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POTENSIAL COMBINATION OF MATOA LEAF EXTRACT (*Pometia pinnata*) AND MORINGA LEAF EXTRACT (*Moringa oleifera*) AS ANTIDIABETIC IN ALLOXAN-INDUCED MICE (*Mus musculus*)

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disease whose prevalence continues to increase globally. Plant-based alternative therapy is becoming an increasingly popular option due to its minimal side effects. This study aims to test the potential of a combination of matoa (*Pometia pinnata*) and Moringa (*Moringa oleifera*) leaf extracts as an antidiabetic in alloxan-induced male mice (*Mus musculus*). The study was conducted experimentally with five treatment groups, including negative control, positive control, and three groups of extract combination doses (100, 225, and 300 mg/kg BB). Phytochemical tests showed the content of active compounds alkaloids, flavonoids, and steroids in the combination of extracts. Blood glucose level test results showed that the combination dose of 300 mg/kg BB (Dose III) was able to reduce blood glucose levels significantly and had comparable effectiveness with glibenclamide as a standard drug. Statistical analysis (One Way ANOVA and Post Hoc Bonferroni) confirmed that Dose III showed a significant difference compared to the lower dose, and was not significantly different from the positive control.Beyond these results, this study contributes new insights by highlighting the synergistic effect of combining two medicinal plants, providing a scientific basis for the development of standardized herbal formulations as potential alternatives in diabetes management.

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1. INTRODUCTION

Diabetes mellitus (DM) is a serious global health problem, with a prevalence that continues to increase every year, including in Indonesia (Shawputri *et al.,* 2024). According to the International Diabetes Federation (IDF), in 2022 there were approximately 537 million adults (aged 20–79 years) living with diabetes worldwide, and this number is projected to rise to 643 million by 2030 and 784 million by 2045 (IDF, 2021). In Indonesia, the Ministry of Health reported that the number of people with diabetes reached 19.47 million in 2021 (Kemkes, 2024).Pathophysiologically, DM is characterized by chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or a combination of both. This condition triggers various clinical symptoms such as polyuria, polydipsia, polyphagia, weight loss, fatigue, blurred vision, paresthesia, erectile dysfunction, and pruritus vulvae. Moreover, uncontrolled hyperglycemia can lead to oxidative stress through mitochondrial dysfunction, resulting in the overproduction of reactive oxygen species and ultimately inducing cell apoptosis(IDF, 2021).

The most common type of diabetes is type 2 DM, which is closely associated with unhealthy lifestyles and poor dietary patterns(Wijayanti *et al.,* 2020). The Indonesian Health Survey (IHS, 2023) reported that approximately 50.2% of diabetes cases in the country are type 2. This type often develops gradually and is initially asymptomatic, making early detection challenging. Common manifestations include persistent thirst, frequent urination, fatigue, blurred vision, and delayed wound healing. Risk factors include obesity, sedentary lifestyle, poor diet, and genetic predisposition. Current management strategies primarily involve insulin therapy and oral hypoglycemic agents. However, these approaches have several limitations, including high cost, long-term side effects, and reduced patient adherence, which underline the urgent need for safer and more affordable alternatives (Purwaningsih*et al.,* 2024).

Traditional medicinal plants represent a promising alternative in diabetes management. Matoa leaves (*Pometiapinnata*) and Moringa leaves (*Moringa oleifera*) have been widely recognized for their bioactive compounds with antidiabetic properties. *P. pinnata* leaves contain flavonoids, alkaloids, and steroids that function as antioxidants and hypoglycemic agents, while *M. oleifera* leaves are rich in phytochemicals such as flavonoids, phenolics, and saponins that reduce blood glucose and cholesterol levels(Hasan *et al.,* 2024).Previous studies have predominantly investigated the effects of each plant extract individually, confirming their potential antihyperglycemic effects (Rahman *et al.,* 2023).

However, the novelty of this research lies in the exploration of a combined extract of*P. pinnata*and*M. oleifera***,** which has not been explicitly studied before**.** While individual extracts have demonstrated efficacy, the potential synergistic interaction between both plants may enhance their antioxidant and antihyperglycemic effects, providing a more effective natural alternative for diabetes therapy. Identifying such synergistic potential is crucial, as combination therapies from natural sources may reduce the required dosage and minimize adverse effects compared to synthetic drugs (Susanti*et al.,* 2023).Therefore, this study aims to investigate the antidiabetic potential of the combined extracts of P. pinnata and M. oleifera in alloxan-induced male mice. The findings are expected to contribute not only as empirical evidence for herbal-based diabetes management but also as a novel scientific insight into the synergistic role of plant extract combinations in metabolic disorder therapy.

2. METHOD

The research was experimental using a design of 5 treatment groups and 5 replicates. The research was conducted for 3 months from January 2025 to March 2025. The treatment of a combination of *P.pinnata* and *M.oleifera* leaf extracts, measurement of blood glucose levels, and the percentage reduction in blood sugar levels in alloxan-induced test animals (*M.musculus*) was carried out at the Ruyani Life Science Learning Resources Laboratory (SBIH), Faculty of Teacher Training and Education, Bengkulu University. SBIH Ruyani is a place for student research to seek new knowledge so as to improve the quality of science education (Ruyani et al., 2018). Before testing the material on *M.musculus*, researchers conducted phytochemical tests first at the Basic Science Laboratory FMIPA, Bengkulu University.The research procedure can be seen in the following diagram in Figure 1.

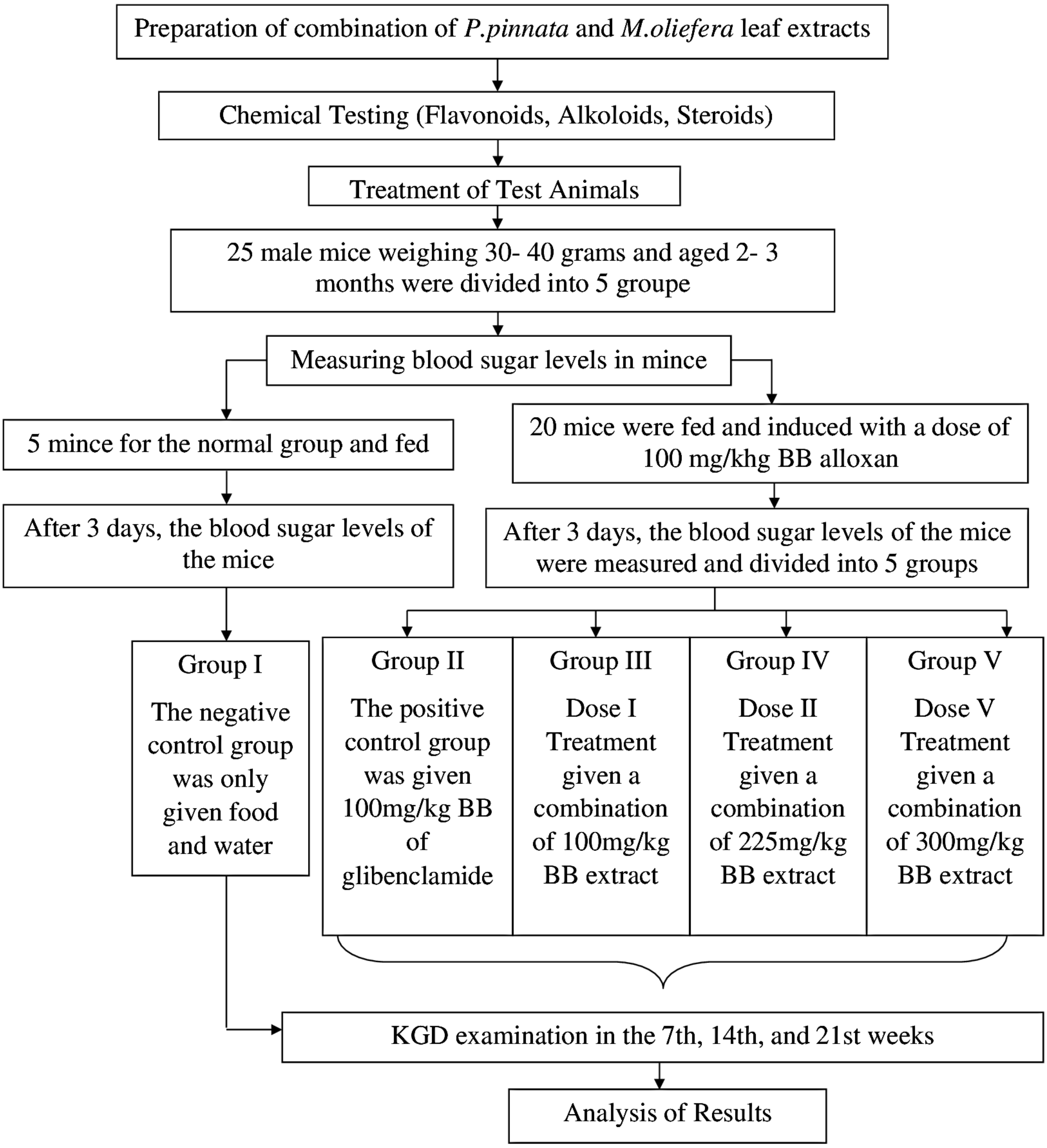

Figure1. Research Procedure

The Figure 1 tools used in this research are cage, plastic tray, analytical balance, 80ml drinking bottle, blender, filter paper, mesh number 40 sieve, 1L maceration jar, rotary evaporator, electric balance, spatula, 500 ml measuring cup, sonde, 1ml spluid, EasyTouch glucometer, and glucose test strips, scalpel. The materials needed are *P.pinnata* and *M.oleifera* leaf extracts, *M.musculus* feed, 96% ethanol, distilled water, alloxan, glibenclamide drug, male mice aged 2-3 months with BB ± 30 grams and mice feed.

2.1 Prosedures

2.1.1 Sampling

Sampling of *P.pinnata* and *M.oliefera* leaves is done on good dark green leaves. *P.pinnata* and *M.oliefera* leaves are then washed with running water to clean dirt and dust attached to the leaves and then drained and dried using an oven.

2.1.2 Preparation of *P.pinnata* and *M.oliefera* Leaf Powder

P.*pinnata*and M.*oliefera* leaves that have been washed with water are then dried using an oven at 50ºC until they reach dry conditions. The drying process aims to obtain stable and non-perishable simplisia, thus allowing storage for a long period of time (Voight 1994). Drying using an oven at a controlled temperature is considered more effective in maintaining the content of active compounds than other methods such as direct sun drying, because it can minimize the degradation of compounds due to exposure to excess heat and ultraviolet light. This is in line with research conducted by(Widarta & Wiadnyani, 2019)showing that the drying method has a significant effect on the content of bioactive compounds in simplisia. In the study, drying was carried out by two methods, namely drying in the sun and drying using an oven. The results showed that the maturity level of the leaves as well as the drying method affect the content of bioactive compounds and antioxidant activity in avocado leaf extracts. Mature, oven-dried leaves showed the highest antioxidant activity, accompanied by specific moisture, total phenolics, flavonoids, and tannin contents. Thus, oven drying proved to be more effective in maintaining and producing higher flavonoid levels in the simplisia extract.

After the drying process, the leaves were dried and then pulverized using a blender to obtain dry powder. The powder was then sieved using a sieve with mesh size number 40 to obtain a powder with a more homogeneous and fine particle size, thus facilitating the extraction process and increasing the efficiency of solvent absorption.

2.1.3 Preparation of Ethanolic Extract of *P.pinnata* and *M.oliefera* leaves

Extraction of *P.pinnata* and *M.oliefera* leaf powders was carried out separately using the maceration method. Each leaf powder of 1000 grams was put into an 8L maceration jar, then 6 liters of 96% ethanol solvent was added. The mixture was tightly closed, wrapped in black cloth and soaked for three days in a dark room to maintain the purity and effectiveness of the active substances in the extract. Shaking the ethanolic extract was done every day for 15 minutes to help the diffusion process of active compounds. After the maceration process was complete, the macerate was filtered and squeezed using gauze to obtain the filtrate. The filtrate from each material was then combined with a ratio of 50% *P.pinnata* extract and 50% *M.oliefera* to carry out the concentration process using a rotary evaporator at 40 ° C, followed by evaporation using a waterbath to obtain a thick extract from the extract *P.pinnata* and *M.oliefera* leaves in Figure 2 and Figure 3.

Figure 2. Rotary Evaporator Combination Extract P.*pinnata* leaves dan M.*oliefera* leaves

Figure 3. Waterbath Combination Extract P.*pinnata* leaves dan M.*oliefera* leaves

2.1.4 Preparation of Glibenclamide Suspension

In the 0.01 glibenclamide solution is made in 100ml by taking glibenclamide as much as 2 2x5 mg tablets (Priscilia & Nasution, 2022), the glibenclamide is then crushed using a mortar until smooth. Then add distilled water solution to 100 ml, after adding distilled water to 100 ml shake it until homogeneous.

2.1.5 Preparation of 1% Alloxan Monohydrate Solution

In the 1% alloxan monohydrate solution was made in 100ml and then weighed 1 g of alloxan powder and added distilled water until 100ml and stirred until homogeneous. The alloxan solution is given to mice using the oral gavage method, administering the drug using a special tool such as a sonde needle which is done by inserting the sonde through the mouth and esophagus until it reaches the mice's stomach.

2.1.6 Combination Solution of *P.pinnata* and *M.oliefera* leaf extracts

A combination solution of *P.pinnata* and *M.oliefera* leaf extracts was made for three doses of a combination of ethanol extracts of *P.pinnata* and *M.oliefera* leaves, namely dose I (100 mg/kg BB), dose II (225 mg/kg BB), III (300 mg/kg BB). Each solution that has been prepared is given by oral gavage (needle sonde) to the treatment group mice in accordance with the predetermined dose. The solution is given by oral gavage or strangulation to the test animal, the strangulation is done using a sonde needle.

2.1.7 Preparation of Experimental Animals

This study researchers used male white mice as experimental animals, before carrying out the treatment the mice were adapted first for 1 week to familiarize the animals to stable conditions and were given enough food and drink before being treated. Male white mice were used in this study because the speed of drug metabolism in male mice is higher than female mice (Yusuf *et al.,* 2022).

2.1.8 Data analysis

2.1.8.1 Phytochemical Test

Phytochemical tests are a series of procedures to detect and identify classes of secondary metabolites (such as alkaloids, flavonoids, phenols, saponins, tannins, terpenoids) in plant extracts. Typical steps include plant preparation, extraction, qualitative screening, followed by quantitative testing and bioactivity such as antioxidant or antibacterial (Febriliana, 2023).

2.1.8.2 One Way Anova Test

The data obtained in the form of blood glucose levels were statistically analyzed using one-way anova analysis (*One Way Anova*) at the 95% confidence level. The test criteria is if the significance value is smaller than 0.05 then the data is said to be not normally distributed. If the data meets the requirements for ANOVA test, the analysis is continued with Post Hoc Test to determine whether the mean difference between the groups is significant or not using the SPSS for Windows Release program

3. RESULTS AND DISCUSSION

This study aims to determine the potential antiperglycemic effectiveness of extracts given in three different doses on blood glucose levels of mice induced by alloxan. This study uses a maceration extraction method using 96% ethanol solvent with 1000 grams of *P.pinnata* and *M.oliefera* leaf powder resulting in 10 liters of filtrate, 5 liters of *P.pinnata* filtrate and 5 liters of *M.oliefera* leaves then evaporated using a rotary evaporator with each extract 50% in one evaporator. After that, to produce a thick extract, researchers used a waterbath and produced a thick extract of a combination of *P.pinnata* and *M.oliefera* leaf extracts as much as 500 mg.The results of phytochemical tests conducted by researchers in the laboratory, secondary metabolite compounds that have the potential to reduce blood sugar levels as follows;

3.1. Phytochemical Test Results

This studyresearchers identified 3 secondary metobolite compounds in *P.pinnata* leaves and *M.oliefera* leaves using the Visible Spectrophotometry method. There are 3 metabolite compounds tested, namely Alkoloid, Flaphonoid, and steroid which have the potential to reduce blood sugar levels in Table 1.

Table 1. Phytochemical Test Results

Sample	Parameter	Units	Result	Method
FT 1	Alkoloids	mg/L	465.89	Visible Spectrophotometry
FT 1	Flavonoids	mg/L	75.53	Visible Spectrophotometry
FT 1	Steroids	mg/L	0,078	Visible Spectrophotometry

Table 1 based on the results of phytochemical tests on sample FT 1 (Combination of *P.pinnta* and *M.oliefera* leaf extracts) showed the presence of active compounds in the form of alkaloids (465.89 mg/L), flavonoids (75.53 mg/L), and steroids (0.078 mg/L) identified using visible spectrophotometric methods. The most dominant alkaloid content has great potential as an antidiabetic because it can stimulate insulin secretion, inhibit carbohydrate-breaking enzymes, and increase insulin sensitivity (Novalinda *et al.,* 2021). Flavonoids, which were also detected quite high, play an important role in reducing blood sugar levels through antioxidant activity, protection of pancreatic β cells, and inhibition of carbohydrate digestive enzymes (Alfani *et al.,* 2021). This is in line with the research of (Rahmawati *et al.,* 2021)which explains that flavonoids are protective against damage to pancreatic β cells as insulin producers. Meanwhile, although the steroid content is relatively low, this compound still has a contribution to glucose regulation through influences on hormone and lipid metabolism. Thus, the presence of these three compounds synergistically supports the potential of FT 1 extract as an antidiabetic natural ingredient.

After phytochemical testing, the researchers tested the ingredients on test animals. Data analysis presented in this study is in the form of bivariate analysis to analyze the difference in blood sugar levels in *M.musculus* before and after being given a combination preparation of *P.pinnata* and *M.oliefera* extracts. The first step taken by researchers is to raise blood sugar levels by giving alloxan solution to *M.musculus*. Making diabetic conditions in experimental animals (male mice) is done by inducing alloxan orally (gavege method) using a sonde needle(Cahyaningrum*et al.,* 2019). Alloxane is a compound toxic to pancreatic β-cells, which induces a state of hyperglycemia by selectively damaging insulin-producing cells. According to (Wulandari *et al.,* 2024)Alloxan is a diabetes (DM) inducing compound used for experimental diabetes treatment.

3.2. Results of Observations of Test Animals (*M.musculus*)

This study, researchers used 25 *M.musculus* which were divided into 5 groups randomly with 5 replicates. The negative control group was given regular feed and drink without being treated, the positive control group, dose I, dose II, and dose III were treated by giving alloxan solution to *M.musculus* to raise blood sugar levels and a combination preparation of *P.pinnata* and *M.oliefera* extracts after mice were known to have increased blood sugar levels. The results of observations of blood glucose levels of mice are presented in Table 2, which shows the average changes in blood glucose levels on days 0, 3, 7, 14, and 21 after treatment in Table 2.

Table 2. Mean Blood Sugar Level *M.musculus*

Treatment Group	**Mean Blood Glucose *M.musculus* (mg/dL) (X±SD)**						
	N	**Day to- 0**	**Day to-3 (A)**	**Day to-7**	**Day to- 14**	**Day to- 21 (B)**	**A-B**
KN	5	153,0±24,4	174,4±16,4	165,2±20,1	174,4±23,0	125,4±11,0^{bc}	49,0
KP	5	137,0±16,1	211,0±20,9	144,6±18,1	118,4±6,5	79,6±16,3^{a}	131,4
Dose I	5	115,4±44,3	203,4±8,8	182,4±14,0	175,0±13,3	161,4±16,1^{c}	42,0
Dose II	5	134,0±22,7	228,6±33,5	185,2±9,0	177,2±12,8	153,4±10,8^{c}	75,2
Dose III	5	129,0±34,4	199,0±10,9	171±22,1	147,8±19,6	97,8±15.8^{ab}	101,2

Different table 2 notations indicate significant differences ($p \leq 0.05$) based on the results of the Duncan test. Dose I (100 mg/kg BB), dose II (225 mg/kg BB), dose III (300 mg/kg BB), KP (glibenclamide drug treatment), KN (normal group without treatment).

According to Ernawati (2020), normal blood glucose levels in humans are 80-160 mg/dL, while in mice, normal blood glucose levels are 62.8-176 mg/dL. If the level exceeds this range, it can be considered hyperglycemia.Based on the results of blood glucose measurements in *M.musculus* conducted on days 0, 3, 7, 14, and 21, there was a significant difference between the control group and the treatment group. The negative control group showed an increase in blood glucose levels from 153.0 ± 24.4 mg/dL on day 0 to 174.4 ± 16.4 mg/dL on day 3. This initial increase is a temporary response due to metabolic stress or environmental adaptation, which is common in laboratory animals. The study by (Marin *et al*. (2023). showed that blood glucose levels in healthy mice can fluctuate during the adaptation phase, especially in the first week of the experiment, due to changes in the cage environment, stress, or circadian rhythm cycles. Although blood glucose levels gradually decreased to 125.4 ± 11.0 mg/dL on day 21, this decrease was a natural physiological response without pharmacological intervention. This is consistent with Haq (2018)research, which confirms that in healthy mice, glucose regulation systems such as basal insulin secretion, GLUT4 activity, and liver function remain normal, so glucose levels tend to return to normal even after a temporary increase. The positive control group experienced an increase in blood glucose levels after alloxan induction on day 3 (211.0 ± 20.9 mg/dL), followed by a significant decrease in blood glucose levels after administration of glibenclamide to 79.6 ± 16.3 mg/dL (day 21), with a total decrease of 131.4 mg/dL. This demonstrates the efficacy of glibenclamide as an antidiabetic agent, in line with Paisal (2022) which explains that glibenclamide effectively lowers blood glucose levels through the mechanism of increasing endogenous insulin secretion.

In the treatment group, the combination of*P.pinnata* leaf extract and *M.oleifera* leaf extract showed varying results depending on the dose administered. Group Dose I experienced a decrease in blood glucose levels of 42.0 mg/dL from day 3 to day 21, from 203.4 ± 8.8 mg/dL to 161.4 ± 16.1 mg/dL, but the value was not significantly different from the negative control group. The Dose II group showed a decrease of 75.2 mg/dL from 228.6 ± 33.5 to 153.4 ± 10.8 mg/dL, which was still considered less effective. Interestingly, the Dose III group showed better results with a decrease in blood glucose levels of 101.2 mg/dL, from 199.0 ± 10.9 to 97.8 ± 15.8 mg/dL.This final value is close to the positive control group and is not statistically significantly different from the positive control group. This indicates that the combination of*P.pinnata* leaf extract and *M.oleifera* leaf extract at a high dose (300 mg/kg BB) has efficacy comparable to the standard drug in lowering blood glucose levels, thereby potentially serving as a natural-based antidiabetic agent. The average blood glucose reduction graph for *M. musculus* can be seen in Figure 1.

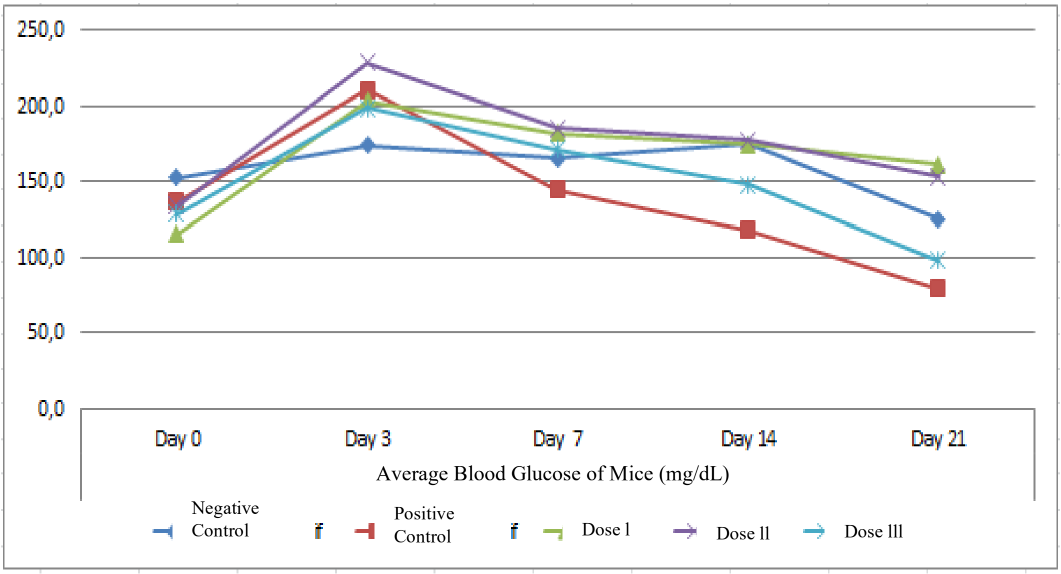

Figure 4. Graph Showing the Average Decrease in Blood Glucose Levels in *M. Musculus*

The Figure 4 results of blood glucose level observations in mice (*M.musculus*) in Figure 4 show a decrease in blood sugar levels in all treatment groups from day 3 to day 21. The positive control group, which was administered glibenclamide after alloxan induction, exhibited the most significant decrease in blood glucose levels, amounting to 62.27%. On the other hand, the Dose III group showed a reduction of 50.85%, approaching the efficacy of the positive control, while Dose I and Dose II showed reductions of 20.65% and 32.89%, respectively. This indicates a clear dose–response relationship, where higher doses of the extract combination provide more effective blood glucose reduction.The phenomenon of dose–response is also reported in herbal antidiabetic research by Hasan et al. (2024)who found that increasing the concentration of plant extract significantly enhanced hypoglycemic activity through synergistic action of secondary metabolites.

The observed antihyperglycemic activity of the extract combination can be explained by several mechanisms. Alkaloids may stimulate insulin secretion and improve sensitivity, flavonoids act as antioxidants and protect β-cells, while steroids can influence lipid and hormone metabolism.Wu & Wang (2023)reported that bioactive compounds such as flavonoids and alkaloids regulate insulin signaling pathways, inhibit α-glucosidase, and reduce oxidative stress without causing adverse toxic effects, making them promising alternatives to synthetic drugs.

The statistical analysis using the Shapiro–Wilk normality test and homogeneity test on the average blood sugar levels (KGD) of *M. musculus* showed that the data are normally distributed and have homogeneous variance. The results of the One-Way ANOVA test indicate that there are significant differences between the treatment groups: $F = 3.817$; $p = 0.006 < 0.05$. Bonferroni post-hoc analysis revealed a significant difference only between the positive control group and Dose II ($p = 0.007$), while no significant difference was observed between the positive control and Dose III. Duncan's test confirmed that the positive control and Dose III groups belonged to the same subset, indicating statistical similarity in their hypoglycemic effect.

These findings provide evidence that the combination of *P. pinnata* and *M. oleifera* leaf extracts, particularly at high dose (300 mg/kg BB), demonstrates strong potential as a natural-based antidiabetic agent comparable to glibenclamide. Unlike single extract studies (Purwaningsih et al., 2024), this study highlights the synergistic effect of combining two different medicinal plants, offering a novel perspective for herbal-based diabetes management.These findings not only strengthen the evidence of the antihyperglycemic activity of plant-based bioactive compounds but also open opportunities for further research in the development of standardized herbal formulations. Future studies can explore molecular mechanisms, toxicological safety, and clinical trials to validate the efficacy of this combination, thereby contributing to the advancement of alternative diabetes therapy based on natural products.

4. CONCLUSION

Thecombination of *Pometia pinnata* and *Moringa oleifera* leaf extracts contains bioactive compounds such as alkaloids, flavonoids, and steroids that demonstrate potential in lowering blood glucose levels. Among the three tested doses, the highest dose (300 mg/kg BB) proved to be the most effective in reducing blood glucose in alloxan-induced mice, showing comparable efficacy to the standard drug glibenclamide. These findings not only confirm the antidiabetic properties of each extract individually but also highlight a possible synergistic effect of their combination, which has been rarely reported in previous studies. The study provides a meaningful scientific contribution to the development of standardized herbal formulations as alternative antidiabetic therapies and warrants further investigation, particularly through clinical trials in humans.

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