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Effect of Longan Leaf Extract on Blood Glucose Tolerance and Langerhans Islets of Mice with type 2 Diabetes Mellitus

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Abstract
Blood glucose tolerance is an important measure of how the body regulates glucose levels. It is caused by insulin resistance, pancreatic β-cell dysfunction, excess glucose production by the liver, defective glucose utilization in peripheral tissues, or oxidative stress. This study was aimed to analyse the effect of longan leaf extract on blood glucose tolerance and pancreas alteration in rats with type 2 diabetes. In this study, a completely randomized design was utilized with six groups: a negative control, a positive control (HFD + alloxan monohydrate), a group that received metformin, and three additional groups receiving longan leaf extract at doses of 28, 42, and 56 mg/kg body weight. Treatments were administered for seven days. Blood glucose tolerance was assessed on day eight, while pancreatic histopathology was evaluated through measurement of Langerhans islet diameter in pancreatic sections. Blood glucose tolerance data were analysed with the Kruskal–Wallis test followed by the Dunnett test, whereas pancreatic histopathology data were analysed using ANOVA and Duncan's test. The results showed that longan leaf extract significantly affected blood glucose tolerance and pancreatic histopathology in type 2 diabetic mice. The dose of 56 mg/kg body weight demonstrated the most effective improvement, enhancing glucose tolerance and increasing the diameter of Langerhans islets.

Keywords: Blood glucose tolerance, Diabetes mellitus, Langerhans islets, Longan.
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INTRODUCTION

Diabetes mellitus can occur in individuals who experience damage to pancreatic β cells or insulin resistance. Type 2 diabetes mellitus (T2DM) is caused by a combination of genetic factors related to insulin secretion disorders and insulin resistance due to environmental factors such as obesity, overeating, and stress (Lestari and Zulkarnain, 2021). The prevalence of diabetes mellitus patients in Indonesia increases by 3-4 million people every decade, with a prediction of reaching 6.4 million people by 2040 compared to 2019 (International Diabetes Federation, 2020). High blood glucose levels are a condition where blood glucose level increases above the normal limit, resulting in hyperglycemia (Syokumawena *et al.*, 2024). Hyperglycemia in DM patients activates certain metabolic pathways, increasing the number of free radicals as a result of reactions in the body in the form of reactive oxygen species (ROS) (Hendriyani *et al.*, 2018; Volpe *et al.*, 2018). The presence of ROS causes damage to beta cells in the pancreas. ROS formed by non-enzymatic glycation of proteins, glucose oxidation, and increased lipid peroxidation can cause enzyme damage (Chandra *et al.*, 2019The oral glucose tolerance test checks how well the body handles glucose in the blood by giving a set amount of glucose. According to Nadrati et al. (2021), this test is used to look for diabetes. The results show if a person has normal glucose levels, trouble regulating glucose, or diabetes. Checking blood glucose levels is a key first step in finding out if someone has diabetes.

Reactive Oxygen Species (ROS) play a big role in damaging pancreatic β-cells. When there is too much ROS, it can happen because of processes like non-enzymatic protein glycation, glucose oxidation, and high levels of lipid peroxidation. These processes stop enzymes from working properly and lead to insulin resistance (Chandra et al., 2019). Insulin resistance occurs when the body's cells don't respond well to insulin, which is needed to keep blood sugar levels balanced. High blood glucose levels over time cause more ROS to build up in the body. This oxidative stress can also hurt pancreatic tissue and reduce the ability of beta cells to make insulin. (Putriningtyas et al., 2022).

Insulin is a hormone that helps control how much sugar is in the blood. People with type 2 diabetes and those with high cholesterol may have trouble using insulin properly, which makes it hard for their bodies to handle sugar. Hypercholesterolemia is when there is too much cholesterol and fat in the blood vessels, which is more than what is normal. Eating a lot of fat can affect how much cholesterol is in the body. Several factors affect how cholesterol is produced in the body, one of which is the HMG-CoA reductase enzyme that plays an important role in regulating this process. Endogenous cholesterol synthesis can be inhibited by reducing the activity of this enzyme (D'Erasmo *et al.,* 2020).

Type 2 diabetes mellitus is caused by decreased sensitivity of body cells to insulin, resulting in less effective glucose absorption. Hypercholesterolemia is a condition characterized by excessive accumulation of cholesterol and lipids in the walls of blood vessels, exceeding normal limits (Fitriani *et al.,* 2021). Total cholesterol levels in the body are influenced by several factors, one of which is the consumption of nutrients from foods rich in fat. Long-term hyperglycemia is a cause that results in further damage to β cells, worsening the condition. (Zarmal *et al.,* 2016)

Oral glucose tolerance test (OGTT) indicates the body's response to consuming a glucose-containing solution and is characterized by normal glucose tolerance, impaired glucose tolerance, or diabetes. This test will provide these results. In most cases, early indicators of diabetes are also found here. This makes blood sugar levels synonymous with screening for this deadly disease, which has claimed millions of lives worldwide. (Nadrati et al., 2021). Glucose tolerance is defined as an organism's ability to control and return its blood glucose levels to normal after experiencing a glucose load. The OGTT is a commonly used test to diagnose type 2 diabetes mellitus and gestational diabetes mellitus, which refers to hyperglycemia first detected during pregnancy (Munggarans *et al.,* 2020). The glucose tolerance test has become the standard method for measuring the body's response to glucose and is used to detect insulin resistance or diabetes (Azizah *et al.,* 2022).

Metformin is a synthetic drug which, works by suppressing glucose production in the liver, increasing insulin sensitivity, and reducing glucose absorption in the intestines, thereby effectively lowering blood sugar levels (Kurniawati and Darini, 2024). However, treatment using synthetic materials causes long-term side effects such as diarrhoea, bloating, fatigue, acidosis, kidney disorders, and hypoglycemia (Khairunnisa *et al.,* 2014). A number of natural ingredients have been studied as alternatives to metformin.

Logan leaves can potentially act to lower blood glucose tolerance because they contain secondary metabolite compounds such as flavonoids, saponins, and tannins that have antidiabetic activity (Haryoto and Devi, 2018). The action mechanism of flavonoids is as inhibitors of enzyme α-glucosidase and antioxidative agent that prevents damage to pancreatic β cells (Nurfitria, 2024). Tannins reduce nutrient absorption by inhibiting glucose absorption in the intestines (Yokozawa, 2012), while saponins similarly work by inhibiting the action of α-glucosidase enzyme, which hinders glucose absorption in the small intestine, thereby lowering blood sugar levels (Fiana and Oktaria, 2016).

Previous research found that longan leaves could lower blood glucose levels in male mice (Hardini *et al.,* 2023). Based on this information, this study is conducted by administering various doses of longan leaf ethanol extract to determine the optimal dose for blood glucose tolerance and improve the diameter of Langerhans islets in type 2 diabetic mice, which were induced with a combination of a high-fat diet (HFD) and alloxan monohydrate.

MATERIALS AND METHODS

This study was laboratory experimental research with a completely randomized design consisting of a negative control treatment, a positive control (HFD) + alloxan monohydrate), a metformin control group (HFD + alloxan monohydrate + metformin), and three treatment groups with different doses of longan leaves (28 mg/kgBW, 42 mg/kgBW, and 56 mg/kgBW) that were given HFD and alloxan monohydrate before treatment. Each treatment group consisted of four replications. This research was conducted from February to May 2025 in the Experimental Animal Laboratory, Basic Biology Laboratory, and Biological Microtechnique Laboratory at Universitas Negeri Surabaya.

Logan leaves were extracted using a maceration method using 96% ethanol. Before the extraction process began, the selected leaves were washed carefully and then dried in an oven at 60°C for three days. Once they were dry, the leaves were crushed into a fine powder. For the maceration step, this powder was soaked in 96% ethanol three times. The first time, the ratio was 1:3, and for the next two times, it was 1:2. Each soaking lasted 24 hours. The liquid from the soaked powder was then filtered and heated using a rotary evaporator at 60°C, which made a thick and concentrated extract (Tuldjanah et al., 2020). This extract was then mixed with a 1% NaCMC solution to prepare three different dosage levels: 28, 42, and 56 mg per kilogram of body weight.

This study used 24 male Deutschland Dunken Yoken (DDY) mice that were approximately two months old and weighed between 25 and 30 grams. Before starting the experiment, the mice stayed in their cages for seven days and had constant access to CP511 feed and water. After this adjustment period, the mice were given a high-fat diet (HFD) made by mixing 84 ml of beef tallow with 84 ml of duck egg yolk. The HFD was given by mouth using a tube at a daily dose of 0.5 ml. This process was done for the positive control group, the metformin group, and the treatment groups that received doses of 28, 42, and 56 mg per kilogram of body weight. Once hypercholesterolemia had developed, the mice were injected intraperitoneally with alloxan monohydrate at a dose of 110 mg/kgBW. Three days after induction, fasting blood glucose levels were measured to confirm the diagnosis of hyperglycemia, based on glucose level criteria >126 mg/dL (Firdaus *et al.,* 2017)

Blood glucose tolerance measurement was conducted after the extract treatment on the 8th day. Before the blood glucose tolerance test, the mice were fasted for 12 hours. Fasting blood sugar levels were measured, after mice were induced with 1% of body weight glucose solution orally. Blood sample was collected from peripheral vein of the mice using a blood lancet and measured with an EasyTouch GCU and blood glucose test strips. Measurements were taken at interval; on 0, 30, 60, 90, and 120 minutes (Sinata *et al.,* 2021).

The preparation of pancreatic histopathology was carried out on the 9th day. Mice were anesthetized and dissected. The pancreas was removed and fixed in neutral buffer formalin solution. Pancreas tissue was washed and soaked in graded alcohol for 30 minutes each. The clearing process was performed with xylene twice, first for 15 minutes, then overnight. The infiltration process was conducted by soaking the organ in a xylene : paraffin solution (1:1) for 30 minutes, followed by soaking in pure paraffin three times, each for 1 hour. The samples were then embedded in paraffin blocks. Sectioning was performed using a microtome to produce sections 4–5 µm thick. Paraffin-embedded sections were placed in a water bath at 40°C and then transferred to slides coated with Mayer's albumin. The sections were then oven-dried at 50°C for at least 2 hours. Slides were stained with hematoxylin-eosin (Khaleyla et al., 2021).

The slides were observed using a light microscope. The diameter of the islets of Langerhans was measured using ImageJ version 1.53 (Rahmania, 2020). The average cell diameter was measured using the method described by Shofiati (2021).

Blood glucose tolerance data were obtained by calculating the area under the curve (AUC) for all treatment groups. Statistical analysis of blood glucose tolerance AUC Kruskal-Walls test, followed by the Dunnett test (P<0.05). The data on diameter of Langerhans islets (µm) were analyzed using ANOVA test. To determine the differences between the data, the Duncan test was conducted (P<0.05).

RESULTS

The results of blood glucose tolerance measurements in mice at minutes 0, 30, 60, 90, and 120 using the AUC method showed an increase in the KP and KI groups, reflecting hyperglycemic conditions and insulin resistance (Table 1). The AUC values decreased slowly in the KI, KII, and KIII groups, getting closer to the levels seen in the normal and metformin groups. The KIII group (56 mg/kgBW) showed potential hypoglycemic effects, providing the closest results to the normal group.

Table 1. Blood glucose tolerance in mice.

Treatment	Glycemia (mg/dL)
KN	13.83 ± 1.32^{a}
KP	19.56 ± 2.00^{a}
KM	15.76 ± 1.25^{a}
KI	21.33 ± 1.93^{a}
KII	16.69 ± 1.50^{a}
KIII	15.31 ± 1.18^{a}

Notes: KN or negative control (NaCMC 1%), KP or positive control (HFD+alloxan+NaCMC 1%), KM or metformin group (HFD+alloxan+Metformin), KI or Dose 1 (HFD+alloxan+longan leaf extract 28 mg/kgBW), KII or Dose 2 (HFD+alloxan+longan leaf extract 42 mg/kgBW), KIII or Dose 3 (HFD+alloxan+longan leaf extract 56 mg/kgBW). Different notations indicate significant differences based on the Duncan test (p<0.05).

Table 2. Mean diameter of islets of Langerhans in mice

Treatment	Diameter of islets of Langerhans in mice (μm)
KN	111.00 ± 2.80[d]
KP	69.91 ± 5.05[a]
KM	97.62 ± 7.38[bc]
KI	76.89 ± 7.60[a]
KII	89.96 ± 2.20[b]
KIII	101.73 ± 2.80[cd]

Notes: KN or negative control (NaCMC 1%), KP or positive control (HFD+alloxan+NaCMC 1%), KM or metformin group (HFD+alloxan+Metformin), KI or Dose 1 (HFD+alloxan+longan leaf extract 28 mg/kgBW), KII or Dose 2 (HFD+alloxan+longan leaf extract 42 mg/kgBW), KIII or Dose 3 (HFD+alloxan+longan leaf extract 56 mg/kgBW), Different notations indicate significant differences based on the Duncan test ($p<0.05$).

The results of diameter of the Langerhans islands evaluation is presented in Table 2, while Langerhans islands sections from each treatment group is shown in Figure 1. Based on Table 2, it was found that the diameter data of the Langerhans islands in all of the groups treated with HFD and alloxan were smaller compared to KN. The results of the analysis using the ANOVA test ($p<0.05$) indicate that the longan leaf extract affected the diameter of the Langerhans islands in DM mice. The measurement results of the diameter of the Langerhans islands show that the groups with extract doses of 28 mg/kgBW, 42 mg/kgBW, and 56 mg/kgBW showed improvement in the diameter of the Langerhans islands. Mice given 56 mg/kgBW extract resulted in most optimal improvement, as Langerhans islets diameters were not significantly different from that of KN.

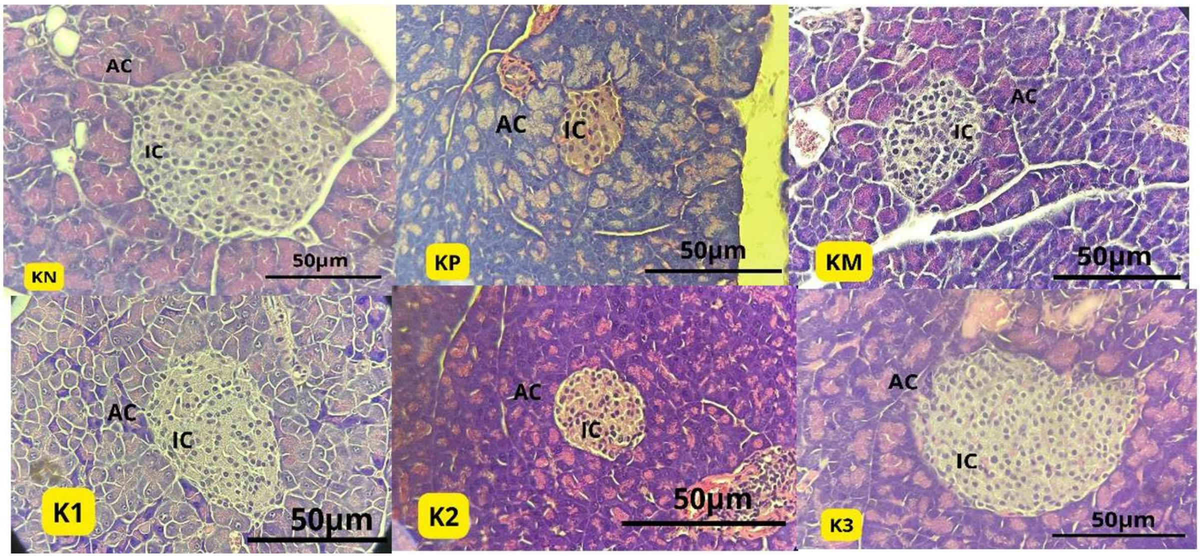

Figure 1. Histology of the islets of Langerhans Notes: KN=negative control; KP= positive control; KM= Metformin; KI= 28 mg/kgBW extract dose, KII= 42 mg/kgBW extract dose; KIII= 56 mg/kgBW extract dose IC= Islet cell; AC= Acinar Cell

DISCUSSION

In this study, type 2 diabetes mellitus was modeled through a high-fat diet (HFD) and alloxan monohydrate induction. The HFD was administered orally via gavage for 14 days to increase blood cholesterol levels, which subsequently triggers diabetes mellitus. This high-fat diet served as a method for a positive control group, a metformin group, and treatment groups with extract doses of 28 mg/kgBW, 42 mg/kgBW, and 56 mg/kgBW. The HFD composition consisted of a combination of 84 ml beef fat and 84 ml chicken egg yolk. Beef tallow contains about 50.3% saturated fatty acids, as stated by Ridwan et al. in 2022. Duck egg yolk also has a lot of saturated fat, which can raise LDL cholesterol in the blood, according to Alifah et al. in 2022. Too much fat can cause oxidative stress, which affects how the body handles glucose. This makes cells less sensitive to insulin, leading to poor glucose absorption and higher blood sugar levels, (Liberty et al, 2023).

The way our body uses glucose is very important for keeping blood sugar levels in check, especially after eating (Nakrani et al., 2020). Usually, the pancreas sends out insulin, which connects to special receptors on muscle and fat cells. This connection starts a series of steps that begin with IRS-1, then move to PI3K and Akt. As a result, a protein called GLUT-4 moves from inside the cell to the outside. When GLUT-4 is on the cell surface, it helps move glucose from the blood into the cells. This process works smoothly when the insulin signal is strong. However, if someone is overweight or has a lot of extra fat, oxidative stress can mess up this process. This weakens IRS-1 and lowers the amount of GLUT-4, which means less glucose gets taken in. This can lead to insulin resistance (Ahmed et al., 2021).

Too much fat can interfere with how insulin signals work by altering the way receptors function. This makes cells less able to respond to insulin. As a result, insulin resistance occurs, which makes it harder to control blood sugar levels (Sinulingga et al., 2020). Insulin resistance arises when the body's cells cannot appropriately react to insulin due to disruptions in the signaling pathway. As a result, cellular glucose intake falls and glucose accumulates in the bloodstream. Particularly in muscular and hepatic tissues, this process is closely tied to the accumulation of fat within cells as well as long-term inflammation brought on by Proinflammatory cytokines released from adipose tissue. These elements help to suppress the activity of proteins engaged in the insulin signaling pathway (Zatterale *et al.*, 2020). Hyperinsulinemia, a condition where the pancreas compensates for insulin resistance over time, produces more insulin. Demand may deplete the pancreatic beta cells, causing their failure and a following reduction in insulin synthesis. Hyperglycemia worsens as a consequence and results in towards the onset of type 2 diabetes mellitus (Chandrasekaran *et al.*, 2024).

Mice received 110 mg/kg body weight of alloxan to create type 2 diabetes mellitus. This disease is distinguished by raised blood glucose values above 126 mg/dL (Yisahak and Narayan, 2017). An high-fat diet (HFD) followed by alloxan induction is intended to produce a more constant experimental model that mimics the properties of type 2 Diabetes in humans. This technique causes insulin resistance; initially the pancreas tries to compensate by producing more insulin. Alloxan works to damage a section of the pancreas. pancreatic β-cells, hence lowering insulin secretion and producing hyperglycemia. The combination of HFD and alloxan has been proven to cause more consistent and extended hyperglycemia giving it a truer representation of type 2 diabetes (Putu *et al.*, 2020).

The experimental design in this study comprised a positive control group, a metformin-treated group, and treatment groups getting doses of 28, 42, and 56 mg/kgBW. Three days following induction, fasting blood glucose was determined; Alloxan induction was done following 14 days of high-fat diet (HFD) feeding of the mice. Measurements of levels verified that the animals were genuinely diabetic. Due to alterations in free radical production and cell membrane permeability (Irdalisa *et al.*, 2015). Alloxan is structurally related to glucose; hence, when alloxan is injected into a mouse, the glucose transporter GLUT2 in the β-pancreatic cells will interpret alloxan as glucose. Alloxan will be transported to the cytosol and undergo a redox reaction, thereby creating superoxide. Radicals are transformed to dialuric acid (Palupi *et al.*, 2022). Superoxide radicals dismute to generate hydrogen peroxide, which subsequently engages in iron-catalyzed reactions to produce hydroxyl radicals. These hydroxyl radicals may harm pancreatic β-cells, hence causing insulin-dependent diabetes (Karita *et al.*, 2021).

Constant stimulation such high glucose intake, insulin resistance, and chronic inflammation in obesity can cause oxidative stress in pancreatic β cells brought on by excessive insulin production (Made *et al.*, 2021). Producing and releasing insulin, pancreatic β cells are vital in preserving blood glucose balance. These cells, nevertheless, are extremely sensitive to oxidative stress since Their antioxidant protection systems are quite poor (Han *et al.*, 2023). Overproduction of free radicals or ROS can harm β cells structure and function significantly reducing their capacity to make insulin. The consequent reduction in insulin synthesis directly reduces blood glucose tolerance which can worsen hyperglycemia (Yang *et al.*, 2024).

Blood glucose tolerance is the body's ability to maintain glucose levels within normal limits after a glucose load or consumption. A blood glucose tolerance test measures how the body responds to elevated blood sugar levels, indicating how well insulin controls glucose metabolism. In people or animals with metabolic disorders such as type 2 diabetes, glucose tolerance is often impaired, as evidenced by high blood glucose levels that persist for longer after glucose is administered. Based on the results of the glucose tolerance test, obtained from the Area Under the Curve value, there is variation in effectiveness between the test groups. The negative control group (KN) had the lowest value of AUC at 13.83 ± 1.32 mg/dL, indicating that the glucose tolerance levels of the mice were normal. Interestingly, the positive control group (KP), who were fed with high calorie diets and alloxan without treatment, had the highest value of AUC at 19.56 ± 2.00 mg/dL. In normal conditions, the body's ability to restore glucose levels in the blood back to normal through insulin secretion, glucose absorption by cells, glucose storage in the liver, and glucose metabolism. In normal glucose tolerant conditions, it can be expected that blood glucose levels return to normal within 2-3 hours postprandially (Pratiwi et al., 2024). In contrast, when glucose tolerant levels become poor, the body tries to restore glucose levels. Nevertheless, it takes much longer. These delays may be due to slow insulin secretion levels, poor insulin sensitivity levels, and increased gluconeogenesis. These delays were studied by Senja et al., 2021. In addition, the findings of this research showed that longan leaves extract possessed impacts on glucose tolerant levels. The impacts may be used as evidence towards the content of certain metabolites found on the leaves of longan plants. These metabolites include those of flavonoid compounds, saponins, and tannins. The impacts of the antidiabetic activity of longan leaves may be used as evidence towards Haryoto and Devi (2018).

The flavonoids in longan leaf extracts have been seen to contribute towards enhancing glucose intolerance by triggering the IRS1/PI3K/AKT signaling pathway, which makes an important contribution towards glucose metabolism. The triggering of the pathway increases cell sensitivity to insulin and helps glucose assimilation (Wang et al., 2021). In addition, suppressing lipid accumulation within insulin-resistant cells also assists in the revival of the IRS-1/PI3K/AKT pathways that quicken GLUT4 migration towards the cell surface (Simon et al., 2024). The heightened activity of GLUT4 makes an important contribution towards improving glucose assimilation efficiency. This, in turn, reduces blood glucose and assists glucose intolerance (Zanaria et al., 2019).

Saponins are secondary glycoside compounds found naturally in various plants, including longan leaves. These compounds are known to have antidiabetic, cholesterol-lowering, and anti-inflammatory effects. They help improve glucose tolerance and reduce hypercholesterolemia (Syahla et al., 2023). In individuals with type 2 diabetes mellitus, hypercholesterolemia can worsen metabolic risk by increasing levels of low-density lipoprotein (LDL), triglycerides, and free fatty acids (FFA). Furthermore, elevated blood glucose levels in patients with type 2 diabetes mellitus are typically caused by insulin resistance in peripheral tissues, followed by hyperinsulinemia as a compensatory effort to compensate for impaired insulin function (Bingga et al., 2021). This results in decreased glucose tolerance, as evidenced by the length of time it takes the body to reduce blood glucose levels after consuming carbohydrates (Ekasari and Dhanny, 2022).

Tannins were one of the bioactive compounds contained in longan leaves and had antioxidant, antihyperglycemic, and antihypercholesterolemic activities. In type 2 diabetes mellitus, hypercholesterolemia or increased blood cholesterol levels worsened glucose tolerance because it could trigger insulin resistance and metabolic dysfunction (Elkanawati *et al.,* 2024). This condition caused disturbances in GLUT4 translocation to adipose tissue, so glucose could not efficiently enter the cells and remained in the bloodstream (Chadt and Hasani, 2020). Tannins worked through several mechanisms directly related to the improvement of blood glucose tolerance. First, tannins could bind to and inhibit the absorption of cholesterol and lipids, thereby helping to reduce total cholesterol and LDL levels (Ajebli *et al.,* 2019). The reduction in cholesterol levels improved cell membrane composition, increased membrane fluidity, and enhanced insulin receptor sensitivity (Sinulingga, 2020).

Administration of longan leaf extract can also improve the diameter of the islets of Langerhans. The results of the Duncan test showed that group KIII 56 mg/kgBW was able to improve the condition of the islets of Langerhans optimally was not significantly different from the control group (KN). Flavonoids as antioxidants in longan leaves extract help to scavenge ROS and minimize oxidative stress thus β cells were able to regenerate (Hermawati *et al.,* 2020). Cell regeneration was indicated by an increase in the diameter of the islets of Langerhans observed after administration of the extract.

CONCLUSION

Longan leaf extract had a positive effect on blood glucose tolerance and Langerhans islet diameter in type 2 diabetic mice. The effective dose for blood glucose tolerance and improving Langerhans islet diameter induced by a high-fat diet (HFD) was 56 mg/kg body weight. Therefore, longan leaf extract had the potential to be a diabetes mellitus medication and affected the diameter of Langerhans islets in diabetic mice.

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CONFLICT OF INTEREST

There is no conflict of interest.

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