



# The Effect of Arumanis Mango Rind (*Mangifera indica* L) Extract as Antidiabetic in Rats Model

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**ABSTRACT:** Arumanis mango (*Mangifera indica* L) rind is one of the organic wastes containing flavonoid compounds. The objectives of this study were to find out the effect of arumanis mango rind extract on alloxan-induced blood glucose reduction in rats, to find out the most effective dose for reducing the levels of blood glucose in diabetic rats, and to find out the histopathology of the pancreas in diabetic rats. We used experimental method. In this study, 24 rats were divided into six groups consisting of I negative control, II positive control, III, IV, V different doses of 100 mg/kg BW, 200 mg/kg BW, 400 mg/kg BW and VI comparison group (glibenclamide). Groups II to VI were administered alloxan at 150 mg/kg BW for 3 days, and then the extract was administered to each group for 14 days, except group II. The levels of blood glucose were measured using a glucometer via the capillary of rat's tail, before and after induction and after administration of extract to all groups. The results are analyzed by the one-way ANOVA it showed significantly different results ( $p < 0.05$ ). The extract of arumanis mango rind in all doses, had an effect on decreasing the level of blood glucose in diabetic rats effectively in dose of 400 mg/kg BW (group V) and histopathology descriptive results showed that arumanis mango rind extract could reduce damage to the pancreatic islet of Langerhans with histopathology of the exocrine glands and endocrine glands at group V was better than at group III and IV.

**Keywords:** arumanis mango rind; antidiabetic; extract; histopathology; rats.

## Introduction

Diabetes Mellitus is the complaint that characterized by an increase in the level of blood glucose above normal limits due to impaired or deficient insulin production by the  $\beta$ -Langerhans cells of the pancreas or because the body's cells no longer respond to insulin [1]. Tracing from data of the 2018 Basic Health Survey, it was reported that the prevalence of diabetes mellitus in the population aged 15 years and older increased by 8.5% in 2018 [2]. Modern and traditional medicine can be used to treat diabetes mellitus. Due to high medical costs, traditional medicine is becoming more and more popular among the general public. Traditional medicine is an alternative to medicine. In addition to being cheaper than modern medicines, traditional medicines are available without a doctor's prescription, can be prepared by oneself, there is no need to import raw materials, medicinal plants can be grown by the user themselves, and there is no risk of side effects, less effective than chemicals.

Diabetes Mellitus can be treated with one part of

the plants as arumanis mango rind. It can be used as an alternative treatment option for diabetes. Arumanis mango rind contains compounds such as flavonoids, steroids, polyphenols, tannins, and saponins [3]. Based on previous research, arumanis mango rind contains active compounds that are effective in lowering blood sugar levels, especially large amounts of phenolic and flavonoid compounds, especially in the form of mango [4]. Mangiferin can be extracted from young leaves (172 g/kg), stem peel (107 g/kg), mango rind (101 g/kg), and old leaves (94 g/kg) [5].

A diabetogenic substance used to increase the level of blood glucose is alloxan. Alloxan is a chemical commonly used to induce diabetes because it selectively breakages pancreatic  $\beta$  cells and reduces the sensitivity of cells with insulin receptors within a few days [6]. The use of arumanis mango rind extract (EKBMA) as an antidiabetic agent has been carried out in previous studies. According to a study by Bhowmik A. [7], arumanis mango leaf extract taken at a dose of

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250 mg/kg BW can lower the level of blood glucose in diabetic rats. Numerous studies have shown that arumanis mango leaves have the ability to reduce the levels of blood glucose. Zulfiqar in 2018 [8] added that arumanis mango leaf extract could reduce the levels of blood glucose in rats with the most effective dose of 500 mg/kg BW, whereas arumanis mango rind extract, it wasn't studied [7]. Considering the above background, researchers are interested in investigating the effect of arumanis mango rind extract on lowering the level of blood glucose in rats and examining the histopathological description of rat pancreas. The purpose of this study is to find out the effect of arumanis mango rind extract on alloxan-induced the blood glucose reduction in rats and to find out the effective dose of arumanis mango rind extract on alloxan-induced blood glucose reduction in rats, also find out the histopathological description of the pancreas of arumanis mango rind extract induced by alloxan.

## Methods

### Make Ethanol Extract From Arumanis Mango Rind.

Sampling of arumanis mango fruit (*Mangifera indica* L.) was carried out by taking  $\pm$  3 kg of fresh arumanis mango rind. Then it is cleaned from adhering dirt using running water, then chopped, air-dried for a day at room temperature. Then it was macerated in a dark bottle after that 70% ethanol was added until submerged. The maceration bottles were left in a dark place for 3 days, stirring occasionally. After 3 days of soaking, the maceration results were filtered using cotton. The maceration process was carried out repeatedly until the solvent becomes clear, the obtained maceration results were combined, they were evaporated on a rotary evaporator until a condensed extract is obtained, and then weigh it.

### Evaluation of Arumanis Mango Rind Extract and It's Characteristics.

Characteristics Extract were Organoleptic Examination, Yield Check, Drying Loss Examination, Ash Content Examination, and Phytochemical Screening Test. Arumanis mango rind extract was placed into a test tube, then shaken with 5 ml of distilled water and 5 ml of chloroform that added before it, and left until two layers were formed, a layer of water and chloroform, using the suitable reagents for asses the flavonoid, alkaloid, phenolic, steroid, triterpenoid, saponine, and tannin [9].

### Evaluation of Arumanis Mango Rind Extract Activity.

The experimental animals used were 24 white

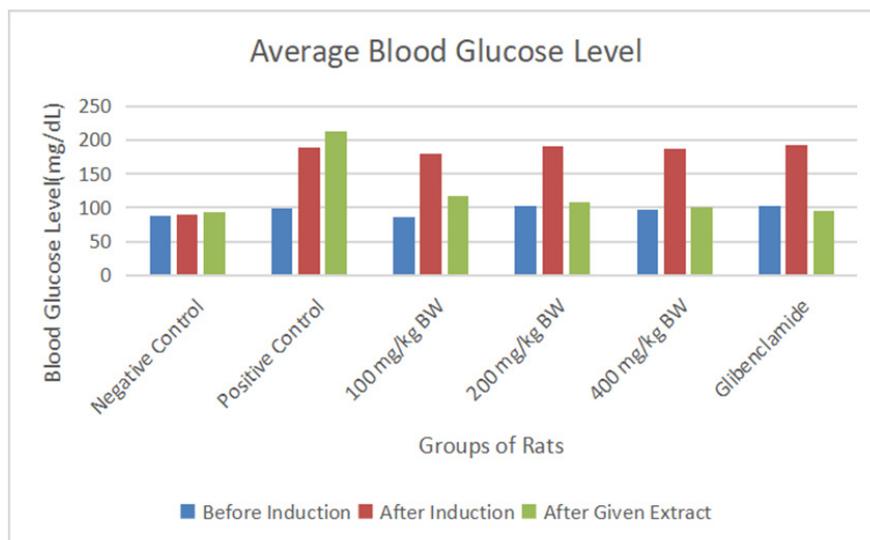
male rats. Rats are *Rattus novergicus* (*wistar strains*). The requirements for experimental animal are 2-3 months of age, body weight of approximately 180 - 200 grams with an increase in body weight of no more than 10% after the acclimatization process. This research got the ethical clearance from The Health Ethics Committee of Perintis Indonesia University registered number 317A/KEPK.F2/ETIK/2022 tanggal 22 Oktober 2022. There 24 rats are divided into six groups, consisting of negative control, positive control, group III (100 mg/kg BW), group IV (200 mg/kg BW), group VI (400 mg/kg BW) and comparison drug (glibenclamide), where each group consisted of 4 rats. The first, the animal was acclimatized for 7 days and was given their food and water standardly with temperature 22°C and enough light for 12 hours. The animal was fasting for 16 hours, and then measured their blood glucose level as initial blood glucose level. The animals were induced with Alloxan for 3 days per intraperitoneal, except group I. After alloxan-induced for 3 days, their blood glucose level was measured again. Rats in group I and II were not given the extract but group III, IV, V, and VI were given extract once a day per orally for 14 days. Evaluation was carried out on 15<sup>th</sup> day. The method employed was level of blood glucose using the glucometer (GlucoDR®, Indonesia) with cutting their capillary of their tails. Finally the animal was killed for histopathology test.

### Evaluation of Histopathological Pancreatic Glands.

After the animal was sacrificed, the pancreas was removed for histopathological examination, pancreases were fixed in 10% formalin. It was dehydrated in graded alcohol percentage (starting with 70%, 80%, 96%). Cleared using xylol. Embedding (making paraffin blocks). Dissection observation of the regularity of the shape of the islands of Langerhans (cutting blocks of tissue using a microtome). Staining with Hematoxylin -Eosin. Mounting (covering the preparation) with Canadian balm and cover glass, to see the pancreatic glands (exocrine channel and langerhans island with 100 x zooming by digital microscope).

### Data Analysis

Data analysis for level and percentage of decreasing blood glucose were asserted as mean  $\pm$  SD. The method of one way ANOVA were used to analyze for data rat's doses groups and blood glucose level with a confidence level of 95% and following *Post Hoc Test* (*Duncan*). Histopatophatological picture is analyzed descriptively..



**Figure 1.** Diagram from average of blood glucose level

Dose I: Alloxan 150 mg/kg BW + EKBMA 100 mg/kg BW.  
 Dose II: Alloxan 150 mg/kg BW + EKBMA 200 mg/kg BW.  
 Dose III: Alloxan 150 mg/kg BW + EKBMA 400 mg/kg BW.  
 Comparison: Alloxan 150 mg/kg BW + Glibenclamide.  
 Series 1 : before alloxan-induced  
 Series 2 : after alloxan-induced  
 Series 3 : after given extract

## Result and Discussion

The results of the identification of arumanis mango plants have been carried out in the ANDA herbarium, Department of Biology, Faculty of Natural Sciences (FMIPA), Andalas University which states that the samples used in this research were arumanis mango fruit (*Mangifera indica* L.) that was taken the rind of fruit, which belongs to the Anacardiaceae family, then the rind of the fruit is taken as a sample (No: 50A/K-ID/ANDA/X/2022). The result of organoleptic showed that the ethanol extract of arumanis mango rind (*Mangifera indica* L.) had a blackish brown color, thick shape, and a distinctive odor. Rendement of the ethanol extract of arumanis mango rind (*Mangifera indica* L.) it can be gotten that the yield is 248,6 grams or 12.43%. Phytochemical test examination of the ethanol extract of arumanis mango rind containing flavonoids, phenolics and tannins. Drying loss of arumanis mango rind is 5.35%.The ash content of the arumanis mango rind extract was found to be 1.28%. The average initial blood glucose levels (mg/dL) for groups I, II, III, IV, V and VI were: 88.25; 98.25 ; 86.75 ; 102 ; 97 ; 101.5 mg/dL. Average blood glucose levels (mg/dL) after alloxan induction in groups I, II, III, IV, V and VI were: 90.25; 188.75 ; 180.5 ;

190.25 ; 187.5 ; 192.25 mg/dL. Blood glucose levels after administering the test preparation for 14 days in groups I, II, III, IV, V and VI were: 93.25; 213 ; 117 ; 108 ; 100.25 ; 95.5mg/dL. The percentage of decreasing in the average of blood glucose level of rats after administering the test preparation for 14 days to groups III, IV, V and VI was 33.89%, 42.08%, 45.75%, 50.22%. Histopathological test of the effect of ethanol extract of arumanis mango rind on the pancreas glands of experimental animals after alloxan induction showed histological differences between the negative control and treatment and comparison groups.

Discussion for the study was that rat blood sampling was done in the rat's capillary. The mechanism of action of rat glucose measurement is to first swab the rat's tail with 70% alcohol, then cut off the rat's tail and discard the first drop of blood, then add the next drop of blood to the strip of glucose bottle. and then a blood sample is taken. The levels of blood glucose are displayed on the GlucoDR screen. This tool is very simple and easy to collect samples, requires only a small amount of sample (1-2 drops of blood), and provides quick results. Glucometers typically use the biosensor glucooxidase method. Glucose in the capillary blood test material reacts with the glucooxidase enzyme in the test strip. This

enzymatic reaction produces electrons, which are captured by the glucometer's electrodes. The number of captured electrons is proportional to the glucose content in the sample material [10].

In this study, glibenclamide, a sulfonylurea oral antidiabetic drug, was used as a comparator because of its lower potential for hypoglycemia. Glibenclamide can lower blood sugar levels in diabetics and non-diabetics. The mechanism of glibenclamide can provide to increase the release of insulin in pancreatic  $\beta$ -cells, and by increasing the increase in calcium to pancreatic  $\beta$ -cells, the sulfonylurea binds to receptors on pancreatic  $\beta$ -cells, increasing the release of insulin. Affects triggers. It can promote insulin production, increase calcium ions in Langerhans  $\beta$  cells, increase insulin production, and the secretion of the hormone insulin can be stimulated from the granules of pancreatic  $\beta$  cells. Glibenclamide stimulates the beta cells of the pancreas to secrete insulin, which controls sugar levels in the body [12]. The reason for choosing the glibenclamide comparator was based on previous research [8]. This glibenclamide comparator was chosen because it can reduce blood glucose levels significantly from hyperglycemia to normal blood glucose levels [9].

The initial step taken in this research was to measure initial the levels of blood glucose in rats. The rats were fasted for 16 hours. This is done in order to avoid increasing blood glucose levels due to the food it eats. Before administering the inducer, the initial levels of blood glucose of the rats were gauged to find out the initial levels

of blood glucose so that they could be compared with the levels of blood glucose after induction. The inducer used in this research was alloxan. In this study, alloxan was able to inhibit the glucokinase enzyme found in pancreatic beta cells, thereby reducing the formation of ATP which is useful for secreting insulin, so that insulin secretion was inhibited and alloxan was able to form Reactive Oxygen Species (ROS) which could produce selective necrosis of pancreatic  $\beta$  cells [13].

These two mechanisms are thought to be able to cause an increase in blood glucose levels in rats. Induction using alloxan at a dose of 150 mg/kg BW intraperitoneally (i.p.) is one of the appropriate ways to produce experimental diabetic conditions (hyperglycemia) in experimental animals. Alloxan can damage pancreatic beta cells due to essential substances in pancreatic beta cells, causing a reduction in insulin-carrying granules in pancreatic beta cells [14]. Damage to pancreatic beta cells is caused by hydroxyl radicals resulting from the reaction of alloxan with intracellular thiols (glutathione) which can result in necrosis of pancreatic beta cells resulting in insulin dependent alloxan diabetes [15].

In this study, the results of examining the blood glucose levels of rats on day 4<sup>th</sup> showed that the levels of blood glucose of the positive control had increased compared to the negative control, which is a reference for normal levels of blood glucose, where normal levels of blood glucose indicate that glucose levels are stable within the normal range. namely  $\leq 126$  mg/dL [16].

The choice of alloxan induction was based on

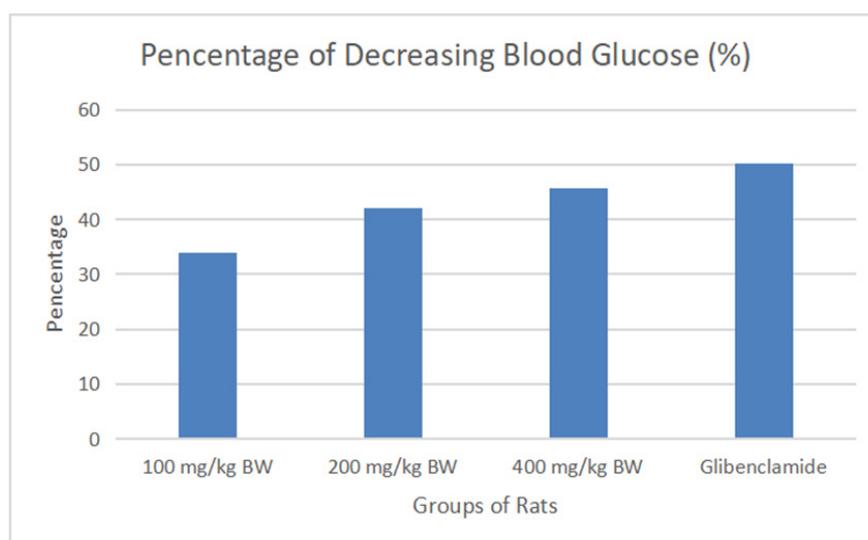


Figure 2. Diagram from percentage of decreasing blood glucose after given extract for 14 days

previous research that alloxan can increase normal blood glucose levels until hyperglycemia occurs, by administering alloxan for 3 days intraperitoneally (i.p.) once a day [9].

Measurement of levels of blood glucose in rats was enforced at the initial blood glucose examination in rats, after the induction administration and after administration of the preparation for 14 days. Measurement of initial glucose levels as a benchmark for normal levels of blood glucose in rats and measurement of levels of blood glucose after induction aims to look at the success of induction which is characterized by an increase in blood glucose levels in rats, while measuring glucose levels after 14 days of administration of the preparation aims to see the effect of administering ethanol extract of arumanis mango rind given per orally once a day for 14 days.

Administration of ethanol extract of arumanis mango rind can render a decrease in the levels of blood glucose. This is thought to be due to the secondary metabolite content found in the rind of the arumanis mango such as flavonoids, phenolics and tannins as well as antioxidant activity which can prevent and stop further damage to pancreatic beta cells and tannins can stimulate glucose and fat metabolism resulting in the accumulation of these two sources of calories. in the blood can be avoided.

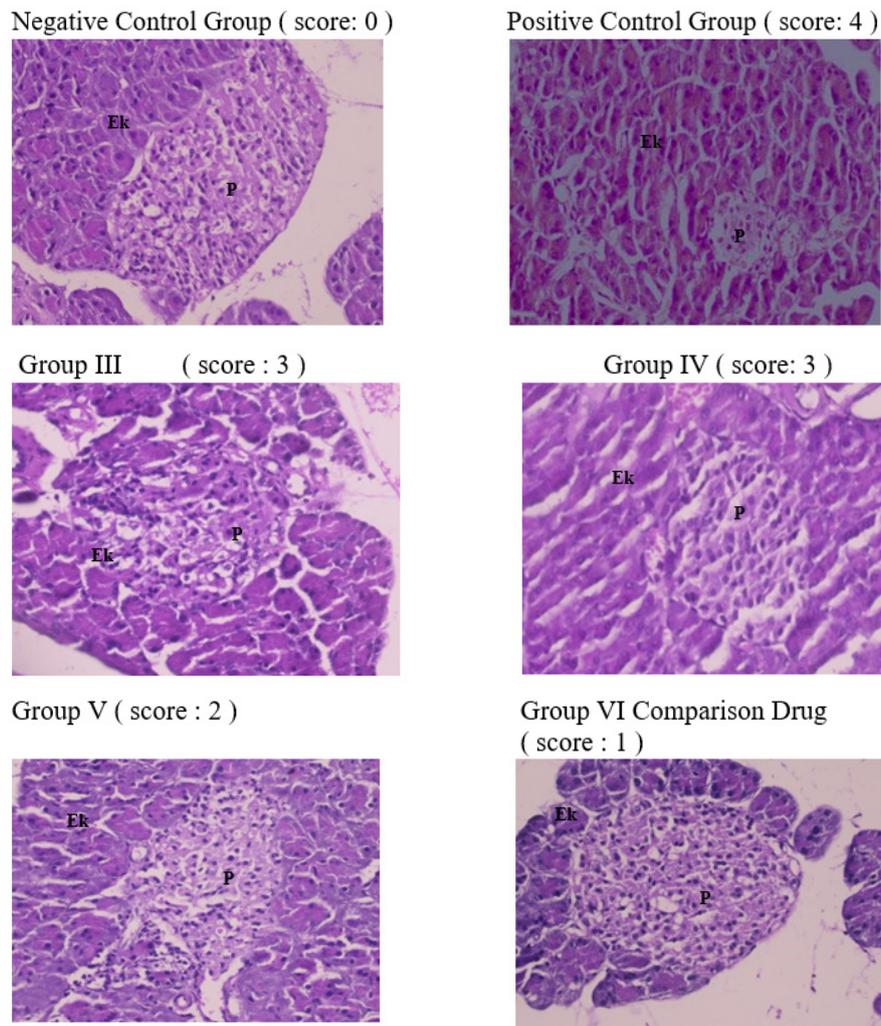
Tannins also have hypoglycemic activity, namely by increasing glycogenesis. Apart from that, tannins also function as astringents or chelators which can shrink the epithelial membrane of the small intestine thereby reducing the absorption of food essence and as a result inhibiting glucose intake and the rate of increase in blood glucose is not too high [17]. These results are in accordance with previous research conducted by Zulfiqar in 2018 [8] where testing the effectiveness of the ethanol extract of mango leaves (*Mangifera indica* L.) arumanis which was induced using alloxan showed that the ethanol extract of mango leaves was able to reduce blood glucose levels in rats with the most effective dose, namely 500mg/kg BW, research conducted by Bhowmik in 2019 proved that ethanol extract of arumanis mango leaves 250 mg/kg BW can reduce blood glucose levels in diabetes, but none researches for arumanis mango rind [9].

The flavonoids contained in the rind of the arumanis mango are able to confer as antioxidants. Flavonoids have the effect of reducing oxidative stress by binding to free radicals. It has been proven that the ethanol extract of arumanis mango rind is able to maintain the integrity of pancreatic beta cells. Mangiferin can reduce blood glucose and fat levels in diabetic rats via oral or intraperitoneal methods. The anti-inflammatory activity of flavonoid compounds and antioxidant activity can prevent and stop

further damage to pancreatic beta cells. This can be seen from the percentage decrease in blood glucose levels of rats on the 15<sup>th</sup> day after being given the test preparation, namely at a dose of 400 mg/kg BW, the percentage was 45.75%.

After being given treatment, changes in the levels of blood glucose can be seen from the beginning, after induction and after 14 days of administering the test preparation. The average blood glucose level after 14 days of administering the test preparation in the negative control group as a reference for normal rats were 94.25 mg/dL, the positive control group as a reference for diabetic rats were 214 mg/dL, group VI as a comparison used was glibenclamide dose 5 mg/kg bw was 96.25 mg/dL. The aim of using a comparison is to differentiate diabetic rats after being given standard medication from the test preparation, groups III, IV, and V.

The results of the data obtained were tested for normality using the Shapiro-Wilk test (samples  $\leq 50$ ). Based on the normality test using the Shapiro Wilks Test, it showed that the data on changes in the level of blood glucose of rats induced by alloxan after administering the extract of arumanis mango rind were distributed normal ( $p > 0.05$ ). Next, blood glucose levels were examined using a paired T-test which aims to determine the difference in blood glucose levels in rats before induction and after alloxan induction, the results obtained were  $p < 0.05$  (if sig:  $p < 0.05$  then There is a difference). Based on the results of the paired T test, all groups induced by alloxan experienced an increase in blood glucose levels. The results of one-way statistical analysis of variance (ANOVA) calculations on rat blood glucose levels appeared significant, expressed as ( $p < 0.05$ ). The results of one-way ANOVA statistical testing on blood glucose levels showed that the extract of arumanis mango rind had an antidiabetic effect which was marked by a significant  $p < 0.05$ , meaning that there was a significant difference between the groups. given a test preparation and a comparison with a positive control. After carrying out the ANOVA test, it was continued with the Duncan test. Duncan's test is a further test to test differences between all treatment pairs. The results of the analysis of the Duncan test on blood glucose levels can be concluded that the negative control group was not significantly different from the dose III group and the comparison group, but was significantly different from the dose I group and dose II group and significantly different from the positive control group. However, it can be seen that dose III group is closest to the negative control, namely dose III group which is the best at decreasing blood glucose levels in diabetic rats.



**Figure 3.** Histopathology of pancreatic cells in experimental animals

**Information:**

1. Exocrine glands ( Ek )
  2. Langerhans Island ( P )
- Histopathological Assesment
- Score 0 : no damage
- Score 1 : little damage
- Score 2 : light damage
- Score 3 : moderate damage
- Score 4 : heavy damage

Histopathological observations of pancreatic glands were carried out with paraffin blocks using the hematoxylin-eosin (HE) staining method. Histopathological examination was carried out to determine the structure of the pancreatic glands in each treatment. The following are the results of observing the histopathological images of each group after preparations and staining were made. The negative control group had the lowest pancreatic histopathology score of 0, that is, no damage was found in the histopathological structure of pancreatic cells in

rats. In this group, pancreatic glands appears with exocrine components in the form of tubular glands, as well as endocrine components with islets of Langerhans within normal limits. In contrast to the positive control, group III, IV, V and the comparison showed damage to endocrine and exocrine components. Characterized by reduced island size (atrophy), degenerative cells and necrosis.

In the positive control group with alloxan induction without treatment, endocrine cell degeneration in the islets of Langerhans was seen accompanied by atrophy

of the islets of Langerhans. The exocrine glands appear degenerative with some cells experiencing degeneration and necrosis damage. Previous research reported that histopathological damage to the diabetic pancreas is characterized by changes in the shape of the pancreas, In the positive control group with alloxan induction without treatment, endocrine cell degeneration in the islets of Langerhans was seen accompanied by atrophy of the islets of Langerhans. The exocrine glands appear degenerative with some cells experiencing degeneration and necrosis damage. Previous research reported that histopathological damage to the diabetic pancreas is characterized by changes in the shape of the pancreas in the form of shrinkage and reduction in the size of the islets of Langerhans [18]. The results of this study showed that the increase in blood glucose levels of test animals after induction was related to damage to the pancreas organ. The administration of alloxan had an effect on the degradation of  $\beta$  cells in the islets of Langerhans, namely the organ responsible for making insulin in the body [19]. Process of induction of alloxan which works specifically can damaged pancreatic  $\beta$  cells. An increase in the amount of reactive oxygen species (ROS) free radicals compared to the amount of antioxidants can trigger oxidative stress so that the presence of ROS can cause damage to beta cells in the pancreas. This increase occurs through the ROS reaction cycle which produces dialuric acid. Then, dialuric acid is involved in the redox cycle to form superoxide radicals (free radicals). Superoxide radicals dismutase into hydrogen peroxide which in the final stage produces hydroxyl radicals [20].

In group III and group IV (moderate necrosis) there was an improvement in the pancreatic histopathology with a reduced percentage of damage to the islets of Langerhans. The damage that occurred was not severe compared to the positive group. Administration of arumanis mango rind ethanol extract at a dose of 100 mg/kg BW and 200 mg/kg BW was able to repair pancreatic cell damage in rats induced by alloxan, but not as good as group V and the comparison.

In group V (mild necrosis), the level of histopathological damage shown was low. Administration from the extract of arumanis mango rind at a dose of 400mg/kg BW was able to improve pancreatic damage in rats induced by alloxan when compared to the positive control group. And the histological picture at group V is better than the other doses. This can to be influenced by the increasing number of bioactive compounds along with increasing doses given [21]. Increasing the dose given resulted in an increase in the number of bioactive

compounds contained in the extract.

In the glibenclamide as comparison group, there are able to improve in the histopathological description of pancreas had the best picture compared to the variant of dose groups and the positive control. The histopathological picture of the comparison group was close to the negative control but there was still pancreatic cell damage. Glibenclamide works primarily in increasing insulin secretion and repairing pancreatic  $\beta$  cells. Glibenclamide acts to inhibit ATP-sensitive potassium channels in pancreatic  $\beta$ -cells so that the cell membrane is depolarized causing the opening of voltage-dependent calcium channels so that  $\text{Ca}^{2+}$  enters the cytosol causing intracellular calcium levels to increase in pancreatic  $\beta$ -cells, ultimately stimulating insulin release and repair of pancreatic  $\beta$ -cells [22].

Administration of arumanis mango rind extract showed improvement in the histological appearance of the pancreas with a reduction in the percentage of damage to the islets of Langerhans. The ability of ethanol extract of arumanis mango rind to reduce damage to the islets of Langerhans in the pancreas of diabetic rats is also due to the flavonoid compounds contained in it. The flavonoid compounds contained in mango peel play an important role improves the diameter of the islets of Langerhans by stimulating an increase in antioxidants in pancreatic beta cells. Increased antioxidants can inhibit ROS and lipid peroxidase [23]. The process of repairing damaged cells involved antioxidants. The presence of free radicals can be overcome by the presence of antioxidants caused the cell damage, which function as agents that reduce oxidants before they damage cells so that cell damage can be reduced. Apart from that, flavonoids are known to play a role in capturing free radicals or functioning as natural antioxidants. This antioxidant activity allows flavonoids to capture or neutralize free radicals (such as ROS or RNS) so that they can repair the condition of damaged tissue, in other words the inflammatory process can be inhibited. Flavonoids are reported to have antidiabetic activity which can regenerate cells in the islets of Langerhans.

## Conclusion

The extract of arumanis mango rind (*Mangifera indica* L) in all doses, had an effect on decreasing the level of blood glucose in diabetic rat induced by alloxan, but group V (400 mg/kg BW) gave effect effectively, because its histopathology descriptive results showed that arumanis mango rind extract could reduce damage to the pancreatic islet of Langerhans with histopathology of the exocrine

glands and endocrine glands, was better than at group III and IV.

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