg/kgBW), T3 (EM 250 mg/kgBW + EB 1125 mg/kgBW).

^{a,b,c,d,e}) Numbers followed by the same letter indicate no significant difference (post-hoc Tukey HSD test, α=95%).

Table 4 shows that as per the one-way ANOVA statistical test, the group's body weight did not change before the intervention (p = 0.787). However, after the intervention, there was a significant difference in the body weight (p = 0.003) between the groups. Furthermore, the fasting blood glucose level of the group changed significantly following the intervention (p = 0.024), whereas it did not change significantly before the intervention (p = 0.695). The results of the analysis indicated that the subjects' body weight and fasting blood sugar levels were both significantly affected by the intervention. Significant alterations were observed in these two variables in the intervention group. However, there was no discernible difference between the group that received it beforehand and the other group. This implies that the intervention had a discernible and quantifiable impact on the subjects' body weight and fasting blood glucose levels.

Table 4. Differences between pre- and post-STZ + NA induction in body weight and fasting blood sugar levels.

Variabel	Mean	P value
Weight Before Intervention	3.311	0.787
Weight After Intervention	1166.444	0.003
Fasting Blood Glucose Before intervention	10.650	0.695
Fasting Blood Glucose After intervention	29809.180	0.024

One-Way ANOVA Test

DISCUSSION

These mice were given an adjustment period of 7 days in the artificial environment provided, this was useful to ensure that there were no other variables that could influence the research results apart from the treatment itself (Mutiarahmi, Hartady and Lesmana, 2021). The acclimatization phase aims to minimize confounding variables and ensure accurate data collection. Rats were monitored for pain and suffering and provided with ample food and liquids to maintain their wellbeing. This careful acclimation set a baseline for behavior and physiological reactions, making the research results more reliable.

The average body weight of the rats in the combination extract therapy was 209.53 ± 3.21 grammes, almost the same for all groups. After being administered the extract mixture for 21 days, the body weights of all the rats, aside from the C- group, increased. The T1 group had the greatest increase in body weight; they received a dose of Phaleria macrocarpa extract + 750 mg/kg + Averrhoa bilimbi L extract at 375 mg/kg BW. All intervention groups showed increases in body weight; however, none of them showed a statistically significant difference from the C+ group, which received glibenclamide at a dose of 0.45 mg/kg BW. Overall, the treatment increased body weight in mice, which was observed in the T1 group, which showed the most significant increase. Additionally, none of the intervention groups showed statistically significant differences compared to the C+ group receiving glibenclamide.

The higher body weight in the intervention groups is believed to be a result of better type 2 diabetes in rats and restored insulin function. Increased pyruvate, alanine, and lactate levels resulted from improved insulin function. These rises then stimulate α-glucosidase enzyme activity, decrease gluconeogenesis, boost ATP synthesis (Krebs cycle), and promote glycolysis (Gray, Tompkins and Taylor, 2014; Giri et al., 2018). These metabolic changes may also facilitate the utilization of glucose and fatty acids, resulting in an overall increase in body weight. Moreover, increased insulin activity may promote the storage of glycogen and fat, contributing to the weight gain observed in the intervention groups (Ludwig and Ebbeling, 2018; Ahmed, Sultana and Greene, 2021a; Chandrasekaran and Weiskirchen, 2024)(Ahmed, Sultana and Greene, 2021b). Furthermore, increased glucose absorption by cells for energy production owing to enhanced insulin action may result in weight gain. All things considered, these metabolic alterations indicate that people going through the interphase are heading towards an anabolic condition that encourages weight growth (Petersen and Shulman, 2018). Additionally, increased muscle mass and overall growth can also occur because of the anabolic state during the interphase. In general, a balanced diet and regular exercise routine are important in this metabolic process (Malm, Jakobsson and Isaksson, 2019; Scheffer and Latini, 2020).

Except for the normal control group, which did not experience hyperglycemia due to STZ + NA induction, all groups experienced hyperglycemia after induction. Because STZ induction may interfere with insulin secretion, it can result in hyperglycemia. Once it enters pancreatic β-cells through the glucose transporter GLUT2, it fragments and alkylates the DNA, causing damage. It also causes more cell damage by activating poly ADP-ribose polymerase, which also stops insulin from being synthesised and secreted (Mallek et al., 2018). Within three days of administering STZ, a hyperglycemic state may develop (Damasceno et al., 2014; Vieira et al., 2019). Another study conducted by (Muhlishoh, Wasita and Patriado Nuhriawangsa, 2019) additionally mentioned that giving rats STZ+NA could cause a hyperglycemic state in 3 days, with each rat having blood glucose levels ≥ 200 mg/dL during fasting.

The results showed that administering a mixture of P. macrocarpa and Averrhoa bilimbi L extracts to type 2 diabetic rats for 21 days significantly reduced FBG levels in rats. Phaleria macrocarpa extract treatment significantly reduced fasting blood glucose levels (Sutrisna et al., 2020). Rats with type 2 diabetes induced by aloxan showed a significant reduction in fasting blood glucose levels when administered Averrhoa bilimbi L extract (Kurup and Mini, 2017)(Verangga, Qomariyah and Khaleyla, 2024). With Averrhoa bilimbi L extract at 375 mg/kg and Phaleria macrocarpa extract at 750 mg/kg body weight, the T1 group demonstrated the greatest reduction in fasting blood glucose levels, possibly as a result of saponins. These compounds can inhibit digestive enzymes such as pancreatic α-amylase, sucrase, isomaltase, and maltase (Barber, Houghton and Williamson, 2021; Farazi et al., 2024; Santos et al., 2024)(Salehi et al., 2019).

Saponins convert carbohydrates, such as glucose, into monosaccharides, downregulate glycogen phosphorylase and glucose-6-phosphatase expression, and upregulate GLUT4. They inhibit α-glucosidase, increase glycogen synthesis, suppress gluconeogenesis, and encourage insulin release(Mata-Torres, Andrade-Cetto and Espinoza-Hernández, 2021; Alam et al., 2022; Meckawy et al., 2022) (Barky et al., 2017).

Blocking pancreatic enzymes like α-amylase and α-glucosidase leads to hypoglycemic reactions, including increased glycogen synthesis, decreased blood sugar, decreased plasma insulin, and restored insulin sensitivity (Luyen et al., 2018) (Xu et al., 2018) (Sprague and Arbeláez, 2013). Tannins in fruit of the gods can lower blood sugar levels by promoting protein production by mucous membranes, creating an intestinal barrier that prevents glucose absorption (Zubaidi et al., 2023) (Agustin, Insanu and Mauludin, 2023). Alkaloids can lower blood glucose levels by inhibiting enzymes like fructose-1,6-bisphosphatase and glucose-6-phosphatase, improve glucose transit, decrease absorption, encourage glycogen synthesis, and promote glucose oxidation (Timson, 2019)(Park et al., 2020).

Policy implications should focus on implementing similar interventions to effectively manage body weight and blood sugar levels in humans. Drug development using this material can also be a safer and more natural alternative for diabetes management. In addition, this material should be implemented in the pharmaceutical industry to produce environmentally friendly products with better health benefits for consumers. Thus, the combination of Averrhoa bilimbi and Phaleria macrocarpa extracts can provide innovative solutions for diabetes management through a natural and sustainable approach. Patents and drug feasibility tests from this research can be the most important steps to commercialize new products that are safer and more effective for patients with diabetes. With the support of the government and pharmaceutical industry, it is hoped that

this discovery will provide great benefits to the wider community. Further research is needed to ensure the safety and effectiveness of this product in the long term before it is widely sold to consumers. Through collaborative efforts between researchers, governments, and the pharmaceutical industry, it is hoped that a holistic and sustainable solution will be created to manage diabetes.

CONCLUSION

This combination of plants for 21 days is known to be able to reduce fasting blood sugar levels in mice which are the object of research. Together, these plants can effectively reduce the fasting blood sugar levels. These findings point to a possible natural therapeutic alternative for type 2 diabetes by indicating that A. bilimbi L and Phaleria macrocarpa extract may cooperate to lower blood glucose levels in patients with diabetes. Further investigation is required to ascertain the underlying mechanisms and assess the long-term effects of combination therapy.

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