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# Effectiveness of Durian Seed Extract (*Durio zibethinus Murr*) on Blood Sugar Levels and Pancreatic Histopathology in Streptozotocin-Induced Wistar Rats

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**Abstract:** Diabetes mellitus is a global health problem with a growing prevalence. Blood glucose levels that remain high can cause damage to various body tissues. including the pancreas. Durian seeds contain bioactive compounds such as alkaloids. triterpenoids. phenolics. and flavonoids that can reduce blood sugar levels. This study is an experimental study with a posttest only controlled group design conducted at the Pharmacology Laboratory of the Faculty of Pharmacy. University of North Sumatra and the Anatomical Pathology Laboratory of the Royal Prima Medan Hospital for more than 3 months. From the results of this study. durian fruit seed extract (*Durio zibethinus Murr*) in the phytochemical compound test contained alkaloids. saponins. flavonoids. and glycosides. With doses of 150 mg. 300 mg. and 450 mg proven to reduce blood sugar levels (KGD) in streptozotocin-induced Wistar rats. The highest dose in reducing blood sugar levels (KGD) with a dose of 450 mg. The group with a dose of 300 mg showed the best results in increasing the diameter of the islets of Langerhans.

**Keywords:** Blood Sugar Level; *Durio zibethinus Murr*; Histopathology; Pancreas.

## Introduction

Diabetes mellitus is a global health problem with an increasing prevalence. According to the WHO 2020 global status report the global prevalence of diabetes mellitus reached 9%. Diabetes causes 4% of total deaths from non-communicable diseases, with 80% of those deaths occurring in low- and middle-income countries (WHO. 2020). WHO estimates that by 2030. diabetes mellitus will be the 7th leading cause of death in the world (Fatmawati et al., 2023; Sutriyawan et al., 2022). Based on the 10th edition of the IDF report. Indonesia is in 5th place with 19.47 million people with diabetes and a prevalence of 10.6%, most of which are type 2 diabetes (Magliano et al., 2021).

Diabetes mellitus is a metabolic disease characterized by elevated blood glucose levels. The disease consists of several types, namely type 1 diabetes mellitus type 2 diabetes mellitus and gestational diabetes mellitus. Type 2 diabetes mellitus is the most common type, characterized by elevated blood glucose levels due to insulin resistance (Arjita et al., 2023; Berbudi et al., 2019). This insulin resistance can be caused by pancreatic beta cell dysfunction. In addition. an unhealthy lifestyle, such as lack of physical activity, is also a major contributing factor to type 2 diabetes mellitus. Lack of physical activity can affect the number of insulin receptors, thereby reducing GLUT-4 (glucose transporter-4) activity. This decrease in GLUT-4 function contributes to an increased risk of type 2 diabetes mellitus (Chiuman et al., 2022; Galicia-garcia et al., 2020).

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This condition causes the body to be unable to convert glucose or carbohydrates into energy, as glucose cannot enter the cells for use. As a result, blood glucose levels remain high and cause damage to various body tissues, including blood vessels, eyes, kidneys, heart and nerves. An increase in blood glucose levels (hyperglycemia) occurs due to impaired insulin secretion, especially in pancreatic β-cells (Basit et al., 2018; Kaihena et al., 2024). A person with hyperglycemia who experiences insulin resistance, the GLUT-4 transport process from the cell to the plasma membrane is disrupted, thus inhibiting the process of glucose uptake by cells (Trisia & Augustina, 2022).

Damage to pancreatic β-cells, which results in decreased insulin function and secretion, and triggers histopathological changes in the pancreas (Mentari et al., 2023). Examination of tissues that show abnormalities is one of the important factors in establishing a disease diagnosis. Histopathology allows observation of changes in morphology, structure, and other signs of damage in organs or tissues, including those resulting from injury, infection, exposure to toxic chemicals. or mutagenic processes. The pancreas is an important glandular organ for the body, consisting of exocrine tissue and endocrine tissue. Pancreatic endocrine tissue. known as islets of Langerhans, is distributed throughout the organ. Histopathological changes in the islets of Langerhans can be qualitative. such as necrosis, or quantitative, such as a decrease in cell number or size, as well as atrophy characterized by cell shrinkage (Tandi et al., 2023).

Streptozotocin is a compound used to induce experimental diabetes mellitus due to its toxic properties to pancreatic β-cells. It has a high affinity for the GLUT-2 transporter, which is present on the plasma membrane of pancreatic β-cells, as well as in liver and kidney tissues, so these organs are also affected. Upon entry into β-cells via GLUT-2, streptozotocin causes oxidative stress and DNA damage, which triggers apoptosis or β-cell death. This damage results in pancreatic dysfunction characterized by tissue swelling. β-cell degeneration in the islets of Langerhans, and decreased insulin production. The accumulation of these effects ultimately plays a role in the development of hyperglycemia conditions typical of diabetes mellitus (Al-Awaida et al., 2020; Simarmata et al., 2021).

Diabates mellitus cannot be cured but can be managed to keep blood glucose levels stable. By doing nonpharmacological and pharmacological therapies. Nonpharmacological therapy includes dietary management. physical activity such as exercise, and the use of herbal ingredients as supportive treatment. Meanwhile. pharmacological therapy includes the administration of oral hypoglycemic drugs, antihyperglycemic agents, or insulin. Although effective, pharmacologic therapy often comes with side effects, such as swelling of the peripheral area, which can affect patient comfort (Dewi et al.. 2022).

Indonesia has abundant biodiversity, including various types of plants that have been widely utilized by the community. Besides having many benefits, herbs and spices are often used as traditional medicine because they tend to be safe and do not cause harmful side effects to the human body. It is recorded that Indonesia has around 30 thousand types of flora that grow in its territory. The utilization of plants as traditional medicine is a cultural heritage that has been carried out for generations by the people of Indonesia. Apart from being a medicinal material. these plants are also used as food. Cosmetics, beverages, and medicinal products (Hamzah et al., 2023).

One of the plants used as traditional medicine by Indonesians to help treat diabetes is durian. Durian (*Durio zibethinus Murr*), which is widely found in Indonesia. has a complete nutritional content, such as potassium. Magnesium, iron, phosphorus, omega 3 and 6. as well as vitamins B and C (Yayu et al., 2018; Ramdan et al., 2024). Durian also contains antioxidants that function to protect the body from free radicals, which can play a role in the development of diseases such as cancer, diabetes, and cataracts (Rohman et al., 2023). Durian seeds contain bioactive compounds such as alkaloids, triterpenoids, phenolics, and flavonoids. Flavonoids found in durian seeds have various benefits, including as antioxidants, antibacterial, antiviral, anti-inflammatory, antiallergic, and anticancer (Safitri, 2020). These compounds can also capture free radicals and act as natural antioxidants, and repair pancreatic tissue damage caused by DNA alkylation (Charoenphun & Klangbud, 2022). In addition, durian seeds can reduce blood sugar levels because flavonoids are proven to have antidiabetic activity, which can stimulate the regeneration of cells in the islets of Langerhans and increase insulin production, thus helping to reduce blood glucose levels (Amir et al., 2020; Muhtadi et al., 2016).

Research conducted by Amir et al, (2020) with the title Anti Diabetes Mellitus Activity of Durian Plants (*Durio zibethinus Murr*.) on Fasting Blood Glucose Levels of Alloxan-Induced Mice, showed that durian extract has a significant antidiabetic effect. In mice induced by alloxan, the administration of durian extract successfully reduced fasting blood glucose levels (Amir et al.. 2020). The purpose of this study was to determine the effectiveness of durian seed extract (*Durio zibethinus Murr*) on reducing blood sugar levels (Charoenphun & Klangbud, 2022). In addition, this researcher also wants to know the histopathological picture of the pancreas of Wistar rats induced by Streptozotocin.

## Method

This study is an experimental study with posttest only controlled group design on wistar rats (Pratama et al., 2023). The research was conducted at the Pharmacology Laboratory of the Faculty of Pharmacy. University of North Sumatra and the Anatomical Pathology Laboratory of Royal Prima Medan Hospital for more than 3 months from April to June 2024. The experimental animal research protocol was approved by the Prima Indonesia University Health Research Ethics Committee (097/KEPK/UNPRI/III/2024).

This study used 96% ethanol solution, durian seeds, filter paper, ketamine, Hematoxylin-Eosin (HE). metformin, and Streptozotocin (STZ). While the tools used rotary evaporator, scalpel, drip pipette, mask, gloves. This research was initiated by extracting durian seeds (*Durio zibethinus Murr*) using the maceration method using 96% ethanol (Agustina et al., 2020; Jusril et al., 2024). A total of 1.5 kg of durian seeds were washed and sliced thinly then dried in the oven at 40o for 1 week. The dried durian seeds were pulverized into powder, after which they were extracted using the maceration method accompanied by stirring until homogeneous. Maceration is continued by evaporation using a vacuum rotary evaporator to produce a solvent-free thick extract (Saraswati. 2019; Savitri et al., 2024). The thick extract of durian seeds was subjected to phytochemical screening to determine secondary metabolites by alkoloid test. terpenoid/steroid test, flavonoid test, tannin test, and saponin test (Aprinaldi, 2020; Fernanda et al., 2024).

Phytochemical screening tests were carried out by several methods to detect bioactive compounds in thick extracts of durian seeds. The alkaloid test was carried out by adding 1 mL of HCl and 3 mL of distilled water to the extract, then the solution was heated on a water bath for two minutes, cooled, and filtered. After that, 2 drops of Dragendorff reagent were added, where the color change to orange indicates the presence of alkaloid compounds. The saponin test is done by mixing 1 mL of extract with 10 mL of distilled water in a test tube, then shaken. If the foam formed lasts for one minute. the results are positive for saponins. Tannin test is done by adding 2 drops of 5% $FeCl_3$ solution to the extract. If a blackish green color is formed, this indicates the presence of tannin compounds. Furthermore, the flavonoid test was carried out by adding a little magnesium (Mg) metal powder and a few drops of concentrated HCl to the extract. The formation of a reddish orange color indicates the presence of flavonoid compounds (Wardani et al., 2024).

Blood sampling was performed by dissecting the heart of Wistar rats to obtain more blood volume compared to blood collection from the tail or eyes of rats. Prior to the procedure, rats were fasted for 12 hours and then euthanized until they lost consciousness. The rats were placed in a supine position on a surgical tray, with the legs pierced using a needle to maintain the position. An incision was made along the midline of the abdominal wall muscle from the tip of the sternum to the symphysis pubis, taking care not to hit the diaphragm to avoid pneumothorax. The heart is then sought on the left side of the chest, between the 3rd and 4th ribs, and a syringe is inserted into the heart to a depth of 5 mm, forming an angle of 25-30° to the chest surface. A total of 5 ml of blood was immediately drawn using a syringe and collected in a vacutainer (Brahmananda et al., 2023).

Test animals in each group were placed in the same cage. Groups IV to VI were given durian seed extract (*Durio zibethinus Murr*) orally according to the specified dose, while the negative control group was given 1% Na CMC solution, the positive control group was given 500 mg/KgBB metformin, and the normal group was only given food and drink without treatment. Grouping of test animals consisted of: Group I (normal, without treatment), Group II (negative control, given 1% Na CMC), Group III (positive control, given metformin 500 mg/KgBB), Group IV (given durian seed extract dose 450 mg/KgBB), Group V (given durian seed extract dose 300 mg/KgBB), and Group VI (given durian seed extract dose 150 mg/KgBB) (Ubang et al.. 2022; Velanie et al.. 2017). Blood sugar checks were carried out on day 0. then the rats were fed for 8 hours. On day 1, rats were induced streptozotocin intraperitoneally at a dose of 45 mg/KgBB and checked blood glucose levels on day 3. Rats were declared hyperglycemia if blood glucose levels reached ≥ 135 mg/dL (Adhikary et al., 2021; Pratama et al., 2023; Ukratalo et al., 2023).

Pancreas samples were taken on day 28 from the test animals. Once obtained, the pancreas was cleaned and fixed using 10% solution (Buffer Formalin Bio Analitika Pro Analysis) for at least 24 hours. The pancreas samples were then dehydrated using graded alcohol, followed by clearing using xylol, and impregnated and embedded with paraffin. The paraffin blocks formed were cut to 5 μm thick using a microtome, then the samples were stained using the Hematoxylin-Eosin (HE) method for histopathological observation of the pancreas of Wistar rats (Zebua et al., 2024). Hematoxylin and eosin are dyes that are commonly used to clarify tissue structures so that they are easier to observe using a microscope. The principle of this staining is that the acidic cell nucleus will bind the basic dye, so it appears blue, while the alkaline cytoplasm will bind the acidic dye, producing a red color. In this study, histopathological observations were made with a microscope at 400x magnification. Histopathology assessment uses scoring based on the level of tissue damage. Score 0 indicates no degeneration or necrosis in one field of view. Score 1 indicates the presence of 1-20% degeneration and necrosis, score 2 indicates 21-50% degeneration and necrosis, score 3 indicates 51-75% degeneration and necrosis (mild damage), and score 4 indicates more than 75% degeneration and necrosis (severe damage) in one field of view (Hermawati et al.. 2020; Wardani et al., 2024).

The data were analyzed using the SPSS program, The Kruskal-Wallis test was used to analyze the data on the scoring of damage to the islets of Langerhans, followed by the Mann-Whitney test to identify differences between all treatment groups (Setiadi et al.. 2020). The workflow procedure in this research can be seen in the following diagram on Figure 1.

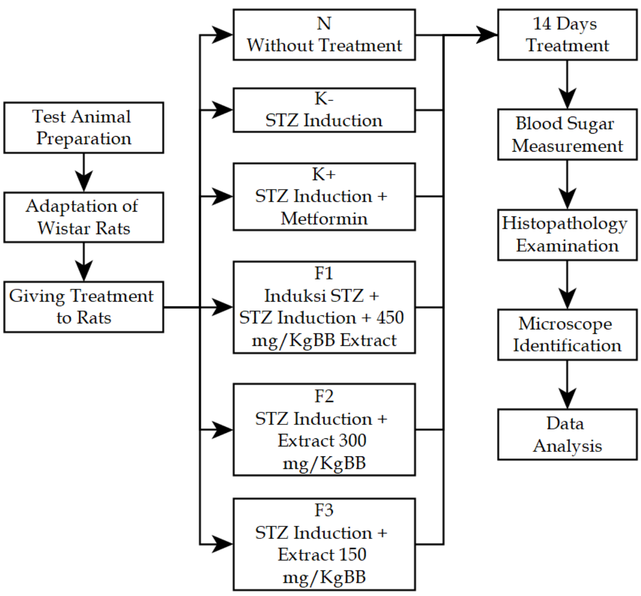


**Figure 1.** Research flow diagram

## Result and Discussion

Phytochemical screening is a qualitative test method carried out as a first step to analyze secondary metabolite compounds in durian seed extract (*Durio zibethinus Murr*). The purpose of this screening is to identify the compounds contained in durian seed extract. The results of phytochemical screening can be seen in Table 1. The table 1 shows that durian seed extract contains several phytochemical compounds, namely alkaloids, saponins, flavonoids, and glycosides, which are known to have various benefits in therapeutic activities.

**Table 1.** Phytochemical Screening Results of Durian Fruit Seed Extracts

| Secondary Metabolite Compounds | Reagents | Results |
|---|---|---|
| Alkaloids | Bouchardart | + |
| | Maeyer | + |
| | Dragendroff | + |
| | Wagner | + |
| Steroids and Triterpenoids | Salkowsky | - |
| | Lieberman-Burchad | - |
| Saponins | Aquadest + Alkohol 96% | + |
| Flavonoids | FeCl3 5% | - |
| | Mg(s) + HCl(p) | - |
| | NaOH 10% | - |
| | H2SO4 (p) | + |
| Tannins | FeCl3 1% | - |
| Glycosides | Mollish | + |

Based on the results of phytochemical screening of durian (*Durio zibethinus Murr*) seed extract, it can be seen that durian seed extract contains several secondary metabolite compounds, such as alkaloids, saponins, flavonoids, and glycosides. These compounds are known to have various therapeutic benefits. Alkaloids have analgesic, anti-inflammatory, and anticancer properties, while saponins can function as antioxidants, and antimicrobials. Flavonoids, which are also found in the extract, have anti-inflammatory and antidiabetic potential. Glycoside compounds are known to have cardiotonic and antidiabetic activities that can be useful in the management of blood sugar levels. This is in line with research conducted by Sijabat et al, (2021) who reported that binahong leaves contain active secondary metabolite compounds, such as alkaloids, saponins, flavonoids, and glycosides that have the potential to reduce blood glucose levels in diabetic rats (Sijabat et al., 2021). Blood sugar levels were measured 3 times, namely: before STZ induction, after STZ induction, and after treatment for 14 days in each group. The following are the results of blood sugar levels in Wistar rats after treatment shown on Table 2.

**Table 2.** Oneway anova test of blood sugar levels

| Group | Mean | Std. deviation | P-value |
|---|---|---|---|
| N | 118.00 | 8.19 | 0.00 |
| K+ | 136.60 | 12.10 | |
| K- | 390.60 | 111.22 | |
| P1 | 161.00 | 11.38 | |
| P2 | 189.80 | 13.70 | |
| P3 | 237.80 | 16.13 | |

The One-Way ANOVA test results in table 2. show that there is a significant difference in blood glucose levels (KGD) between treatment groups, with a p-value of 0.000. The normal group (N) had the lowest mean KGD. which was 118.0 mg/dL with a standard deviation of 8.19, indicating stable glucose levels and within normal limits. In the positive control group (K+), the mean KGD was 136.6 mg/dL with a standard deviation of 12.10, indicating a small but still relatively controlled increase. In contrast, the negative control group (K-) had the highest mean KGD of 390.6 mg/dL with a standard deviation of 111.22, indicating that without special treatment, blood glucose levels remained very high. In the treatment groups P1 and P2, the mean KGD was 161.0 mg/dL (standard deviation 11.38) and 189.8 mg/dL (standard deviation 13.70). respectively, indicating a decrease in KGD from the negative control group.

The results of the blood glucose level (KGD) test showed that durian seed extract had a significant effect in reducing blood glucose levels in the treatment groups. The negative control group (K-) which did not receive treatment had very high blood sugar levels, while the treatment groups (P1. P2. P3) showed a significant decrease even though it had not reached the level of blood sugar levels of the normal group (N). One-Way ANOVA and Post Hoc tests confirmed a significant difference between the treatment groups and the negative control, indicating that durian seed extract can provide a potential blood glucose level lowering effect. This finding is in line with the study conducted by Amir et al. (2020) who reported that durian seed extract can reduce blood glucose levels in mice induced diabetes using alloxan (Amir et al., 2020).

**Table 3.** Post Hoc Test of Blood Sugar Level

| Group | Comparison Group | Sig. | Description |
|---|---|---|---|
| N | K+ | 0.217 | No difference |
| | K- | 0.040 | Significantly different |
| | P1 | 0.002 | Significantly different |
| | P2 | 0.000 | Significantly different |
| | P3 | 0.000 | Significantly different |
| K+ | K- | 0.049 | Significantly different |
| | P1 | 0.113 | No difference |
| | P2 | 0.002 | Significantly different |
| | P3 | 0.000 | Significantly different |
| K- | P1 | 0.072 | No difference |
| | P2 | 0.110 | No difference |
| | P3 | 0.242 | No difference |
| P1 | P2 | 0.075 | No difference |
| | P3 | 0.001 | Significantly different |
| P2 | P3 | 0.012 | Significantly different |

The results of the Post Hoc test showed that the normal group (N) had significant differences with the negative control group (K-) and the treatment groups P1. P2. and P3, with p values below 0.05, but not significantly different from the positive control (K+). The positive control group (K+) showed significant differences with the negative control group (K-) and treatment groups P2 and P3, but not with P1. The negative control group (K-) did not show significant differences with the P1, P2, and P3 groups. Meanwhile, the P1 group was not significantly different from P2 but had a significant difference with P3. Likewise, the P2 group has a significant difference with P3. These results indicate that certain treatments have a significant effect on blood glucose levels in some groups.

Histopathological examination was performed by measuring the diameter of the islets of Langerhans and scoring the damage to pancreatic cells in rats that had received treatment for 14 days. The following is a graph of the average measurement of the diameter of the islets of Langerhans on Figure 2.

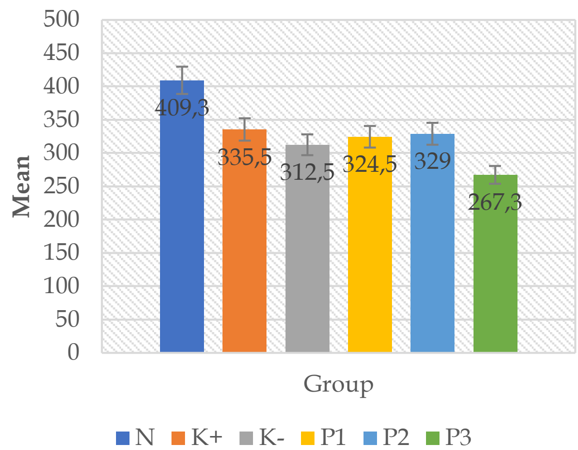


**Figure 2.** Average diameter of islets of Langerhans

The graph shows that the normal group (N) had the largest diameter of islets of Langerhans with an average of 409.3. The negative control group (K-) showed a significant decrease in the diameter of the islets of Langerhans (312.5), while the groups receiving durian seed extract (P1, P2, P3) showed a variation in diameter with the highest result in P2 (329) and the lowest in P3 (267.3). The P3 group, which probably received the highest dose of extract, had the smallest diameter, suggesting a possible effect of durian seed extract on the structure of the islets of Langerhans.

One-Way ANOVA test results on the diameter of Langerhans islets showed significant differences between groups with a p value = 0.047. The normal group (N) had the largest diameter (409.3 ± 29.46). while the induced group (K-) and treated with durian seed extract (P1, P2, P3) showed a smaller diameter, with the P3 group having the lowest diameter (267.3 ± 13.64). These results indicate that the administration of durian seed extract to STZ-induced rats has an effect on reducing the diameter of Langerhans islets. especially at the highest dose in the P3 group

**Table 4.** Oneway Anova Test diameter of islets of Langerhans

| Group | Mean ± Std. deviation | P-value |
|---|---|---|
| N | 409.3±29.46 | |
| K+ | 335.5±110.38 | |
| K- | 312.5±47.79 | 0.047 |
| P1 | 324.5±7.14 | |
| P2 | 329.0±13.64 | |
| P3 | 267.3±13.64 | |

In the histopathological examination, the results of measuring the diameter of the islets of Langerhans showed that the administration of durian seed extract had an effect on the structure of the islets of Langerhans, although the decrease in the diameter of the islets of Langerhans was more pronounced in the P3 group that received the highest dose. The normal group had the largest diameter of islets of Langerhans, while the treated groups showed variations in diameter, with P3 experiencing a significant decrease. This decrease may indicate a positive impact or adaptation to the functional improvement of the pancreas due to durian seed extract. These results are also consistent with the findings by Aulia (2020), which showed that durian seed extract which produces antioxidants can repair damage to pancreatic cells and improve the function of islets of Langerhans in diabetic rats (Huljanah, 2023).

**Table 5.** Pancreatic Cell Score

| Group | Score |
|---|---|
| N | 0 |
| K- | 0 |
| K+ | 0 |
| P1 | 0 |
| P2 | 0 |
| P3 | 0 |

Table 5 shows that all groups. namely the normal group (N), negative control (K-), positive control (K+), as well as durian seed extract treatment groups (P1, P2, and P3), have a pancreatic cell score of 0. Pancreatic cell scores that show no damage in all groups indicate that durian seed extract does not cause significant pancreatic cell damage. This is important because damage to pancreatic cells, especially to the islets of Langerhans. can worsen the condition of diabetes. Thus, durian seed extract not only has the potential to reduce blood glucose levels, but can also help maintain the health of pancreatic cells, which are an important component in the regulation of body glucose levels.

## Conclusion

Diabetes mellitus that remains high can cause damage to various body tissues, including the pancreas. Durian fruit seed extract (*Durio zibethinus Murr*) contains bioactive compounds such as alkaloids, triterpenoids, phenolics, and flavonoids that can reduce blood sugar levels. Durian fruit seed extract (*Durio zibethinus Murr*) with doses of 150 mg, 300 mg, and 450 mg proved to have the ability to reduce blood sugar levels (KGD) in streptozotocin-induced Wistar rats, with a decrease in KGD of 44. 93.2, and 143.6, respectively, which indicates that the higher the dose given, the greater the decrease in blood sugar levels. In addition, the group with a dose of 300 mg (P2) showed the best results in increasing the diameter of the islets of Langerhans, which could compensate for the normal rats and positive control groups. The results of histopathological examination of the pancreas also showed that there was no pancreatic cell necrosis in all experimental groups, indicating that the administration of durian seed extract did not cause damage to pancreatic cells.

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**Author Contributions**
Conceptualization and methodology, V.A.H, T.S and L.C; formal analysis, V.A.H and T.S; Investigation, V.A.H and L.C; writing— original draft preparation, V.A.H; writing—Review and editing, V.A.H, A.Z.T and F.A.N; Visualization, V.A.H and A.Z.T. All authors have agreed to the published version of the manuscript.

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**Conflicts of Interest**
The authors declare no conflict of interest.

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