Indonesian Journal of Medicine (2024), 09(03): 284-295
Masters Program in Public Health, Universitas Sebelas Maret

Research
Open Access

Effectiveness of Ethanol Extract and Ethyl Acetate Fraction of Breadfruit Leaves (*Artocarpus altilis*) as Antihyperglycemic

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Received: May 28, 2023; Accepted: February 19, 2024; Available online: April 10, 2024

ABSTRACT

Background: The rising diabetes mellitus (DM) population is a public health concern. Pharmacotherapy for DM can cause side effects and is often inaccessible, necessitating alternative therapies like medicinal plants. Breadfruit leaves (*Artocarpus altilis*) have antidiabetic effects. This study aimed to examine the antihyperglycemic effect of ethanol extract and ethyl acetate fraction of breadfruit leaves on alloxan-induced diabetic male white rats (*Rattus norvegicus*).
Subjects and Method: This was a randomized controlled trial. Sample was 35 male white Wistar rats (*Rattus norvegicus sp.)* divided into 7 groups. The study was conducted at the Phytochemical Laboratory and Animal House, Faculty of Medicine, Indonesian Methodist University, from April to May 2023. The dependent variables were body weight, blood glucose levels, and diameter of the islets of Langerhans. The independent variables were variations in the dose of ethanol extract and ethyl acetate fraction of breadfruit leaves. Body weight was measured by scales. Blood glucose was measured using glucometer. Diameter of the islets of Langerhans was measured using computer-based image analysis system. Data were analyzed using Anova and Kruskal-Wallis tests.
Results: Weight loss was better in the group given the ethyl acetate fraction at a dose of 200 mg/kgBW compared to the other groups. Administration of ethanol extract at a dose of 200 mg/kgBW showed a better reduction in blood glucose levels compared to the other groups, where $P < 0.05$ between K4 and K3, K5, and K7 on day 5. Ethanol extract at a dose of 200 mg/kgBW was able to improve the diameter of the islets of Langerhans induced by alloxan.
Conclusion: A 200 mg/kg BW dose of ethyl acetate fraction reduces body weight. A 200 mg/kg BW dose of ethanol extract reduces blood glucose and improves pancreatic islet diameter.

Keywords: Breadfruit leaves, body weight, blood glucose, islets of langerhans, diabetes mellitus

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Cite this as:
Daulay AH, Siahaan JM, Syahrir L, Tambunan RTH (2024). Effectiveness of Ethanol Extract and Ethyl Acetate Fraction of Breadfruit Leaves (*Artocarpus altilis*) as Antihyperglycemic. Indones J Med. 09(03): 284-295. https://doi.org/10.26911/theijmed.2024.09.03.01.

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BACKGROUND

Diabetes mellitus (DM) is a chronic condition characterized by increased blood glucose levels (KGD) due to the body not being able to produce one or enough insulin hormones, or not being able to use the insulin produced effectively. According to the International Diabetes Federation (IDF), in 2021, the number of DM sufferers aged 20-79 years in the world is estimated to be 537 million people, in 2030 it will be 643 million people and in 2045 it will be 783 million people (IDF, 2021). The continuous increase in the number of DM sufferers shows that DM is a health problem that requires special attention in public health services. DM can be treated with pharmacotherapy, but it can cause serious side effects such as hypoglycemia, hepatotoxicity, weight gain (BB), and lactic acidosis. Also, DM drugs are not affordable for the general public (Raydian et al., 2017; Sani K et al., 2017). The side effects that occur become a problem for patient compliance in taking medication, thereby increasing the risk of increasing DM mortality and morbidity (Bagonza et al., 2015). Consuming medicinal plants is another therapy for DM (Herman et al., 2019). One of the medicinal plants that has antihyperglycemic activity is breadfruit leaves (Artocarpus altilis) because they have rich phenolic content (Leng et al., 2018; Rante et al., 2019). Polyphenols from Artocarpus altilis can produce insulin-like biological activity, reduce the production of reactive oxygen species (ROS), and increase cellular antioxidant defense mechanisms. The antioxidant capacity of Artocarpus altilis leaf compounds can offer protection against damage due to oxidative stress in pancreatic cells (Iftikhar et al., 2020; Zhong and Jiang, 2019). One of the enzymes involved in glucose metabolism in the blood is α-glucosidase. Phenolic compounds in plants have been shown to inhibit α-glucosidase activity in the intestine by reducing glucose absorption, delaying carbohydrate digestion and increasing digestion time, thus having antihyperglycemic effects (Leng et al., 2018; Olubunmi and Godwin, 2019; Rante et al., 2019). Most of the phenolic chemicals found in nature are flavonoids (Anggraito et al., 2018). The mechanism of action of flavonoids as antihyperglycemics is by reducing glucose absorption from the small intestine, inhibiting tissue gluconeogenesis, increasing tissue glucose absorption, stimulating insulin secretion from beta cells, and protecting pancreatic beta cells against degeneration (Ghorbani, 2017). To separate the flavonoids contained in breadfruit leaves, this can be done using the extraction method. Based on phytochemical screening research on methanol and ethyl acetate extracts of breadfruit leaves, it was found that the flavonoid group of phenolic chemicals in particular is abundant in breadfruit leaves. Breadfruit leaves have also been proven to contain alkaloids, tannins and saponins in addition to flavonoid chemicals (Wardatun et al., 2016). Hyperglycemic conditions can be modeled in experimental animals using alloxan because it has a cytotoxic effect on cells by changing radical anions which damage the pancreas and ultimately reduce insulin levels (Husna et al., 2019). In this study, the author aims to test the antihyperglycemic effect of ethanol extract and ethyl acetate fraction of bread fruit leaves (Artocarpus altilis) on male white rats (Rattus norvegicus sp.) with diabetes mellitus induced by alloxan.

SUBJECTS AND METHOD

1. Study Design

This was is a randomized controlled trial conducted at the Phytochemical Laboratory and Animal House, Faculty of Medicine,

Indonesian Methodist University, from April to May 2023.

2. Population and Sample

The experimental animals used in this study were male white Wistar rats (*Rattus norvegicus sp.*). The selection of mice as experimental animals was based on the consideration that genetically, mice are similar to humans and have the ability to adapt to the laboratory environment. Sample allocation (grouping) used inclusion criteria (age 2.5-3 months, body weight 150-200 grams, male, and healthy) and exclusion (male white mice were unhealthy and died during the study period). The sample size was estimated using the Federer formula, each group used 5 male white rats with 7 treatment groups so that the total number of research samples was 35 rats. Breadfruit leaves were carried out using a purposive sampling method taken from the yards of Tanjung Mulia residents.

3. Study Variable

The dependent variables are BW, KGD, and diameter of the pancreatic islets of Langerhans. The independent variable is the dose of extract and fraction of breadfruit leaves

4. Operational Definition of Variables

a. Weight is a measurement that is generally used to assess nutritional status.
b. KGD during this time is the result of checking blood sugar samples randomly without fasting.
c. The diameter of the pancreatic islets of Langerhans is a histopathological examination by measuring the diameter of the pancreatic islets of Langerhans in mice in the control and treatment groups.
d. Breadfruit leaf ethanol extract is breadfruit leaves extracted using ethanol solvent.
e. Breadfruit leaf ethyl acetate extract is breadfruit leaves that are extracted using ethyl acetate solvent.

5. Study Instrument

BW measurements using scales, KGD measurements using strips and an "Autocheck" glucometer, and measuring the diameter of the pancreatic islets of Langerhans using a computer based image analysis system (Image Raster).

6. Data Analysis

Data obtained from observations were recorded and presented in the form of average and standard deviation (SD). The data were tested for normality and homogeneity. If the data is normally distributed and homogeneous then an ANOVA test is carried out, if the data is not normally distributed and homogeneous then a Kruskal-Wallis test is carried out. The test results are significant if the p value <0.05 then proceed with the Post Hoc test.

7. Research Ethics

A letter of approval for research ethics permission was obtained from the Research Ethics Commission of the Faculty of Medicine, Indonesian Methodist University, Medan, No. 09/KEPK-FKUMI/EC/2023.

RESULT

The results showed that the mice used had a body weight that met the inclusion criteria. The weight of mice after induction of diabetes and after administration of the extract every day for 14 days is shown in Table 1.

Table 1. BW (grams) of mice before and after administration of the extract

Group	Day-0		Day-5		Day-10		Day-15	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	166.62	10.97	183.52	10.77	197.92	8.08	210.97	12.60
G2	197.97	32.89	198.97	35.19	193.70	35.51	199.40	47.01
G3	142.45	3.39	161.90	39.29	156.30	40.17	169.57	32.64

Group	Day-0		Day-5		Day-10		Day-15	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G4	171.32	11.45	172.50	7.97	184.80	14.99	198.02	13.23
G5	164.60	36.03	157.12	45.14	152.02	48.56	162.77	41.49
G6	163.25	27.53	145.65	18.59	136.77	19.98	144.80	18.12
G7	172.95	24.26	155.25	47.12	159.82	42.37	171.30	45.20
p	0.129		0.319		0.115		0.104	

Note: *ANOVA Test

G1: normal, G2: negative control, induced by alloxan 170 mg/kgBW, G3: positive control, induced by alloxan 170 mg/kgBW + metformin 45 mg/kgBW, G4: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 200 mg/kgBW, G5: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 400 mg/kgBW, G6: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 200 mg/kgBW, G7: The treatment group was induced by 170 mg/kgBW alloxan with 400 mg/kgBW breadfruit leaf ethyl acetate fraction.

Based on the BW measurements in Table 1. The lowest BW after diabetes induction and day 0 before administering the extract was K3 as a positive control (Mean= 142.45; SD= 3.39), where mice were given a dose of 45 mg/kgBW metformin. Meanwhile, the highest BW (Mean= 197.97; SD= 32.89) was in K2 as a negative control which was only induced by alloxan at a dose of 170 mg/kgBW without treatment. There were no significant differences between groups assessed on day 0. On the 5th day of extract administration, the lowest BW was found in K6 who were given breadfruit leaf ethyl acetate fraction at a dose of 200 mg/kg BW (Mean=145.65; SD=18.59).

Meanwhile, the highest BW of K2 as a negative control was only induced by alloxan at a dose of 170 mg/kgBW without treatment (Mean= 198.97 ; SD= 35.19). On day 5 there were no significant differences between groups. On the 10th day of administering the extract, the lowest BB remained at K6 (Mean= 136.77; SD= 19.98). Meanwhile, the highest was in K1 as the normal group which was not given any treatment (Mean= 197.92; SD= 8.08). There were no significant differences between groups on day 10. After administering the extract for 14 days, the lowest BB on the 15th day was still found at K6 (Mean= 144.80; SD= 18.12). Meanwhile, the highest BB is still found in K1 (Mean= 210.97; SD= 12.60). However, there were no significant differences between the groups on the 15th day.

Rat blood glucose levels were measured before alloxan induction to exclude rats that had abnormal baseline levels. The KGD of mice after induction of diabetes and after administration of the extract every day for 14 days is shown in Table 2.

Table 2. KGD (mg/dl) of mice before and after administration of the extract

Group	Day 0		Day 5		Day 10		Day 15	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	116.25	12.65	118.25	13.37	130.25	22.55	122.50	20.63
G2	503.00	18.67	326.75	130.97	337.50	173.71	397.25	175.39
G3	534.50	27.62	467.00	64.44	372.25	173.67	441.50	117.28
G4	497.00	70.52	244.25	147.72	328.00	153.85	330.50	173.93
G5	565.50	39.16	492.00	83.08	459.25	62.59	523.25	41.94
G6	505.50	126.16	391.25	129.89	423.75	120.22	498.75	58.72
G7	536.50	76.30	441.50	57.92	481.25	40.37	461.50	68.45
p	0.054**		0.008**		0.072**		0.046**	

Note: **Kruskal-Wallis Test

G1: normal, G2: negative control, induced by alloxan 170 mg/kgBW, G3: positive control, induced by alloxan 170 mg/kgBW + metformin 45 mg/kgBW, G4: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 200 mg/kgBW, G5: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 400 mg/kgBW, G6: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 200 mg/kgBW, G7: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 400 mg/kgBW.

The lowest KGD on day 0 was in K1 as a normal group that was not given any treatment (Mean= 116.25; SD= 12.65). The highest KGD was in K5 (Mean= 565.50; SD= 39.16), which would be given ethanol extract of breadfruit leaves at a dose of 400 mg/kgBW. On day 0, there were no significant differences between groups. The lowest KGD for mice on the 5th day of extract administration was still found in K1 (Mean= 118.25; SD= 13.37). Meanwhile, the highest KGD remains K5 (Mean= 492.00; SD= 83.08). P<0.05 indicates a difference between groups on the 5th day. On day 10 of administering extracts and fractions, the lowest KGD for mice remained in K1 (Mean =130.25; SD=22.25). Meanwhile, the highest was in K7 who were given the ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kgBW (Mean= 481.25; SD= 40.37). However, on day 10 there were no significant differences between the groups. After administering the extract for 14 days, the lowest KGD for mice on day 15 was still found in K1 (Mean= 122.50; SD= 20.63). Meanwhile, the highest KGD returned to K5 (Mean= 532.25; SD= 41.94). P < 0.05 on day 15, which means there is a significant difference between groups.

Statistical testing continued on days 5 and 15 to determine the differences between each treatment group, with the post hoc test used being the Mann Whitney test. The results showed that there was a significant difference in KGD on the 5th day of extract administration between K1 and K2, K3, K5, K6, and K7 (P <0.05), as well as between K4 and K3, K5, and K7 (P <0.05). On the 15th day there was also a significant difference between K1 and K2, K3, K4, K5, K6, and K7 (P <0.05), while there was no significant difference between the diabetes-induced groups. The results of the comparison between two groups using the Mann Whitney test are shown in Table 3.

Table 3. Post Hoc Results with Mann Whitney Test

Group	Day-5			Day-15		
	Mean	SD	p	Mean	SD	p
G1 vs G2	118.25 vs 326.75	13.37 vs 130.97	0.021	122.50 vs 397.25	20.63 vs 175.39	0.029
G1 vs G3	118.25 vs 467.00	13.37 vs 64.44	0.021	122.50 vs 441.50	20.63 vs 117.28	0.021
G1 vs G4	118.25 vs 244.25	13.37 vs 147.72	0.083	122.50 vs 330.50	20.63 vs 173.93	0.021
G1 vs G5	118.25 vs 492.00	13.37 vs 83.08	0.021	122.50 vs 523.25	20.63 vs 41.94	0.021
G1 vs G6	118.25 vs 391.25	13.37 vs 129.89	0.021	122.50 vs 498.75	20.63 vs 58.72	0.021
G1 vs G7	118.25 vs 441.50	13.37 vs 57.92	0.021	122.50 vs 461.50	20.63 vs 68.45	0.021
G2 vs G3	326.75 vs 467.00	130.97 vs 64.44	0.083	397.25 vs 441.50	175.39 vs 117.28	0.773
G2 vs G4	326.75 vs 244.25	130.97 vs 147.72	0.386	397.25 vs 330.50	175.39 vs 173.93	0.773
G2 vs G5	326.75 vs 492.00	130.97 vs 83.08	0.083	397.25 vs 523.25	175.39 vs 41.94	0.248
G2 vs G6	326.75 vs 391.25	130.97 vs 129.89	0.248	397.25 vs 498.75	175.39 vs 58.72	0.564

Group	Day-5			Day-15		
	Mean	SD	p	Mean	SD	p
G2 vs G7	326.75 vs 441.50	130.97 vs 57.92	0.083	397.25 vs 461.50	175.39 vs 68.45	0.773
G3 vs G4	467.00 vs 244.25	64.44 vs 147.72	0.043	441.50 vs 330.50	117.28 vs 173.93	0.386
G3 vs G5	467.00 vs 492.00	64.44 vs 83.08	0.885	441.50 vs 523.25	117.28 vs 41.94	0.309
G3 vs G6	467.00 vs 391.25	64.44 vs 129.89	0.386	441.50 vs 498.75	117.28 vs 58.72	0.468
G3 vs G7	467.00 vs 441.50	64.44 vs 57.92	0.564	441.50 vs 461.50	117.28 vs 68.45	0.885
G4 vs G5	244.25 vs 492.00	147.72 vs 83.08	0.043	330.50 vs 523.25	173.93 vs 41.94	0.149
G4 vs G6	244.25 vs 391.25	147.72 vs 129.89	0.149	330.50 vs 498.75	173.93 vs 58.72	0.248
G4 vs G7	244.25 vs 441.50	147.72 vs 57.92	0.043	330.50 vs 461.50	173.93 vs 68.45	0.248
G5 vs G6	492.00 vs 391.25	83.08 vs 129.89	0.149	523.25 vs 498.75	41.94 vs 58.72	0.663
G5 vs G7	492.00 vs 441.50	83.08 vs 57.92	0.149	523.25 vs 461.50	41.94 vs 68.45	0.110
G6 vs G7	391.25 vs 441.50	129.89 vs 57.92	0.773	498.75 vs 461.50	58.72 vs 68.45	0.468

G1: normal, G2: negative control, induced by alloxan 170 mg/kgBW, G3: positive control, induced by alloxan 170 mg/kgBW + metformin 45 mg/kgBW, G4: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 200 mg/kgBW, G5: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 400 mg/kgBW, G6: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 200 mg/kgBW, G7: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 400 mg/kgBW.

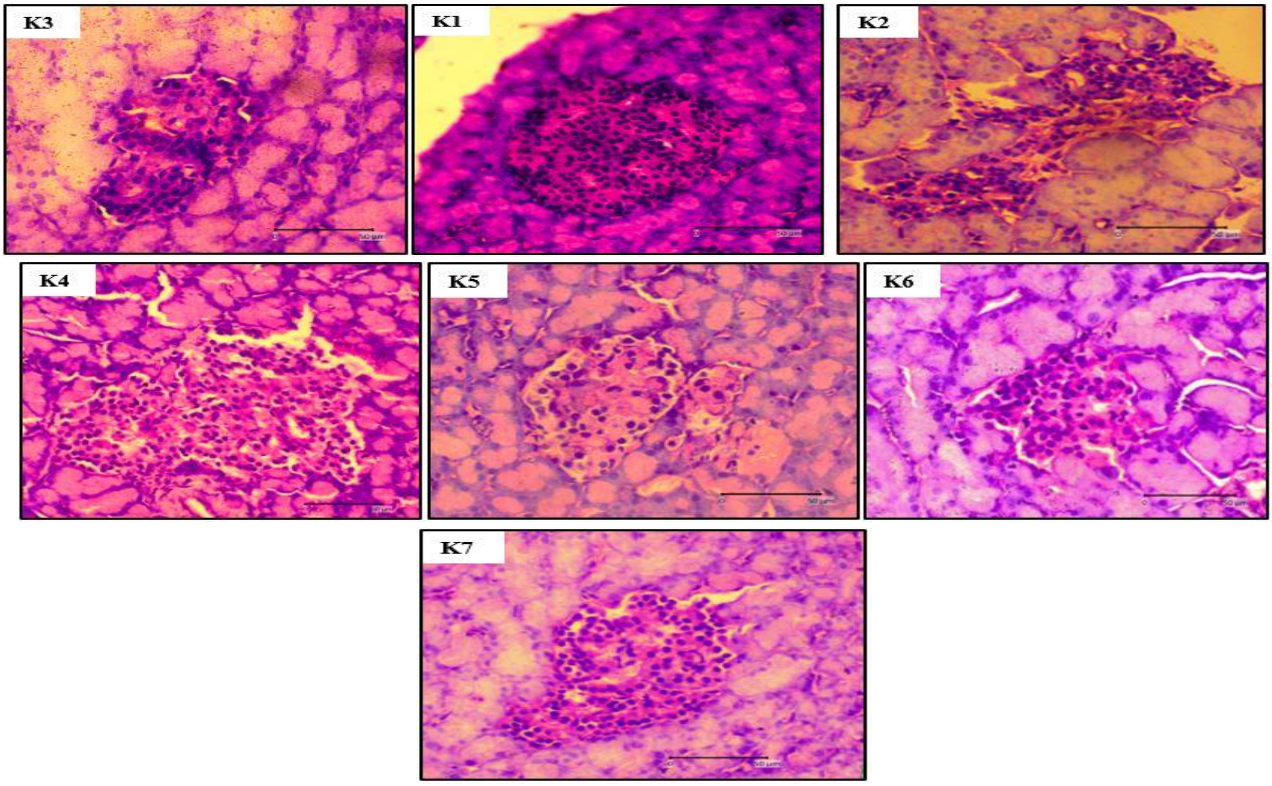

Figure 1. Histopathology of Islets of Langerhans Rat Pancreas (HE, 40× Objective Lens)

G1: normal, G2: negative control, induced by alloxan 170 mg/kgBW, G3: positive control, induced by alloxan 170 mg/kgBW + metformin 45 mg/kgBW, G4: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 200 mg/kgBW, G5: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 400

mg/kgBW, G6: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 200 mg/kgBW, G7: The treatment group was induced by 170 mg/kgBW alloxan with 400 mg/kgBW breadfruit leaf ethyl acetate fraction.

Measurement of the diameter of the rat pancreatic islets of Langerhans was carried out after administration of the extract for 14 days. This examination only used 1 rat from each group so statistical tests were not carried out. Histopathological observations of the islets of Langerhans in pancreatic tissue preparations with a magnification of 40× objective lens on a microscope are presented in Figure 1 and the results of measurements of the diameter of the islets of Langerhans seen under a microscope in 5 different fields of view are presented in Table 4.

Table 4. Diameter of Pancreatic Islands of Langerhans

Group	Diameter of Langerhans Island (µm)
G1	101.27
G2	77.30
G3	75.64
G4	96.74
G5	78.30
G6	80.15
G7	77.75

Note:
G1: normal, G2: negative control, induced by alloxan 170 mg/kgBW, G3: positive control, induced by alloxan 170 mg/kgBW + metformin 45 mg/kgBW, G4: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 200 mg/kgBW, G5: treatment group induced by alloxan 170 mg/kgBW with ethanol extract of breadfruit leaves 400 mg/kgBW, G6: treatment group induced by alloxan 170 mg/kgBW with ethyl acetate fraction of breadfruit leaves 200 mg/kgBW, G7: The treatment group was induced by 170 mg/kgBW alloxan with 400 mg/kgBW breadfruit leaf ethyl acetate fraction.

The highest diameter of the Langerhans islands was found in K1 as a normal group that was not given any treatment, namely 101.27 µm. Meanwhile, the lowest K3 as a positive control was given a dose of 45 mg/kgBW metformin, namely 75.64 µm. The highest diameter of the islets of Langerhans of all groups induced by diabetes was in group K4 which was treated with ethanol extract of breadfruit leaves at a dose of 200 mg/kgBW.

DISCUSSION

Weight loss was better in K6 who were given breadfruit leaf ethyl acetate fraction at a dose of 200 mg/kgBW on days 5, 10, and 15 compared to all treatment groups. It did not show statistically significant differences between groups but was clinically significant. This research is in line with Siahaan et al. (2020) that the ethyl acetate fraction used is able to reduce weight. This decrease in body weight shows that the pancreatic lipase enzyme, which has an important role in fat metabolism and absorption, can be inhibited by the ethyl acetate fraction. Thus, the mobilization of fat from peripheral adipose tissue to plasma is hampered, resulting in reduced adipose tissue mass in the body. In addition, the ethyl acetate fraction can increase the inhibition of α-amylase and α-glucosidase (Siahaan et al., 2020).

The α-glucosidase enzyme catabolizes complex carbohydrates that cannot be absorbed into monosaccharides that can be absorbed in the small intestine, thereby

affecting blood glucose levels and weight gain (Olaokun et al., 2016). Flavonoids can inhibit the activity of the α-glucosidase enzyme. The ethyl acetate fraction is better at extracting flavonoids than the ethanol extract, because the highest total flavonoid content is found in the ethyl acetate fraction compared to the ethanol extract (Anggraito et al., 2018; Siahaan et al., 2021). In K7 who were given the ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kgBW, there was a decrease in BW only on day 5, while on days 10 and 15 there was an increase in BW.

The results of research conducted by Olaokun, et al. (2016) that the ethyl acetate fraction used cannot reduce body weight. This occurs because the ethyl acetate fraction is unable to inhibit the activity of the pancreatic lipase enzyme, which is an important enzyme in fat absorption. However, in vitro, α-glucosidase can be inhibited by the ethyl acetate fraction (Olaokun et al., 2016). In K4 who were given ethanol extract of breadfruit leaves at a dose of 200 mg/kgBW, there was an increase in BW on days 5, 10, and 15 compared to the other groups. This increase in BW does not indicate clinical worsening because the lowest average BG on days 5, 10, and 15 was found in this group.

In line with research by Hardi, et al. (2022) that ethanol extract of breadfruit leaves can reduce KGD and prevent weight loss in alloxan-induced diabetic rats. This weight gain effect is caused by the presence of saponins. Saponins have insulin-like properties, by stimulating glucose absorption through increasing Glut 4 expression and contributing to glucose storage in the form of glycogen in adipocyte cells (Hardi et al., 2022; Okoduwa et al., 2017). Increased body weight in diabetic mice can occur as a result of increased structural proteins, insulin secretion in the blood, and other repair capabilities of ethanol extract (Rashid and Khan, 2021). K2 (negative control), K3 (positive control), and K5 (ethanol extract of breadfruit leaves at a dose of 400 mg/kgBW) also experienced an increase in body weight. This increase in body weight occurs due to inefficient insulin performance so that lipid, protein and carbohydrate metabolism is disrupted (Rashid and Khan, 2021). However, on the 10th day there was a decrease in body weight in the three groups. Diabetes mellitus patients often experience a sudden decrease in weight due to insulin deficiency. Therefore, the body must compensate for the lack of energy production from glucose by shifting ATP sources to non-carbohydrate molecules, such as fat and protein from muscle tissue which causes a decrease in body weight (Hardi et al., 2022; Solikhah and Solikhah, 2021).

Giving ethanol extract of breadfruit leaves at a dose of 200 mg/kgBW in K4 showed a better reduction in KGD compared to other groups. Statistical results showed significant differences between groups on days 5 and 15. Post hoc results with the Mann Whitney test on day 5 between K4 and K3, K5, and K7 showed significant differences, therefore, the dose of breadfruit leaf ethanol extract 200 mg/kgBW was better in reducing KGD compared to metformin, ethanol extract of breadfruit leaves at a dose of 400 mg/kgBW, and ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kgBW, but on day 15 there was only a significant difference between the normal group and the induced diabetes. These results indicate that ethanol extract has a strong antihyperglycemic effect due to the presence of polyphenols which can increase insulin secretion and intestinal glucose absorption. In line with research by Tandi, et al. (2017), ethanol extract of breadfruit leaves contains secondary metabolite compounds in the form of alkaloids, flavonoids,

saponins, tannins and polyphenols which have an effect in reducing KGD, and the most effective dose of ethanol extract of breadfruit leaves for reducing KGD is 200 mg/kgBB (Tandi et al. al., 2017).

The other extract group and the positive control (K3) given metformin also experienced a decrease in KGD, but the decrease was not better than K4. On the 15th day of KGD examination after 14 days of therapy in mice with DM, there was an increase in KGD in each group, except for K7 which was given ethyl acetate fraction of breadfruit leaves at a dose of 400 mg/kgBW, there was a decrease in KGD. The increase in KGD in Q4 was not too far from the KGD on day 10 and remained the lowest compared to other groups. Meanwhile, on the 10th day, both the control and extract groups experienced a decrease in KGD and some also experienced an increase in KGD, and the statistical results on this day did not show any significant differences between the groups.

The group experienced a decrease in KGD due to the presence of flavonoids which work to reduce glucose absorption from the small intestine, inhibit tissue gluconeogenesis, increase tissue glucose absorption, stimulate insulin secretion from beta cells, and protect pancreatic beta cells against degeneration (Ghorbani, 2017). An increase in KGD can occur due to uninhibited activity of the α-glucosidase enzyme. The α-glucosidase enzyme catabolizes complex carbohydrates that cannot be absorbed into monosaccharides that can be absorbed in the small intestine and enter the blood circulation so that blood glucose will increase in the body (Margono and Sumiati, 2019; Olaokun et al., 2016). . The increase in KGD also occurs due to the toxic effect of alloxan by producing ROS such as hydroxyl radicals through redox reactions. Hydroxyl radicals play a role in pancreatic β-cell necrosis. Pancreatic β cells play an important role in balancing glucose homeostasis through regulating insulin secretion in response to changes in blood glucose concentration. Thus, damage to pancreatic β cells causes a decrease in insulin production (Ighodaro et al., 2017; Zhang et al., 2019).

The islets of Langerhans in the DM group have the smallest diameter, this is because this group has higher levels of oxidative stress and pathological effects that can affect cell function by reducing insulin secretion or causing more dysfunction and cell death thereby reducing overall pancreatic insulin secretion (Newsholme et al., 2019). In the group treated with breadfruit leaf extract and fractions as well as metformin which showed better improvement in the diameter of the islets of Langerhans was K4 who was given a dose of ethanol extract of breadfruit leaves at a dose of 200 mg/kgBW. The ethanol extract of breadfruit leaves contains bioactive compounds that act as antioxidants, namely flavonoids, so that it can reduce oxidants in the pancreatic β cells of rats suffering from DM, and is able to regenerate damaged pancreatic β cells while repairing the islets of Langerhans (Tandi et al., 2017; Wang and Wang, 2017).

The flavonoid compounds contained in breadfruit leaves play a role in improving the diameter of the islets of Langerhans by stimulating an increase in antioxidants in pancreatic β cells. The antioxidant activity of flavonoids occurs directly based on the elimination of free radicals by releasing hydrogen atoms from the flavonoid hydroxyl groups (Anggraito et al., 2018). The diameter of the islets of Langerhans in the normal group (K1) and K4 was almost the same and wider than the negative control group. There was an increase in the diameter of the islets of Langerhans in the group treated with ethanol extract at a dose of 200 mg/kgBW.

The results of this research are in line with Djabir, et al. (2021) that through its antioxidant capacity breadfruit leaf extract protects pancreatic islets against alloxan-induced damage, leading to regeneration or recovery of partially damaged pancreatic cells thereby increasing insulin production, and thus, resulting in better glycemic control in diabetic mice. Therefore, the antidiabetic effect of breadfruit leaf extract occurs simultaneously with the improvement of the histological structure of the islets of Langerhans (Djabir et al., 2021). Other research conducted by Sari, et al. (2019) concluded that ethanol extract of breadfruit leaves can overcome damage to the pancreatic islets of Langerhans, even better than metformin (Sari et al., 2020).

It can be concluded that the ethyl acetate fraction of breadfruit leaves at a dose of 200 mg/kgBW is better for reducing body weight. The ethanol extract of breadfruit leaves at a dose of 200 mg/kgBW is better at reducing KGD and is able to improve the diameter of the islets of Langerhans in the pancreas of alloxan-induced diabetic rats.

AUTHORS CONTRIBUTION

Agus: Main researcher as head researcher who conducted research, collected and processed data, and wrote the manuscript. Jekson: Providing research ideas, guiding research, writing manuscripts, and reviewing. Lesmana: Guiding research and reviewing. Ronald: As a reviewer

FUNDING AND SPONSORSHIP

This study is self-funded.

ACKNOWLEDGMENT

There is no acknowledgement.

CONFLICT OF INTEREST

There is no conflict of interests in this study.

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