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Effects of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. on fasting blood glucose in diabetic rats

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ABSTRACT

Traditional ingredients have been proven to contain many substances that can be used to prevent and treat diabetes. This study aimed to investigate the effects of a combination of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extracts on fasting blood glucose levels. A randomized, post-test-controlled group design was used. Type 2 diabetes mellitus was induced in 36 Sprague Dawley rats by feeding them a high-fat diet for 2 weeks, followed by the administration of streptozotocin (STZ) and nicotinamide to induce type 2 diabetes mellitus. The rats were divided into six groups. The treatment was administered for 21 days, and fasting blood glucose levels were measured. The data were analyzed using one-way analysis of variance (ANOVA). The combined dose of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extract effectively reduced fasting blood glucose levels over 21 days. Group T1 demonstrated the highest efficacy and did not differ significantly from that of the C+ group. The effective dosage that influenced fasting blood glucose levels was a combination of *Phaleria macrocarpa* at 750 mg/kg W/day and *Averrhoa bilimbi* L. at 375 mg/kg. *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extract have a synergistic effect, making them a promising natural medication for controlling blood glucose levels.

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1. INTRODUCTION

Diabetes mellitus is a significant public health concern worldwide. According to the International Diabetes Federation, the bulk of diabetic patients, estimated at 573 million, live in low- and middle-income nations. These nations often face challenges in terms of the healthcare infrastructure and access to affordable treatment options. This highlights the urgent need for international collaboration and support to address the growing burden of diabetes in these regions. Additionally, 6.7 million deaths are directly associated with diabetes each year. The number of patients with diabetes in Southeast Asia is 90 million. This number is predicted to increase to 113 million by 2030 and 151 million by 2045. The estimated number of deaths due to this disease in 2021 is 747,000 [1]. Diabetes is a chronic disease that affects the body's ability to regulate blood sugar levels, leading to serious health complications. It is a major public health concern globally, and the increasing number of patients in Southeast Asia highlights the urgent need for preventive measures and improved healthcare infrastructure in the region [2].

The prevalence of diabetes in Indonesia, based on blood tests among individuals aged ≤15 years, was 6.9% in 2013 and increased to 8.5% in 2018 [3], [4]. Type 2 diabetes mellitus is the most common type of diabetes, accounting for approximately 90% of all cases. Type 2 diabetes mellitus is characterized by

insulin resistance and impaired insulin secretion. It is often associated with lifestyle factors, such as obesity, physical inactivity, and unhealthy diet [5]. An increase in this disease can lead to several complications, such as cardiovascular disease, dyslipidemia, nephropathy, retinopathy, and neuropathy, with death in worst-case scenario [6]. In addition, the increase in diabetes cases is influenced by several risk factors, including both controllable and uncontrollable factors. Controllable risk factors include being overweight or obese, lack of physical activity, dyslipidemia, and smoking habits, whereas uncontrollable risk factors include genetics [7].

A thorough review of the literature reveals significant insights into the properties of both *Averrhoa bilimbi* L. and *Phaleria macrocarpa*. *Averrhoa bilimbi* L. is highlighted for its rich composition of bioactive compounds, including flavonoids, saponins, and phenols, which are believed to exert antioxidant and antihyperglycemic effects [8]. Furthermore, research conducted by Verangga *et al.* [8] established the blood glucose-lowering potential of *Averrhoa bilimbi* L. leaf extract, providing evidence for its application in diabetes management. Additionally, the fruit of *Averrhoa bilimbi* L. has been noted for its traditional uses in treating hyperlipidemia and hypertension, further supporting its role in metabolic health [9].

Individuals with diabetes experience an increase in blood glucose, malondialdehyde, cholesterol, triglyceride, and low-density lipoprotein levels, thus requiring the control of risk factors and the use of medication to prevent complications. Commonly used medications for patients with diabetes include glibenclamide, glipizide, gliclazide, and glimepiride [10]. In addition to their benefits for patients with diabetes, these medications also have side effects such as nausea, vomiting, and hypoglycemia [11]. Therefore, there is a need for new drug therapies using natural ingredients that are more effective, have fewer side effects, are relatively affordable, and are easily accessible. Traditional remedies are often considered safe by the community because they are based on natural ingredients [12], [13]. Natural ingredients used by the community to control blood sugar levels include *Averrhoa bilimbi* L. and *Phaleria macrocarpa*.

Phaleria macrocarpa is commonly used by some communities as an alternative to lower blood sugar levels in patients with diabetes. The fruit extract of this plant possesses various important biological activities, including anti-inflammatory, antimicrobial, and antioxidant properties [14]. *Phaleria macrocarpa* has a high antioxidant content, especially flavonoids. Flavonoids have antioxidant, antidiabetic, antiviral, anticancer, anti-aging, anti-inflammatory, and cardioprotective properties. *Averrhoa bilimbi* L. is also utilized by the community to address health issues such as hypertension, rheumatism, and diabetes. The chemical substances found in *Averrhoa bilimbi* L. include triterpenoids, tannins, flavonoids, and saponins.

Despite the promising findings regarding the individual actions of *Averrhoa bilimbi* L. and *Phaleria macrocarpa*, several unsolved problems remain. The specific mechanisms by which these plants modulate blood glucose levels warrant further investigation, as do the combined effects of both extracts on glucose metabolism. Additionally, few studies have explored their synergistic effects when combined, particularly in the context of type 2 diabetes mellitus.

This study aims to bridge this gap by evaluating the combined impact of these two plants on fasting blood glucose levels, focusing on their biochemical interactions and their potential to offer a holistic approach to diabetes management. The research will contribute novel insights by investigating the combined extract of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. in the context of fasting blood glucose levels among diabetic rats. Previous studies have primarily examined the efficacy of these plants in isolation; therefore, this research strives to elucidate the collective impact of their bioactive compounds. Expected outcomes include an enhanced understanding of their pharmacological synergism and elucidation of optimal dosages, laying the groundwork for future clinical studies that could establish new therapeutic options for diabetes management.

2. METHOD

2.1. Preparation of materials

In this study, the fruits of *Phaleria macrocarpa* (ID no. KLU 58034) were sourced from the Merapi Farma Herbal in Yogyakarta, while the fruits of *Averrhoa bilimbi* L. (ID no. KLU 58035) were obtained from the UPT Laboratory of Herbal Materia Medika Batu. Careful standardization of samples was performed, ensuring that only non-fragile fruits exhibiting smooth surfaces, absence of odor, and zero microbial contamination were utilized. Morphologically, *Phaleria macrocarpa* displayed a light brown color, a round shape, and a distinct bitter taste. In contrast, *Averrhoa bilimbi* L. was characterized by its elongated shape, light green hue, and notably sour flavor. Following collection, both fruit types were processed into a fine powder for subsequent analyses. The reagents employed in this investigation included a working reagent composed of 1,000 µL distilled water mixed with 4,000 µL cholesterol reagent, as well as specific formulations for cholesterol and triglycerides, alongside 0.15 mM 2,2-diphenyl-1-picrylhydrazyl (DPPH) for antioxidant assays. These methodological details are crucial for the reproducibility and reliability of the results obtained in this study.

2.2. Extraction

In this sample extraction procedure, a 1:10 ratio of the flour to solvent was utilized, employing 96% ethanol as the extraction solvent. The extraction followed a two-step maceration and re-maceration protocol, which involves immersing the plant material (simplisia) in the solvent for a duration of 24 hours, allowing maximal solute extraction. Each extraction phase was performed consecutively, enhancing the yield of bioactive compounds. The initial maceration extract was subsequently filtered using Whatman filter paper No. 40 to remove solid residues, ensuring the clarity and purity of the extract. Following filtration, the concentrated extract underwent rotary evaporation at a controlled temperature of 60 °C for approximately 18 hours, facilitating the removal of excess ethanol and resulting in a dense extract. For stability and integrity, the final extract was aliquoted into bottles and stored under refrigeration at approximately 4 °C. This storage condition was chosen to minimize degradation and maintain the functional properties of the extract while protecting it from photodegradation by storing it away from direct sunlight.

2.3. Creation of type 2 diabetes mellitus animal model

A total of 36 male Sprague Dawley rats, aged 8-10 weeks, weighing approximately 150-200 grams, were prepared and adapted for 7 days before being randomized into six groups. The rats were housed individually in polypropylene cages at a temperature of 22 °C-25 °C, humidity of 70%-90%, and a 12-hour light-dark cycle. Rats in the normal group were fed a comfeed AD II diet with an energy content of 20 kJ/kg (5% fat, 52% carbohydrates, 20% protein, and 13% water), whereas rats in the treatment groups were fed a high-fat diet with an energy content of 40 kJ/kg (20% fat, 45% carbohydrates, and 22% protein). Water was provided ad libitum (according to the animals' needs). After the second week, type 2 diabetes model rats were induced with the diabetogenic agent, 110 mg/kg body weight of nicotinamide (NA) in 2 mL/200 g saline, followed by 45 mg/kg body weight of streptozotocin (STZ) in 2 mL/200 g cold citrate buffer administered intraperitoneally after 15 min. The rats experienced hyperglycemia after 3 days of induction, with fasting blood glucose levels of 267.97-271.49 mg/dL.

2.4. Group samples

In this study, 36 type 2 diabetes model rats, characterized by fasting blood glucose levels exceeding 150 mg/dL, were subjected to a 21-day treatment regimen. The administration of extracts from *Phaleria macrocarpa* (EM) and *Averrhoa bilimbi* L. (EB) was achieved through gastric gavage, aimed at evaluating the effectiveness of these extracts in managing hyperglycemia. The rats were distinctly categorized into six experimental groups: Group 1 served as the control normal (CN), reflecting healthy rats; Group 2 was the negative control (C-), receiving no treatment; Group 3 acted as the positive control (C+), receiving glibenclamide at a dosage of 0.45 mg/kg body weight; Group 4 (T1) received 750 mg/kg body weight of *Phaleria macrocarpa* combined with 375 mg/kg body weight of *Averrhoa bilimbi* L.; Group 5 (T2) was treated with 500 mg/kg body weight of *Phaleria macrocarpa* and 750 mg/kg body weight of *Averrhoa bilimbi* L.; and Group 6 (T3) was administered with 250 mg/kg body weight of *Phaleria macrocarpa* and 1,125 mg/kg body weight of *Averrhoa bilimbi* L. This structured grouping facilitates comparative analysis of treatment efficacy among the various interventions based on the glucose-lowering effects observed.

2.5. 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 ≥8 h. Blood was collected from the orbital vein (sinus orbitalis) using a 1 mL syringe with retro-orbital plexus method. One milliliter of blood was collected and placed in an Eppendorf tube. The blood was centrifuged at 3,000 rpm for 10 min to obtain the serum.

Quantitative measurement of blood glucose levels was performed using the enzymatic colorimetric "GOD-PAP" method, both pre-test (before treatment) and post-test (after 21 days of intervention). A total of 10 µL of serum was mixed with 1,000 µL of the glucose standard and incubated at 37 °C for 10 min. Absorbance was measured by directly comparing the results of the test solution with the standard glucose levels at a wavelength of 500 nm.

$$Blood\ glucose\ levels = \frac{sample\ absorbance}{standard\ absorbance} \times standard\ glucose\ concentration\ (\frac{md}{dL}) \quad (1)$$

2.6. Statistical analysis

The processed data are presented in the form of mean, median, minimum, maximum, and standard deviation. The Shapiro-Wilk test was conducted to analyze the normality of the data. The results of the data analysis indicated that the data were normally distributed ($p > 0.05$) and had homogeneous variance ($p > 0.05$). To examine the effects of the dose and duration of combined extracts of *Phaleria macrocarpa* and *Averrhoa*

Bilimbi L. on fasting blood glucose levels, an analysis of variance (ANOVA) test was performed, followed by Tukey's test.

2.7. Ethical clearance

Ethical approval for the study was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (approval number: 32/UN27.06.11/KEP/EC/2024). This approval ensured that all procedures involving animal subjects met ethical standards for animal welfare. It also confirmed compliance with accepted standards for research conduct.

2.8. Data validity management

To ensure the validity of the data, several steps were taken. The samples of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. were standardized for quality, preserving their integrity prior to extraction and analysis. The use of a well-defined type 2 diabetes model, following established induction protocols with NA and STZ, provided a consistent framework for assessing the effects of the plant extracts on blood glucose levels. Blood glucose measurements were conducted using the enzymatic colorimetric method with careful adherence to procedures.

3. RESULTS AND DISCUSSION

The extraction of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. using the maceration method for 48 h and remaceration carried out twice using a 70% ethanol solution produced extracts with yield characteristics, color, texture, and flavonoid levels. These characteristics are important indicators of the quality and potency of the extracts. The yield, color, texture, flavonoids, and saponins can provide valuable information about the effectiveness and potential applications of these extracts in various industries such as pharmaceuticals and cosmetics. The additional information can be seen in Table 1.

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

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

Based on Table 2, it can be observed that all groups experienced an increase in body weight, except for the negative control group. This is because in the negative control group, the rats developed type 2 diabetes but did not receive any intervention, either glibenclamide medication or a combination of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extracts. In contrast, the other groups received interventions, either glibenclamide or a combination of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extracts.

Table 2. Effect of the combination extract of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. on the body weight of type 2 diabetes rats

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±2.33b	10.74
C-	211.17±3.55	206.00±4.09	195.50±3.21	-15.67±-0.34c	7.42
C+	210.50±2.59	215.50±3.62	229.00±3.35	18.50±0.76a,b	8.79
T1	211.33±2.81	215.53±3.44	229.33±3.27	18.00±0.46a	8.52
T2	211.00±3.58	216.00±3.79	227.50±3.84	16.50±0.26a	7.82
T3	208.33±3.93	213.50±3.27	223.33±2.58	15.00±-1.35a	7.20
Average	209.53±3.21	212.92±3.47	221.92±3.56		

Notes: a, b, c: numbers followed by the same letter indicate no significant difference (post hoc Tukey HSD test, α=95%)

Based on Table 3, it can be observed that all groups experienced a decrease in fasting blood glucose levels, except for the normal control group and the negative control group. This is because in the normal control group, rats were not induced with type 2 diabetes and did not receive any intervention, including glibenclamide medication or the combination of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extract. In contrast, in the negative control group, rats were induced with type 2 diabetes but did not receive any intervention. In the other groups, rats received interventions in the form of glibenclamide and a combination of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. fruit extract.

Table 3. Effect of combination doses of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extracts on fasting blood glucose levels in type 2 diabetes rats

Group	*Mean±SD* (Effect of extract combination on fasting blood glucose level) (mg/dL)		Mean difference ± Average (mg/dL)	Percentage change (%)
	Before intervention (H0)	After intervention (H21)		
CN	72.31±1.89	73.99±1.29	1.68±-3.6b	2.32
C-	269.64±4.89	271.77±4.19	2.13±-0.7c	0.79
C+	270.45±3.02	103.57±3.49	-166.88±-1.76a	61.70
T1	271.49±5.25	99.94±5.23	-171.55±-0.02a	63.19
T2	269.15±5.33	123.00±2.02	-146.15±-0.53d	54.30
T3	267.97±2.55	142.37±3.09	-125.60±0.54e	46.87
Average	236.84±3.82	135.77±3.22		

a, b, c, d, e: numbers followed by the same letter indicate no significant difference (post hoc Tukey HSD test, α=95%)

Table 4 showed that based on the one-way ANOVA statistical test, there was a significant difference in body weight (p =0.003) between the groups after the intervention, whereas in the group before the intervention, there was no difference in body weight (p =0.787). There was also a significant difference in the fasting blood glucose level after the intervention (p =0.024), whereas in the group before the intervention, there was no significant difference (p =0.695). From the results of the analysis, it can be concluded that the intervention had a significant effect on the body weight and fasting blood sugar levels. The group that underwent the intervention experienced significant changes in these two variables, whereas the group before the intervention did not show significant differences.

Table 4. Differences in body weight and fasting blood sugar levels before and after STZ + NA induction

Variable	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

The finding indicates that at the beginning of the treatment with the combination of extracts, the body weights of the rats were nearly the same across the groups, with average weight of 209.53±3.21 grams. After 21 days of administration of the combination of extracts, the body weight of the rats increased in all groups except for the C- group. The highest increase in body weight was observed in the T1 group, which received a dose of *Phaleria macrocarpa* extract + 750 mg/kg + *Averrhoa bilimbi* L. extract at 375 mg/kg body weight. The increase in body weight in all intervention groups was not significantly different from that in the C+ group, which received glibenclamide at a dose of 0.45 mg/kg body weight. Consistent with findings by Ogundare *et al.* [15], who reported that combined herbal treatments led to significant restoration of body weight in diabetic rats treated with certain herbal extracts. While the weight increase in intervention groups was statistically similar to the C+ group, which received glibenclamide (0.45 mg/kg), the importance of such combinations in managing weight and blood glucose in diabetic models is emphasized across multiple studies, including those assessing the efficacy of various plant extracts [16]. These findings underline the potential of herbal blends in diabetes management beyond conventional therapies.

The adaptation period for the rats was 7 days to allow the rats to adjust to their new environment. This ensured that all rats were in a homogenous condition and were not stressed because of differences in their previous housing locations [17]. During this period, rats were closely monitored for signs of distress or discomfort. Additionally, they were provided ample food and water to ensure their well-being during the adaptation process. At the beginning of the treatment with the combination of extracts, the body weights of the rats were nearly the same across the groups, with an average weight of 209.53±3.21 grams. After 21 days of administration of the combination of extracts, the body weight of the rats increased in all groups except for the C- group. The highest increase in body weight was observed in the T1 group, which received a dose of *Phaleria macrocarpa* extract + 750 mg/kg + *Averrhoa bilimbi* L. extract at 375 mg/kg body weight. The increase in body weight in all intervention groups was not significantly different from that in the C+ group, which received glibenclamide at a dose of 0.45 mg/kg body weight. The authors [18], [19] stated glibenclamide is one of the sulfonylureas commonly used for treating patients with type 2 diabetes and is known for its effect of increasing insulin release from pancreatic β-cells, which can result in weight changes over time. Comparatively, while both herbal extracts and established antidiabetic drugs like glibenclamide may influence body weight and metabolic parameters, the studies directly linking the herbal extracts' effectiveness to body weight increase require further research for validation.

The increase in body weight in the intervention groups is believed to be due to the improvement in the type 2 diabetes condition in rats and the restoration of insulin function, leading to an increase in pyruvate, alanine, and lactate levels, which in turn enhances glycolysis, inhibits gluconeogenesis, increases adenosine triphosphate (ATP) production (Krebs cycle), and optimizes the activity of α-glucosidase enzymes [20]. These metabolic changes may also contribute to the utilization of glucose and fatty acids, resulting in an overall increase in body weight. Additionally, improvements in insulin function may promote the storage of glycogen and lipids, further contributing to the weight gain observed in the intervention groups [21]–[23].

After the induction of STZ + NA, all groups experienced hyperglycemia (fasting blood glucose level ≥150 mg/dL), except for the normal control group, as hyperglycemia was not induced with STZ + NA. STZ induction can cause hyperglycemia because of it is ability to disrupt insulin secretion. STZ enters pancreatic β-cells through the glucose transporter GLUT2, leading to DNA damage through alkylation and DNA fragmentation as well as the activation of poly (adenosine diphosphate (ADP)-ribose), which further damages pancreatic β-cells and inhibits insulin synthesis and secretion. The administration of STZ can induce a hyperglycemic condition within 3 days [24]. The administration of STZ + NA in rats could induce a hyperglycemic condition within 3 days, with all rats having fasting blood glucose levels ≥200 mg/dL [25].

The results of the analysis showed that administration of a combination of *Phaleria macrocarpa* extract and *Averrhoa bilimbi* L. extract for 21 days significantly reduced fasting blood glucose levels in type 2 diabetic rats. These findings are consistent with those of [26], who reported that the administration of *Phaleria macrocarpa* extract significantly reduced fasting blood glucose levels in rats with STZ-induced type 2 diabetes. Administration of *Averrhoa bilimbi* L. extract significantly reduced fasting blood glucose levels in rats with alloxan-induced type 2 diabetes [8]. Similarly, *Averrhoa bilimbi* L. extracts have been reported to exhibit a blood glucose-lowering effect in diabetic models, including aloxan-induced rats [8]. Prominent mechanisms attributed to these effects include the inhibition of alpha-glucosidase enzymes, which are crucial for carbohydrate metabolism and glycemic control [16]. Furthermore, the antioxidant properties of these extracts may enhance their antidiabetic activity, providing a multifaceted approach to managing diabetes [8].

The most effective combination extract in reducing fasting blood glucose levels was the T1 group, with a dosage of 750 mg/kg body weight of *Phaleria macrocarpa* extract and 375 mg/kg body weight of *Averrhoa bilimbi* L. extract. In the T1 group, fasting blood glucose levels were reduced by 63.19%. The decrease in fasting blood glucose levels is believed to be due to the presence of saponins in *Phaleria macrocarpa* and *Averrhoa bilimbi* L., which act as α-glucosidase inhibitors. These inhibitors can inhibit pancreatic α-amylase and other intestinal enzymes such as isomaltase, maltase, and sucrase [27]. These enzymes hydrolyze carbohydrates into glucose and other monosaccharides. Saponins can also enhance insulin release from β-cells, inhibit disaccharidase activity, activate glycogen synthesis, inhibit gluconeogenesis, inhibit α-glucosidase activity, inhibit the mRNA expression of glycogen phosphorylase and glucose-6-phosphatase, and increase the expression of GLUT4 [28], [29].

It exhibits hypoglycemic properties by inhibiting α-glucosidase and pancreatic α-amylase [27]. Hypoglycemic effects by reducing blood glucose levels, decreasing plasma insulin levels, restoring insulin responsiveness, and stimulating glycogen synthesis [30], [31]. Additionally, tannins present in the fruit of crown-of-the-gods play an important role in reducing blood glucose levels [32]. Tannins are known to have astringent properties that can precipitate mucous membrane proteins and form a protective layer in the intestine, thereby inhibiting glucose absorption [33]–[35]. On the other hand, alkaloids can lower blood glucose levels by inhibiting glucose absorption in the intestine, enhancing glucose transportation in the blood, stimulating glycogen synthesis, and inhibiting glucose synthesis through the inhibition of enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase. Moreover, alkaloids can increase glucose oxidation through glucose-6-phosphate dehydrogenase. Glucose-6-phosphatase and fructose-1,6-bisphosphatase are enzymes involved in gluconeogenesis [36].

3.1. Limitations and implications for future research

This study investigated the effects of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. extracts on body weight and fasting blood glucose levels in STZ-induced type 2 diabetic rats. However, additional research is needed to confirm the long-term efficacy and mechanisms underlying the hypoglycemic effects of these extracts. Specifically, investigations should focus on potential variability in responses across different rat strains and environmental conditions, which may influence metabolic outcomes. Furthermore, the study's sample size may limit the generalizability of the results, necessitating larger cohorts for improved statistical power. Future research may explore the synergistic effects of additional bioactive compounds present in these plants. Understanding the pharmacodynamics and pharmacokinetics of individual components and their interactions will be crucial for optimizing formulations. Additionally, practical methods for scaling the extraction process should be investigated to facilitate the application of these extracts in clinical settings, thus providing a foundation for their integration into therapeutic regimens for diabetes management.

4. CONCLUSION

Recent observations indicate that the combined extracts of *Phaleria macrocarpa* and *Averrhoa bilimbi* L. significantly ameliorate the symptoms of type 2 diabetes in rats, as evidenced by notable reductions in fasting blood glucose levels and alterations in body weight post-intervention. The findings offer definitive proof that these effects are linked to the phytochemical constituents within these extracts, particularly saponins, tannins, and alkaloids, which enhance insulin sensitivity and regulate glucose metabolism. This underscores the potential application of these herbal extracts as complementary treatments for diabetes, highlighting the relevance of traditional herbal remedies in contemporary therapeutic strategies. Future research should investigate the underlying mechanisms of action, optimal dosages, and the long-term safety of these extracts in human populations, alongside exploring synergistic effects from other bioactive components present in these plants to expand their metabolic health benefits.

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AUTHOR CONTRIBUTIONS STATEMENT

This journal uses the Contributor Roles Taxonomy (CRediT) to recognize individual author contributions, reduce authorship disputes, and facilitate collaboration.

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C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (approval number: 32/UN27.06.11/KEP/EC/2024). This approval ensured that all procedures involving animal subjects met ethical standards for animal welfare and research conduct.

DATA AVAILABILITY

Derived data supporting the findings of this study are available from the corresponding author, [LS], on request.

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