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HISTOPATHOLOGICAL PICTURE OF THE PANCREAS OF MICE (MUS MUSCULUS) DIABETES INDUCED BY STREPTOZOTOCIN-SUKROSA BY GIVING PEPAYA SEED EXTRACT (CARICA PAPAYA L.)

Fransiska Sitompul[1], Chatrine Angelica Dwi Christy[2], Yulvian Sani[3], Abraham Simatupang[4]
Universitas Kristen Indonesia
fransiska.sitompul@uki.ac.id

ABSTRAK

This study aimed to investigate the potential of papaya seed extract as an antihyperglycemic agent and to determine the histopathological features of the pancreas of female mice induced by streptozotocin-sucrose. The study used female DDY mice and divided them into five groups, including a negative control group, a positive control group, and three test groups given different doses of papaya seed methanol extract. The parameters measured were the decrease in fasting blood glucose levels, the number, diameter, and area of the islets of Langerhans in each group. The data was analyzed using the one-way ANOVA method with a confidence level of 95% followed by a comparison test using the Least Significant Difference method. The results showed that the methanol extract of papaya seeds has the potential to reduce blood glucose levels and improve the histological structure of the pancreas of diabetic mice induced by streptozotocin-sucrose at an optimum dose of 100 mg/kgBW. There was a significant difference in reducing blood glucose levels between the negative control group and the test group given 100 mg/kgBW papaya seed methanol extract after seven days of treatment. After fourteen days, there was a significant difference between the negative control group and test groups I, II, and III. Although no significant differences were found in the number, diameter, and area of the islets of Langerhans through morphometric photo testing, microscopic photo testing showed that test group I had the best histopathological picture with no vacuolization and necrosis found.

Keywords: *papaya seed, diabetes mellitus, pancreatic histology, streptozotocin-sucrose*

INTRODUCTION

Diabetes mellitus is defined as a multiethnic metabolic disorder characterized by high blood glucose levels or hyperglycemia due to impaired insulin secretion, insulin action, or a combination of both. Chronic hyperglycemia results in microvascular complications including retinopathy, nephropathy, and neuropathy as well as macrovascular complications such as cardiovascular disease (Goldney et al., 2023; Lu et al., 2023; Zakir et al., 2023).

Since the early 1980s diabetes has been considered the biggest problem in Indonesia.2 According to the International Diabetes Federation (IDF) in 2020, the prevalence of diabetes in adults reached 6.2% with a total of 10,681,400 adult cases. Diabetes is a degenerative disease that occurs due to various risk factors both irreversible (genetic factors, ethnicity, race, and age) and changeable (sedentary lifestyle factors, physical activity, and fast-food habits) (Jin et al., 2023; Kokkinos et al., 2023).

Diabetes is related to the pancreas, which has an endocrine function (Ilkhomovich, 2023). The hormone insulin is produced by pancreatic beta cells to regulate blood glucose levels. Hyperglycemia in individuals with diabetes mellitus occurs due to insulin resistance conditions that result in the pancreas being unable to produce insulin or only producing small amounts. Chronic hyperglycemia causes an increase in oxidative stress (ROS) and glucose toxicity resulting in a decrease in antioxidants in the pancreas resulting in damage and decreased pancreatic beta cell function (Dludla et al., 2023).

Efforts to prevent diabetes complications include the administration of drugs. The development of synthetic drugs continues but there are still side effects when used long term. Therefore, traditional medicine is one of the alternatives that diabetes patients are interested in. The World Health Organization (WHO) has recorded 21,000 plants as traditional medicines, and 400 plants are the choice of diabetes treatment (Dludla et al., 2023; Roy et al., 2023).

Chronic hyperglycemia with oxidative stress impairs endogenous antioxidant defenses (Rais et al., 2024), pancreatic beta cell damage, excessive lipid peroxidation, and cellular organelle damage. This suggests that antioxidant administration is one of the effective managements for diabetes. One of the medicinal plants that exhibit antidiabetic mechanisms is papaya seed (Carica papaya L.). Phytochemical analysis shows the chemical content of papaya seeds consists of antioxidant compounds such as saponins, alkaloids, flavonoids, phenols, terpenoids, and steroids (Yusuf, 2023). Therefore, the antioxidant content of papaya seeds can be utilized as an option to reduce damage to pancreatic beta cells from chronic hyperglycemia conditions.

Research in 2019 showed a decrease in glucose levels in male white rats (Rattus novergicus) diabetic Wistar strain induced by alloxan after giving papaya seed extract doses of 75 mg/kgBB, 150 mg/kgBB, and 300 mg/kgBB but there has been no further analysis of the histopathological picture of organs after treatment.8 Based on the description above, the author wants to know the histopathological picture of the pancreas organs of diabetic mice (Mus musuculus) that have been induced by streptozotocin-sucrose and have been treated with papaya seed extract (Carica papaya L.).

The general objective of this study was to determine the histopathological picture of the pancreas of diabetic mice (Mus musculus) after administration of papaya seed extract (Carica papaya L.). The specific objectives of the study were: 1) Knowing the optimum dose or level in repairing damage to pancreatic cells of mice (Mus musculus) diabetes mellitus. 2) Knowing the parameters measured, namely the number, area, and diameter of Langerhans islands of mice (Mus musculus) in each positive control group (with conventional drugs), treatment group (test), and negative control group (without drugs).

METHODS

The scope of the study is experimental with related disciplines are phytochemistry and pharmacology. This study aims to assess blood sugar and see the histopathological picture of the pancreas of mice in 5 groups, namely the positive control group (acarbose), negative control (no drug), and 3 treatments (papaya seed extract with several levels/concentrations). The research design used pre and post-test control group design and true experimental laboratories (Mihret et al., 2023). The research was conducted in 2 places, namely the research laboratory of the Faculty of Medicine, Christian University of Indonesia (FK UKI) and the diagnostic laboratory of the Bogor Veterinary Research Center (BB Litvet) in April 2021 - May 2022. The samples used were female mice (Mus musculus) DDY strain weighing 20-30 grams obtained from BB Litvet Bogor and Papaya Seed Plants obtained from the Traditional Market of Cikupa Village, Tangerang Regency.

The sample size of each treatment group was determined using the Federer formula as follows:

$$(n-1)\,(t-1) \geq 15$$

Description:
n = Number of samples per group
t = Number of treatment groups

From Federer's formula, the number of samples for each treatment group can be calculated, namely:

$(n-1)(5-1) \geq 15$
$(n-1)(4) \geq 15$
$4n - 4 \geq 15$
$4n \geq 19$
$n \geq 4{,}75$ and rounded up to $n \geq 5$

Based on the calculation of the sample population using the Federer formula, each treatment group has a minimum sample of 5 mice.

To anticipate the presence of experimental animals that die prematurely (drop out), the calculation of spare mice is carried out with the sample size correction formula as follows:

$$n' = [n / 1 - f]$$

Description:
n' = number of research samples
n = calculated sample size
f = estimated proportion of drop outs (20% or 0.2)

Based on the sample size correction formula, the number of samples in this study were n' = 5 / (1-0,2) = 6,25 ≈ 6.

RESULTS AND DISCUSSION

Observation of Papaya Seed Methanol Extract Content

The phytochemical content in EMBP based on the test results are flavonoids, tannins, and steroids (Appendix 2). Flavonoids are polyphenols that have functions as antiviral, antiallergic, antibacterial, and anti-inflammatory (Mihret et al., 2023). Based on research, flavonoids which are biologically active secondary metabolites can have a positive effect on metabolic disorders including diabetes. Apart from being antioxidants, flavonoids' antidiabetic activity supports the regulation of carbohydrate digestion, insulin signaling, insulin secretion, glucose uptake, and adipose deposition (Mihret et al., 2023).

Flavonoids have potential as hypoglycemic agents with a mechanism similar to the drug acarbose by inhibiting α-amylase and α-glucosidase which function to reduce glucose absorption in the small intestine, inhibit glucose release from the liver, stimulate pancreatic insulin secretion, and increase glucose uptake by muscle cells and adipose cells (Mihret et al., 2023).

Tannins are widely distributed in the polyphenol group in the kingdom plantae that exhibit pharmacological effects such as antidiabetic (Zeng et al., 2023). The decrease in blood glucose levels is caused by phenolic compounds by mechanisms such as decreased nutrient absorption by inhibiting intestinal glucose absorption, reduced food intake, and inducing cell regeneration and direct action on adipose cells that increase insulin activity (Kumar et al., 2023).

The mechanism of steroids as antihyperglycemic has not yet been elucidated, but the combination of omega-3 fatty acids and sterol dietary supplements was found to significantly reduce fasting blood glucose and insulin resistance in people with impaired glucose regulation or pre-diabetes. The results also showed that plant sterols are efficacious in lowering LDL cholesterol and non-HDL cholesterol that can be elevated by high glucose levels in both diabetics and nondiabetics (Clifton, 2023).

Blood Glucose Observation of Mice

The tested mice were grouped into 5 groups and given treatment intraperitoneally, namely the negative control group given CMC-Na, the positive control group given acarbose drug, and

the test group received papaya seed methanol extract with 3 dose levels, namely 100 mg/kgBB, 200 mg/kgBB, and 400 mg/kgBB.

Fasting blood glucose results of mice before induction showed an average value of 64.3 mg/dL (Table 4.1).

Table 1. Mean blood glucose levels of mice before STZ-sucrose induction

Group	Treatment	Blood glucose level (mg/dL) ± SD
Negative control	CMC-Na 1%	70,4 ± 10,69
Positive control	Acarbose 25 mg/kgBB	52 ± 8,22
Treatment I	EMBP 100 mg/kgBB	52,7 ± 6,82
Treatment II	EMBP 200 mg/kgBB	66,8 ± 8,93
Treatment III	EMBP 400 mg/kgBB	79,83 ± 11,28

Data on the initial blood glucose levels of mice obtained the significance value of the homogeneity test is 0.764 with a value> 0.05 indicating the distribution of data is homogeneous. From these results, it is found that mice in the negative control group, positive control, and treatment group are suitable for use as test animals because they have physiological conditions, namely normal blood sugar levels.

Based on table 4.2, it was found that the average blood glucose level of mice increased after STZ-sucrose induction. Based on these two data, a homogeneity test was conducted and obtained p = 0.389 at 7 days after induction (day 17) and p = 0.064 at 14 days after induction (day 24). Both results showed homogeneous results with > 0.05 so there was no significant difference between the negative group, positive group, and the three treatment groups.

Table 2. Average blood glucose levels of mice after STZ-sucrose induction

Group	Treatment	Blood glucose levels (mg/dL) ± SD	
		7 days	14 days
Control negative	CMC-Na 1%	137,6 ± 19,14	103,8 ± 9,63
Kontrol positive	Acarbose 25 mg/kgBB	149,6 ± 18,12	122,4 ± 6,10
Treatment I	EMBP 100 mg/kgBB	126,7 ± 23,94	180,2 ± 12,08
Treatment II	EMBP 200 mg/kgBB	111,7 ± 16,31	142,2 ± 17,09
Treatment III	EMBP 400 mg/kgBB	209 ± 14,80	134,5 ± 11,06

When measuring blood glucose levels, it was found that there was a group of mice that had blood glucose levels < 150 mg/dL even though all groups showed hyperurination on the 4th day after STZ induction. There was a decrease in blood glucose levels on the 14th day after induction of diabetic agents in the negative control, positive control and EMBP 400 mg/kgBW treatment groups. The decrease in blood glucose levels occurred due to stopping STZ induction, which is one of the agents that trigger diabetes, on day 11 and only continuing with the administration of 30% sucrose for the next 7 days.

The effectiveness of STZ in increasing blood glucose levels in mice is influenced by various factors such as administration technique, dose, frequency and type of experimental animal. STZ is administered using the i.p. injection method. considered less effective when compared with the i.v. method. Induction with multiple small doses is considered better in maintaining blood glucose levels, but does not completely damage pancreatic β cells so that mice's blood glucose levels can return to normal after STZ induction is stopped. Fasting for too long before the injection will also affect the success of developing diabetes in mice (Khalaf et al., 2023).

After finding an increase in blood glucose levels accompanied by the characteristics of hyperglycemia, namely polyuria and polydipsia, treatment was carried out on the five groups of mice on days 26 to 40 (for 14 days). The entire group fasted for 8 hours before checking blood glucose levels on the 33rd and 40th days.

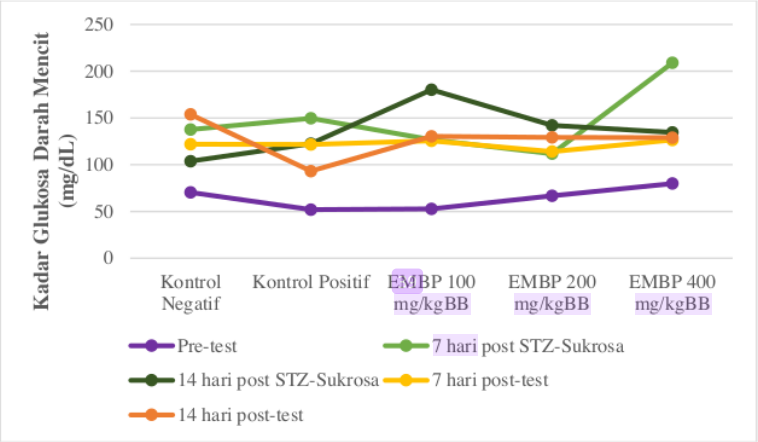


Figure 1. Graph of the results of measuring blood glucose levels in mice pre-test, post-STZ-sucrose induction, and post-test.

Table 3. Percentage reduction in average glucose levels after treatment

Group	Treatment	Percentage reduction (%) ± SD	
		7 days	14 days
Control negative	CMC-Na 1%	-21,8 ± 12	-53,7 ± 16[B]
Control positive	Acarbose 25 mg/kgBB	0,1 ± 7	23 ± 6[A]
Treatment I	EMBP 100 mg/kgBB	27,4 ± 10 [A]	25,6 ± 7[A]
Treatment II	EMBP 200 mg/kgBB	12,6 ± 131	0,5 ± 16 [A]
Treatment III	EMBP 400 mg/kgBB	2,7 ± 9	0,9 ± 9 [A]

Notes:
A = There is a significant difference with the negative control group.
B = There is a significant difference with the positive control group.

The percentage reduction in blood glucose levels in each test group by reducing blood glucose levels after STZ-sucrose induction or day 24 blood glucose levels with blood glucose levels on day 33 and day 40. The data were then statistically analyzed using ANOVA followed

by Least Significant Different (LSD) examination to see any significant differences between the three test groups with negative control and positive control groups.

Based on table 4.3, it was found that there was a decrease in blood glucose levels in mice in the positive control group with a dose of acarbose 25 mg/kgBB and the three test groups with EMBP administration with doses of 100 mg/kgBB, 200 mg/kgBB, and 400 mg/kgBB. The negative control group was only given 1% CMC-Na suspension and found an increase in blood glucose levels that occurred due to long-term effects due to the administration of STZ which is a cytotoxic glucose analog that is toxic to pancreatic cells.

Based on statistical analysis using the LSD method, it was found that there was a significant difference in the results of the decrease in blood glucose levels of mice in the EMBP treatment group at a dose of 100 mg/kgBB on day 33 characterized by a significant value <0.05, when compared to the negative control group. Based on table 4.3, it was found that the administration of EMBP on day 33 showed a higher decrease in blood glucose levels, especially at a dose of 100 mg/kgBB compared to the positive control group using the drug acarbose.

On day 40, there was an increase in blood glucose levels in mice in the negative control group and the test group given three doses of EMBP. The results obtained were different in the positive control showing an increase in the percentage of blood glucose level reduction. Based on statistical analysis, there was a significant difference in the results of reducing blood glucose levels of mice with the administration of acarbose 25 mg/kgBB and the administration of the three doses of EMBP, when compared to the negative control, the significant value was <0.05. Based on LSD analysis, there was no significant difference in the group of animals treated with EMBP 100 mg/kgBB, 200 mg/kgBB, and 400 mg/kgBB when compared to the positive control group that received acarbose 25 mg/kgBB. This indicates similar effectiveness between the three doses of EMBP and acarbose 25 mg/kgBB in reducing blood glucose levels of mice induced by diabetic agents (STZ-sucrose).

Observation of Hyperglycemia Characteristics of Mice

1. Post STZ-Sucrose Induction

Characteristics that are symptoms of hyperglycemia are polyuria, polydipsi, polyphagia, and weight loss. In this study, the characteristics observed were polyuria accompanied by polydipsi which was seen from the wetness of the chaff or mice cage mat. On the 12th day after streptozotocin-sucrose induction for 4 days, the mice experienced urination characterized by wet chaff.

(a) (b)

Figure 2. Hyperurination condition of mice treated with (a) 25% wet chaff, (b) 75% wet chaff.

Polyuria can occur due to increased blood glucose levels (hyperglycemia) induced by diabetic agents such as streptozotocin. Periodic administration of small doses of STZ to mice

can cause progressive hyperglycemia due to a combination of toxic and immunological responses because it can induce gradual destruction of pancreatic cells accompanied by autoimmunity. In addition, sucrose administration also contributes to increasing the blood glucose levels of mice for several minutes after consumption. High blood glucose levels trigger the kidneys to increase urine production to eliminate excess glucose in the body.

When the body loses a lot of fluid, compensation occurs in the form of thirst, increasing the intensity of mice to drink (polydipsi). Polyphagy also occurs when the body is unable to convert glucose into energy so that the body feels hungry. Polyphagi and polydipsi can be assessed by increasing the duration of mice consuming food and drink.

2. Post Treatment Administration

Based on the results of observations after the administration of papaya seed extract, a decrease in the incidence of hyperurination in mice was obtained. The administration of papaya seed extract at a dose of 200 mg/kgBB and 400 mg / kgBB showed a decrease in the incidence of urination after day 29 and did not experience urination after day 30 which was characterized by dry husk conditions. These results showed the same results as the positive control group with acarbose drug administration which showed no urination on the 30th day after treatment. The administration of papaya seed extract in group I at a dose of 100 mg/kgBB showed a slower decrease in the incidence of urination. In this group, mice were declared not hyperurinated on day 33 (treatment for 7 days).

The decrease in the incidence of hyperurination occurred due to a decrease in blood glucose levels after EMBP treatment. Flavonoids and tannins contained in papaya seed methanol extract belong to the class of polyphenols which are strong antioxidants. When blood glucose levels drop, the kidneys do not need to excrete glucose in the blood through urine so that the condition of polyuria can be managed**.**

Pancreas Observation of Mice after Death

On the 40th day, mice were terminated, followed by abdominal dissection to assess the state of the pancreas of mice macroscopically and microscopically.

1. Macroscopic

Macroscopic observations were made by looking and palpating the pancreatic organs of mice to assess the color, consistency, and size changes that occurred after treatment. Based on observations, the negative control group with CMC-Na administration, the test group with EMBP 200 mg/kgBB and 400 mg/kgBB treatment, and most of the positive control group with acarbose administration did not show any specific abnormalities in the pancreatic organs of mice.

In the test group with the administration of EMBP 100 mg/kgBB showed abnormalities, namely the pancreas which was yellow in color with a soft consistency. Abnormalities in the pancreas of mice were also found in one of the mice in the positive control group which showed an enlargement of the size of the pancreas and a change in the color of the pancreas to yellow.

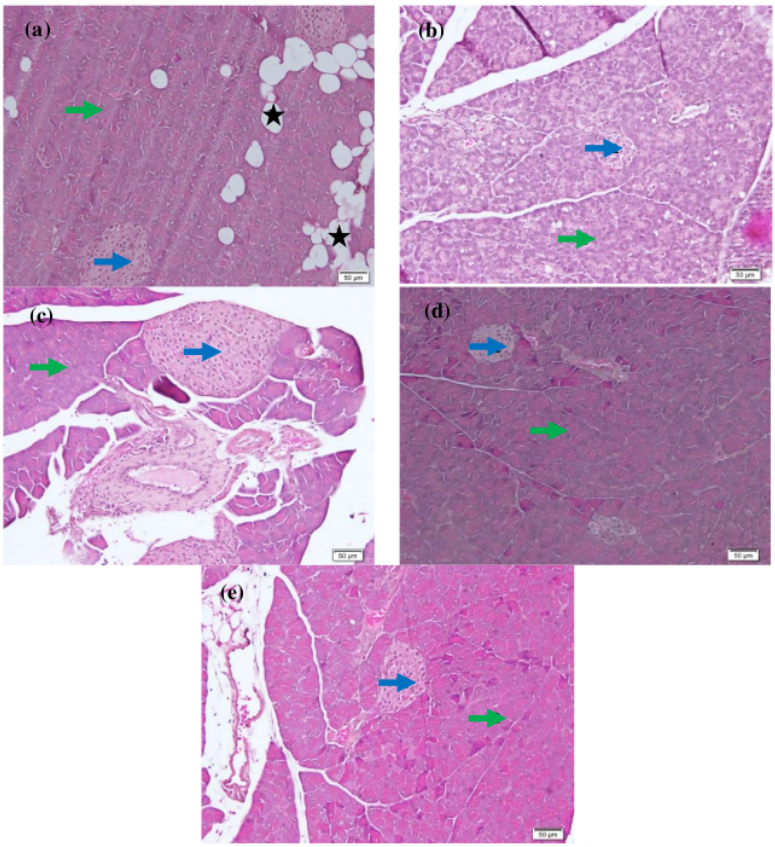
The pancreas of mice is normally light brown or pink in color and is dendritically distributed in the mesentery of the proximal small intestine. The normal consistency of the pancreas is spongy and can become harder or softer due to disease, certain medications, consumption of certain foods or beverages, etc. The pancreas can also become harder or softer due to the consumption of certain foods or beverages.

2. **Microscopic**

a. Microscopic Photo Test

Microscopic examination aims to compare the histopathological picture of the pancreas of mice in the negative control group with CMC-Na administration, the positive

control group with acarbose drug administration, and the three test groups with the administration of EMBP doses of 100 mg / kgBB, 200 mg / kgBB, and 400 mg / kgBB.



Description: → : Langerhans island, → : Acinar, ★ : Vacuolization.

Figure 3. Microscopic Photograph of Mouse Pancreas (H&E, 200X). (a) Negative control, (b) Positive control, (c) EMBP 100 mg/kgBB, (d) EMBP 200 mg/kgBB, (e) EMBP 400 mg/kgBB.

Based on the examination, the negative control group showed cell dominance in four of the five samples. Cell dominance was also found in the EMBP 400 mg/kgBB test group. Normally, cells will dominate the islets of Langerhans up to 65-80%. In conditions of diabetes or hyperglycemia, pancreatic cells will work harder to produce enough insulin to lower blood glucose levels. Cell loss occurs due to excessive cell work in regulating blood glucose which then results in cell destruction without recovery.

Most of the positive control group showed a predominance of cells. This was also found in the microscopic photo results of the EMBP 100 mg/kgBB test group which showed five of the six samples were dominated by cells. In the EMBP 200 mg/kgBB test group, it was found that three of the six samples were dominated by cells. The dominance of cells indicates that the pancreas of mice can still produce insulin that functions to regulate blood glucose levels. This is indicated by a decrease in blood glucose levels in the positive control group and the test group with EMBP administration.

Table 4. Pathological Changes of Mouse Pancreas

Mouse Group	Pathological Changes		
	Vacuolizes	Necrosis	Follicle Lymphoid
Control Negative	3	1	1
Control Positive	-	1	1
EMBP 100 mg/kgBB	-	-	1
EMBP 200 mg/kgBB	1	1	-
EMBP 400 mg/kgBB	2	2	-

Based on the diagnosis results obtained from the analysis of microscopic photographs (Appendix 13), there was pancreatic damage in the negative control which was marked by vacuolization in three of the five samples. Vacuolization also occurred in one sample of the test group with EMBP 200 mg/kgBB and two samples in the test group with EMBP 400 mg/kgBB. Necrosis was also found in all treatments except in the test group with the administration of EMBP dose of 100 mg/kgBB.

STZ induction causes damage to pancreatic cells which triggers hypoinsulinemia and hyperglycemia. Hyperglycemia triggers an increase in ROS production which results in cell death mechanisms through apoptosis, cell necrosis, and vacuolar degeneration resulting in vacuolization (González et al., 2023); (Wu et al., 2023). Vacuolization and necrosis conditions do not occur in the treatment with EMBP dose of 100 mg/kgBB due to the presence of antioxidant content that has the potential to reduce free radical levels.

b. Morphometric Photo Test

The photo morphometric test aims to assess the average number of islets of Langerhans in five randomly selected lobes, the diameter of the islets of Langerhans, and the area of the islets of Langerhans.

Table 5. Mean number, diameter, and area of islets of Langerhans in mice

Mouse Group	**Morphometric Results of Langerhans Island**		
	Total	***Diameter (µm)***	***Wide (µm²)***
Control Negative	1,4 ≈ 1,0	93,0 ± 34,8	12079,7 ± 5522,2
Control Positive	0,9 ≈ 1,0	73,6 ± 23,0	6503,4 ± 2306,2
EMBP 100 mg/kgBB	1,3 ≈ 1,0	109,8 ± 18,0	13308,0 ± 3448,1
EMBP 200 mg/kgBB	2,0	88,2 ± 12,1	9043,0 ± 2217,3
EMBP 400 mg/kgBB	1,0	86,8 ± 30,1	11546,6 ± 5386,1

Based on the results of the study and data analysis using the LSD test, there were no significant differences in the number, diameter, and area of the islets of Langerhans in the five groups of mice characterized by a value > 0.05. These results indicate that the induction of STZ-sucrose diabetic agent does not result in a significant decrease in the number, diameter, and area of islets of Langerhans pancreas of mice. The administration of acarbose and the administration of papaya seed methanol extract also did not show a

significant effect on the number, diameter, and area of islets of Langerhans. The existence of insignificant differences can occur due to differences in the condition of the lobes examined randomly so that there are samples that do not have islets of Langerhans. In addition, improvement in the pancreas also occurred in the group of mice with acarbose and EMBP administration characterized by fibrosis and regeneration.

The highest number of islets of Langerhans was found in the test group with the administration of EMBP 200 mg/kgBB with the other four groups showing similar results. The largest diameter and area of Langerhans islets were found in the test group with EMBP administration of 100 mg/kgBB and the smallest in the positive control group with EMBP administration.

The diameter of the islets of Langerhans of normal mice ranges from 116 to 80 m and is twice as large as the diameter of the human islets of Langerhans (Sasmita et al., 2024); (Rustantina et al., n.d.). Based on morphometric tests, the average diameter of the islets of Langerhans in the test treatment with EMBP administration at a dose of 100 mg/kgBB showed results that were close to the normal diameter of the islets of Langerhans.

The three test groups with EMBP administration showed a higher diameter and area of Langerhans islets when compared to the positive control group. This can occur due to the content of active compounds that work as antioxidants. The ability of flavonoids and tannins as antioxidants in counteracting free radicals can help cell turnover and protect the islets of Langerhans from the cytotoxic effects of streptozotocin on pancreatic cells.

CONCLUSION

Based on the results of research on female mice of the DDY strain of streptozotocin-sucrose-induced diabetes model with five different treatments, namely the negative control group with the administration of 1% CMC-Na, the positive control group with the administration of acarbose drug, and the three test groups with the administration of papaya seed methanol extract at a dose of 100 mg / kgBB, 200 mg / kgBB, and 400 mg / kgBB, it can be concluded that:

1. There is a decrease in blood glucose levels so that the administration of methanol extract of papaya seeds (Carica papaya L.) can function as an antidiabetic with the optimum dose is 100 mg/kgBB.
2. There is a difference in the histopathological picture through photo microscopic and photo morphometric tests so that it can be concluded that the administration of papaya seed methanol extract can improve the structure of the pancreas of mice.

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