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EFFECT OF MORINGA (*Moringa oleifera*) LEAF FLOUR ETHANOL EXTRACT ON REDUCTION OF BLOOD GLUCOSE IN MALE WISTAR STRAIN RATS INDUCED BY ALLOXAN

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ABSTRACT

Penelitian ini untuk mengetahui pengaruh pemberian ekstrak etanol tepung daun kelor (*Moringa oleifera*) terhadap penurunan kadar glukosa darah tikus jantan Wistar *Rattus norvegicus* yang diinduksi aloksan. Menggunakan desain true eksperimen dengan pendekatan randomized pre and post control group. Sampel yang digunakan terdiri dari 35 ekor tikus putih jantan Wistar. Pengumpulan data dengan teknik simple random sampling. Uji t berpasangan memberikan hasil p<0,05 pada semua kelompok perlakuan, artinya terdapat perbedaan kadar glukosa darah puasa tikus hiperglikemik sebelum dan sesudah perlakuan. Uji one way ANOVA memberikan hasil p<0,001 artinya seluruh kelompok perlakuan menunjukkan adanya perbedaan rerata perbedaan kadar glukosa darah puasa yang signifikan sebelum dan sesudah perlakuan. Hasil uji post hoc LSD menunjukkan adanya perbedaan rerata perbedaan bermakna kadar glukosa darah puasa sebelum dan sesudah perlakuan P1 dan P2 dengan semua kelompok perlakuan (p<0,001). Uji analisis probit diperoleh nilai ED_{50}=1447,84 mg/kgBB.

ABSTRACT

This study is to determine the effect of giving ethanol extract of moringa leaf flour (Moringa oleifera) on reducing blood glucose levels of alloxan-induced Wistar Rattus norvegicus male rats. Using a true experimental design with a randomized pre and post control group approach. The sample used consisted of 35 male Wistar white rats. Data collection using simple random sampling technique. Paired t test gives the results of p<0.05 in all treatment groups, meaning that there are differences in fasting blood glucose levels of hyperglycemic rats before and after treatment. One way ANOVA test gave the result of p<0.001, meaning that all treatment groups showed a significant difference in the mean difference in fasting blood glucose levels before and after treatment. LSD post hoc test results showed a significant mean difference in fasting blood glucose levels before and after treatment of P1 and P2 with all treatment groups (p<0.001). Probit analysis test obtained ED_{50}=1447,84 mg/kgBB.

INTRODUCTION

Diabetes mellitus (DM) is a complex disturbance that is marked by hyperglycemia or an increase in glucose in the blood caused by resistance to insulin or disturbance of insulin secretion due to damaged pancreatic β-cells.[1] An increase in HbA1c levels ≥ 6.5%, fasting blood glucose (FBG) ≥ 126 mg/dL, and plasma glucose 2 hours after OGTT ≥ 200 mg/dL is a diagnostic criterion for DM.[2] Currently, diabetes mellitus is still a global health problem. Based on official data in 2021, 537 million adults aged 20–79 suffer from DM worldwide. This number is expected to increase to 643 million in 2030 and 784 million in 2045. In 2021, DM caused 6.7 million deaths worldwide.[3]

Cases of DM sufferers among residents in Indonesia have increased from 3,941,698 people in 2019 to 19.5 million people in 2021, and it is reported that Indonesia ranks 5th out of 10 countries with the largest number of people suffering from DM.[4] Provinces Lampung is one of the regions that has experienced an increase in DM cases from year to year. DM cases are prevalent in residents aged ≥ 15 years in Lampung Province, an increase of 0.57% from 0.8% in 2013 to 1.37% in 2018.[4,5] In 2021, DM cases occupy 9th position out of the 10 most common diseases in the province Lampung with obtained data amount suffered DM as 70,647 people in Bandar Lampung City.[5]

Hyperglycemia in the body can cause the formation of excessive ROS (Reactive Oxygen Species)[6] and will trigger oxidative stress, thereby damaging the pancreatic β-cells that produce insulin, a hormone that plays a role in regulating blood glucose levels.[7] Oxidative stress in the body can be overcome with antioxidant endogenous, but exogens are needed to neutralize free radicals. One example is the leaves of *Moringa oleifera*.[8]

Moringa oleifera leaves contain phytochemical compounds, including tannins, flavonoids, and alkaloids.[9] [10] The flavonoid content in *Moringa oleifera* leaves is known to be higher than that of other leaves, such as pumpkin leaves and fern leaves.[11] One of the flavonoid contents found a lot in the extracted leaf of *Moringa oleifera* is quercetin. 9 Activity quercetin as an antioxidant works with the formation of ROS, and death cell-β pancreatic islet of Langerhans, even regenerate pancreas beta cells, which have degraded, so that can lower blood glucose levels.[12]

A study done by Siddiq in 2019 showed flour leaf *Moringa oleifera* given to rats with experimental diabetic conditions was effective in lowering blood glucose levels.[13] In solvents, water attracts polar active compounds in the form of flavonoids and o-glycosides. However, its effectiveness is not enough as an antioxidant to capture free radicals, while the ethanol solvent can attract active compounds polar in the form of flavonoid c-glycosides, which are more effective as antioxidants because they are easier to use and interact with free radicals, which can damage body cells.[14] Based on the description, this study aims to compare the average blood glucose rate in the blood of the mouse *Rattus norvegicus* male Wistar strain, which has induced alloxan before and after administering an ethanol extract of *Moringa oleifera* leaf flour. Knowing the difference in the average decline rate of glucose in the blood of the *Rattus norvegicus* male Wistar strain between every group treatment after giving the extract of ethanol flour leaf *Moringa oleifera* and knowing Mark ED_{50} (Effective Dose 50) extract ethanol flour leaf *Moringa oleifera* in lower rate blood glucose *Rattus norvegicus* male Wistar.[15]

METHOD

This type of research is true experimental with a randomized pre- and post-control group research design. The research was carried out at the Animal House Faculty of Medicine, University

of Lampung from November 2023 to January 2024. The inclusion criteria for this study were male *Rattus norvegicus* rats of the Wistar strain who were healthy normoglycemia, aged 2-3 months and had a body weight of 200 ± 15 gr, that is 185-215 gr, and the exclusion criteria for this study were rat blood glucose levels after alloxan induction <125 mg/dL. *Rattus norvegicus* rats were used as experimental animals in this research because of their fast reflexes and anatomic body structure that is almost similar to humans, have an omnivorous diet like humans, and are easy to give oral treatment. The gender used was male because they do not experience hormonal fluctuations, such as female gender because it is feared that it could influence research results.[16]

Making *Moringa oleifera* leaf flour extract using the maceration extraction method. *Moringa oleifera* leaf flour was macerated with 2L of 70% ethanol solvent for 3 days in a closed container. After that, it is filtered to separate the filtrate and residue. After the maceration process, the macerate obtained was evaporated using a rotary evaporator at a temperature of 40°C to obtain a concentrated extract. Making glibenclamide preparations involves mixing the drug glibenclamide with equates until homogeneous. The dose of glibenclamide is 0.126 mg/200 grBW/day. Glibenclamide was given to rats orally at 0.126 mg/200 grBW/day dose and given 2 mL/200 grBW/head. Alloxan monohydrate was given at a dose of 125 mg/kgBW intramuscularly in the thigh muscles of rats and given at 2 mL/200 gBW/head. Alloxan was induced in the positive control group and all groups were treated with ethanol extract of *Moringa oleifera* leaf flour.

The extract was administered for 7 days after being induced by alloxan for 3 days. Varying doses of *Moringa oleifera* leaf flour ethanol extract were used, namely doses of 1000, 500, 250, 125, and 62.5 mg/kgBW. Sampling was carried out 3 times. First, an initial FBG examination was carried out, then an FBG examination was carried out after being induced by alloxan for 3 days (before treatment), and finally, an FBG examination was carried out after intervention with *Moringa oleifera* leaf flour ethanol extract for 7 days. The procedure for taking mouse blood samples was carried out, namely first grasping the skin behind the mouse's neck and ears using the thumb and forefinger, then holding the tail against the palm using the hand. The amount of blood needed to measure FBG levels is around 0.05 mL, or one drop, which is taken from the tip of the rat's tail after it has been sterilized with 70% alcohol and cut thinly. A maximum of 1 mm could be cut from the tip of the tail, and only 5 tails were allowed to be cut during the study. After that, stick the blood glucose strip into the blood until the space on the strip is filled, the device monitor screen will display the numbers after 1 minute. After 7 days of treatment, the mice will be terminated with ketamine and xylazine as anesthesia and euthanasia. The rat carcasses will be collected and cremated. Data analysis used a paired T-test to analyze differences in FBG levels before and after intervention in all groups. Before carrying out this test, the data was tested for normality first using Shapiro Wilk. Next, a one-way ANOVA test was carried out because the data was normally distributed, then the homogeneity test was continued, namely the Levene test. The data is found to be homogeneous so it can be continued with the LSD post hoc test. Next, a probit test analysis was carried out to obtain the ED_{50} value of the ethanol extract of *Moringa oleifera* leaf flour on reducing blood glucose. This research has received approval from the Health Research Ethics Committee, Faculty of Medicine, University of Lampung with letter number 55/UN26.18/PP.05.02.00/2023.

RESULTS

In this study, 35 rats were used, who were able to complete all stages of the research until the end without any exclusions. All rats had their FBG levels measured three times. The rats in this

research subject were ensured to have fasted for 8 hours before measurements were taken, and the glucose measurement equipment used had been adjusted and calibrated by applicable standards to ensure the accuracy and consistency of measurement results. Rats' FBG levels were calculated before administration of alloxan (initial FBG levels), 3 days after alloxan induction (FBG levels before treatment), and 7 days after treatment (FBG levels after treatment). The results of the average initial FBG levels, FBG levels before treatment, and FBG levels after treatment obtained, as well as the average difference in FBG levels before and after treatment in each group, can be seen in Table 1.

Table 1. Results of Average FBG Levels and Differences in FBG Levels Before and After Treatment

Group	FBG levels initial (mg/dL)	FBG levels before treatment (mg/dL)	FBG levels After treatment (mg/dL)	Mean difference in FBG levels before and after treatment (mg/dL)
NC	90.6±8.8	94.2±10.9	92.2±8.7	2±2.9
PC	96.8±9.6	143±3.4	108.8±4.2	34.2 ± 0.8
P1	99.6±9.2	148.8±5.2	94.4±7.0	54.4±6.1
P2	103.8±5.6	158.6±6.1	107.8±3.1	50.8±7.5
P3	90.4 ± 13.8	133.4 ± 5.7	100.8±9.1	32.4±8.7
P4	99.6±8.6	148.6±8.6	120.8±1.9	27.8±6.9
P5	103.4±3.5	152±1.2	123.4 ± 2.7	28.6 ± 2.8

Information: NC= Negative Control; PC= Positive Control; P1= Dose 1000 mg/kgBW; P2= Dose 500 mg/kgBW; P3= Dose 250 mg/kgBW; P4= Dose 125 mg/kgBW; P5= Dose 62.5 mg/kgBW

The results of the Saphiro-Wilk data normality test analysis are listed in Table 2. The significance values obtained in the 7 groups before and after treatment were all p> 0.05. This shows that the data is normally distributed. Thus, it can be continued with the paired T-test.

Table 2. Results of Average FBG Levels and Differences in FBG Levels Before and after Treatment

Group Treatment	Significance (p)
Pre -NC Group	0.568
Post -NC Group	0.610
Pre - PC Group	0.341
Post -PC Group	0.566
Pre -Group P1	0.245
Post -Group P1	0.467
Pre -Group P2	0.474
Post -Group P2	0.670
Pre -Group P3	0.299
Post -Group P3	0.868
Pre -Group P4	0.503
Post -Group P4	0.928
Pre -Group P5	0.146
Post -Group P5	0.980

The results of the paired T-test, which differentiated FBG levels before and after treatment in the positive control group, found no difference (p = 0.200), whereas in groups P1, P2, P3, P4, and P5, the value was p<0.05, which means there was a significant difference between before and after treatment in the KP, P1, P2, P3, P4, and P5 groups. The results of the paired T-test are listed in Table 3.

Table 3. Paired T-Test Results for FBG levels Before and After Treatment

Group Sig treatment	(2- tailed)
Pre Ex NC – Post Ex NC	0.200
Pre Ex PC – Post Ex PC	<0.001
Pre Ex P1 – Post Ex P1	<0.001
Pre Ex P2 – Post Ex P2	<0.001
Pre Ex P3 – Post Ex P3	0.001
Pre Ex P4 – Post Ex P4	0.001
Pre Ex P5– Post Ex P5	<0.001

The results of the one-way ANOVA test in this study regarding the decrease in FBG levels in rats showed a p-value <0.001, which means there was a significant difference in the mean decrease in FBG levels in rats after treatment between groups. Next, a data homogeneity test was carried out using Levene's test method, and a value of p = 0.084 was obtained, which means the data was homogeneous, and then this could be done using the LSD post hoc test.

The results of the LSD post hoc test showed a p-value of >0.05 in group PC with P3, PC with P4, PC with P5, P1 with P2, P3 with P4, P3 with P5, and P4 with P5 which means there were no significant differences between groups. Apart from these groups, the other groups obtained a p-value <0.01, which means there are significant differences between each group.

Table 4. Test *Post Hoc LSD*

	NC	PC	P1	P2	P3	P4	P5
NC	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PC		-	<0.001	<0.001	0.666	0.092	0.138
P1			-	0.335	<0.001	<0.001	<0.001
P2				-	<0.001	<0.001	<0.01
P3					-	0.202	0.285
P4						-	0.829
P5							-

In the probit analysis test, the ED_{50} value was found to be 1447.840, which means that to obtain an effective dose that can reduce blood sugar levels in 50% of test animals, a dose of 1447.840 mg/kgBW is required.

DISCUSSION

Rats are said to be diabetic if their FBG levels reach ≥126 mg/dL, and previous studies also used normal FBG levels of ≤126 mg/dL.[17] Normal rats' blood glucose levels are 70–110 mg/dL and are said to be hyperglycemic. if the blood glucose level reaches >110 mg/dL.[18] The average FBG level of rats before being induced by alloxan in treatment group 1 was 99,6 mg/dL, while the average FBG level after being induced by alloxan was 148,8 mg/dL. This shows that there was an increase in rat

FBG levels by 49,4 mg/dL. An increase in FBG levels after being induced by alloxan also occurred in the glibenclamide (PC) treatment group and other *Moringa oleifera* leaf flour ethanol extracts. Increased blood glucose after 3 days of alloxan induction because alloxan can trigger the formation of ROS in pancreatic β-cells and will damage pancreatic β-cells, which secrete the hormone insulin.[19]

The results of the paired T-test (table 3) show that the mean FBG levels before treatment and after treatment in the NC group did not have a significant difference because in this group the rats were not induced by alloxan; they were only given drink ad libitum and eat standard food, whereas in the PC group, P1, P2, P3, P4, and P5 were found in the average FBG levels before and after treatment to have significant differences, so it can be interpreted that there is an influence of the ethanol extract of *Moringa oleifera* leaf flour on the FBG levels of rats; this occurs due to improvements in blood glucose mechanisms. in rats. In KP, this was the group given the drug glibenclamide. This drug works by binding to receptors on pancreatic cells, especially beta cells. After glibenclamide binds to the receptor, it will trigger the closure of potassium channels in the pancreatic beta cell membrane, which causes depolarization, and the opening of calcium channels, which allow calcium ions to enter the pancreatic beta cells and stimulate the release of insulin granules stored in the cells. The insulin contained in the granules will be released into the blood and help the body's cells absorb glucose from blood so that it can reduce blood glucose levels.[13]

In the results of the one-way ANOVA test in this study, the mean difference in FBG levels before and after treatment between groups of rats was found to have a p-value <0.01, which means there was a significant difference between treatment groups. Furthermore, according to the results of the post hoc LSD test, the mean decrease in FBG levels after treatment between P1 and P2 did not have a significant difference, with the mean value of the decrease after treatment with ethanol extract of *Moringa oleifera* leaves in P1 was 54,4 mg/dL, while in P2 it was 50,8 mg/dL, which means that administering ethanol extract of *Moringa oleifera* leaf flour at a dose of 1000 mg/kg BW has a greater effect on reducing blood glucose compared to a dose of 500 mg/kgBW, although the difference in the reduction obtained between the two doses is not very significant.

Between P1 with P3, P4, and P5 as well as between P2 with P3, P4, and P5 there was a significant difference in the reduction in FBG levels after treatment, meaning that the administration of *Moringa oleifera* leaf flour ethanol extract at a dose of 1000 mg/kgBW and 500 mg/kgBW was more effective in lowering blood glucose compared to administering the ethanol extract of *Moringa oleifera* leaf flour at a dose of 250 mg/kgBW, 125 mg/kgBW, and a dose of 62.5 mg/kgBW. Between groups P3 P4 with P5 there was a significant difference in the reduction in FBG levels after treatment, with the mean value of the reduction in FBG levels after treatment with *Moringa oleifera* leaf ethanol extract at a dose of 250 mg/kgBW of 32.4 mg/dL, this difference was greater, although not significant, compared with a dose of 125 mg/kgBW of 27.8 mg/dL and a dose of 62.5 mg/kg BW of 28.6 mg/dL. This is in line with previous research in 2019, administering *Moringa oleifera* leaf flour extract at a dose of 125 mg/kgBW had a lower blood glucose lowering effect compared to a dose of 250 mg/kgBW because the greater the amount given of *Moringa oleifera* leaf flour, the greater the decrease in blood glucose levels in rats.[13,20]

In P4, who received an ethanol extract of *Moringa oleifera* leaf flour at a dose of 125 mg/kgBW, the average decrease in FBG levels after treatment was 27,8 mg/dL, while the P5 group with a dose of 62,5 mg/dL had a mean of 28,6 mg/dL. There is no significant difference between P4 and P5, meaning that the effects obtained by the two groups are equivalent. What differentiates the average decrease in FBG levels after treatment at P5, which is slightly higher compared to P4, is that the body's response in each mouse is different.

Rats have different eating patterns for each rat, there could be variations in eating patterns between rats in the P4 and P5 groups.[21] Dietary fiber can slow the absorption of glucose from the small intestine into the blood, thus keeping blood glucose levels more stable.[16] Some rats in the P4 group may have had a leaner diet compared to some of the rats in the P5 group, resulting in differences in the response to glucose absorption from the small intestine into the blood. This could cause the P4 group to consume less fiber so that it is less effective in slowing the absorption of glucose into the blood and resulting in higher glucose levels, while the P5 group could experience a greater diet and higher fiber content, which could experience a slowdown in glucose absorption so that their blood glucose levels are more stable. The ED_{50} value in this study was 1447,84 mg/kgBW, which means that to achieve a 50% reduction in blood sugar levels in male Wistar *Rattus norvegicus* rats, a dose of 1447,840 mg/kgBW was required.

In future research, further research needs to be carried out using other solvents, such as water, n-hexane solvent, and methanol solvent, so that we can compare the effects provided by ethanol solvent on *Moringa oleifera* leaf flour extract.

CONCLUSION

There were differences in the mean blood glucose levels of male Wistar *Rattus norvegicus* rats induced by alloxan before and after administration of *Moringa oleifera* leaf flour ethanol extract and differences in the mean decrease in blood glucose levels of male Wistar *Rattus norvegicus* rats induced by alloxan between each treatment group, and the ED_{50} value obtained for the ethanol extract of *Moringa leaf* flour was 1447,84 mg/kg BW.

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