# Ethanol Extract Activity of Teak Leaves (Tectona grandis L) Against Histopotological Appearance of Pancreatic Organs in Rats (Rattus norvegicus) Model Type II DM

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DOI: https://10.46496/medula.v10i2.1

Received 1 December 2022
Accepted 1 May 2023
Available online 28 July 2023

***ABSTRACT***

***Background:*** *Diabetes mellitus is a disease characterized by increased blood glucose levels and changes in the histopathological structure of the islets of Langerhans of the pancreas. One of the plants used empirically as an antidiabetic is the teak plant (Tectona grandis Linn). The content compounds that are thought to act as antidiabetics are flavonoids.* ***Purpose:*** *The purposes of this study is to determine the activity of the ethanol extract of Tectona grandis L leaves which has antihyperglycemic activity as seen from the histopathology of the pancreas of white rats (Rattus norvegicus).* ***Methods:*** *Modeling diabetes mellitus in test animals was carried out by inducing 40 mg/kg BW streptozotocin intraperitoneally. There were 6 treatment groups, namely the normal control group, the positive control group, the negative control group, and the teak leaf ethanol extract group at doses of 100, 200, and 300 mg/kg.* ***Results:*** *The ethanol extract of Tectona grandis leaves has repair activity for regenerating endocrine cells in the islets of Langerhans with an average number of endocrine cells in the normal control group of 483 cells, positive control group 474 cells, negative control 318 cells, dose 100 mg/kg body weight 450 cells, a dose of 200 mg/KBB 462 cells and a dose of 300 mg/KBB 469 cells and it can regenerate endocrine cells.* ***Conclusion:*** *the ethanol extract of Tectona grandis L leaves at a dose of 300 mg/kg BW has activity in repairing endocrine cells with cell morphology almost resembling normal cells.*

***Keywords:*** *diabetes mellitus; histopathology; rattus novergicus; tectona grandis L*

## INTRODUCTION

Diabetes mellitus (DM) is a non-communicable disease related to lifestyle. Diabetes is also known as the "Mother of Disease" because it is the parent of other diseases such as hypertension, heart and blood vessel disease, stroke, kidney failure and blindness (Upadhyay, 2016).

Basic Health Research in 2018 showed that the prevalence of DM based on blood tests in people aged over 15 years, in 2013-2018, namely in 2013 (6.9%) and in 2018 (10.9%), where it can be seen that the prevalence diabetes from 2013-2018 continues to increase. Based on the gender, more women experience diabetes mellitus than men

with prevalence (9.0%) for men and (12.7%) for women. Meanwhile, based on the area of residence, diabetes mellitus is more likely to be suffered by people in rural areas (11.2%) and urban areas (10.6%) (Suastika et al., 2011; Kemenkes RI, 2018).

Treatment of diabetes such as the use of insulin and oral antihyperglycemic drugs is relatively expensive, therapy with synthetic drugs often causes side effects and high costs due to long-term treatment (Lubis, R. dan Rahmat, 2015). There are so many natural antidiabetic plant products that treat diabetes and directly affect pancreatic insulin secretion. The use of natural plant products as alternative medicinal ingredients is gaining popularity because of fewer side effects and relatively low costs (Walean et al., 2020).

One of the plants that can be developed as an anti-diabetic potential is teak (*Tectona grandis* Linn). The content of chemical compounds from Tectona grandis Linn are Triterpenic hemiterpene compounds, Lignin, Quinones, Phenolic acids and Flavonoids. The pharmacological activity of *Tectona grandis* Linn in various medications, such as anti-inflammatory, antioxidant and lipid hypoglycemic, antidiabetic and diuretic (Kushwah, 2018).

Flavanoids are known to have antioxidant activity related to antidiabetic activity. Flavanoids are believed to improve insulin receptor sensitivity, thus it provides a beneficial effect on diabetes mellitus (Marianne et al., 2011).

The high anti-diabetic potential of teak leaves still requires scientific evidence, so an activity test of the ethanol extract of teak leaves (*Tectona grandis* L) was carried out which has been used empirically by the community to have antihyperglycemic activity as seen from the histopathology of the pancreas of white rats (*Rattus norvegicus*).

## RESEARCH METHODS

### Tools and materials

The tools used in this study were Vacuum Rotary Evaporator (Buchi®), dropper pipette, vial, ordinary filter paper, knife, blender, cutter, spatula, beaker (Pyrex®), oven (Stuart®), analytical balance (Explorer Ohaus®), measuring cup (Pyrex®), waterbath, sonde, porcelain cup, cutting board, scalpet knife, tweezer, tissue cassette, automatic processor machine (Kadde®), blocking tool, freezer (-20°C), microtome machine (Kadde® ), microtome knife, microtube, centrifuge, slide, cover slip, special rack for staining, microscope (Irmeco®).

The materials used in this study were teak leaves (Tectona grandis L) taken from the Danagoa Village, Tongkuno, Muna, Southeast Sulawesi Province, ethanol (technical), distilled water, Mayer's reagent, Wagner's reagent, Dragendroff's reagent, Liebermann Burchard's reagent, hydrochloric acid (HCl), sodium citrate buffer, FeCl3, 10% BNF, toluene, 0.9% NaCl, streptozotocin.

### Sample Preparation and Extraction

Samples of Tectona grandis L. leaves that had been collected were wet

sorted, then dried and then dry sorted. After that, they were crushed using an electric chopper to produce 20 kg of simplicia.

The simplicia produced was macerated using ethanol solvent for 3×24 hours. The maceration results were then separated using filter paper and then evaporated using a rotary vacuum evaporator at a temperature of 40-45°C at a speed of 65-90 rpm to obtain a concentrated extract.

**Grouping of Test Animals**

The test animals used were 25 wistar strain white rats (*Rattus norvegicus*) which were grouped into 6 groups. Each group consisted of 4 test animals, namely the normal group (Kn), the positive control group (K+) which was given 5 mg of glibenclamide, the negative control (K-) which was given 2% Na-CMC, the treatment group 1 (K1) which was given ethanol leaf extract. teak (*Tectona grandis* L.) 100 mg/KgBW, treatment group 2 (K2) was given teak leaf ethanol extract 200 mg/KgBW and treatment group 3 (K3) was given teak leaf ethanol extract 300 mg/KgBW.

**Test Animal Treatment**

The test animals used were fasted for 8 hours and then injected once with streptozotocin as a diabetogenic substance at a dose of 40 mg/kgBW which was dissolved in 0.1 M sodium citrate buffer pH 4.0 to increase the blood sugar levels of the test animals (Konda et al., 2019; Nuralifah, et al., 2022). Furthermore, the treatment of each test group was given orally once a day for each rat for 7 days (Mongi, Simbala and De Queljoe, 2019).

**Preparation of Pancreas Histology Preparations**

Pancreatic organ retrieval was performed surgically but first the white rats were general anesthetized using chloroform dosage. Then the rats were dissected along the thorax to the pubis (Amudha, Manna and Ns, 2018). The pancreas was taken, then washed using a physiological solution of 0.9% NaCl for 30 minutes. Then it was fixed with 10% BNF (*buffer neutral formalin*) solution (Adeoye et al., 2017).

In the *cleaning* stage, the samples were washed with toluene 3 times, each for 1-2 hours. The embedding stage is immersing the sample in liquid paraffin with a temperature of 60°C 3 times, each for 2 hours, then the process of printing the paraffin block is then sliced and soaked in the bath attached to the glass object then the sample is heated in the oven for 2-3 minute.

In the *coloring* stage, the sample that has been heated using an oven is immersed in xylol 3 times for 5 to 10 minutes each. Rinse using 90%, 80% and 70% alcohol for 5-10 minutes. After that, the staining process was carried out using a haemotoxylin solution for 2-3 minutes, followed by an eosin solution for 2-3 minutes. Then the samples were washed/rinsed using 70%, 80%, and 90% alcohol for 5-10 minutes. The sample is dried at room temperature for 3-5 minutes then covered with a glass object, then observed under a microscope.

**Histopathological Observations**

The paraffin-embedded pancreas was sectioned at 4 μm using a semiautomated microtome. The tissue

sections were then mounted on glass slides using a hot plate. Afterward, the tissue sections were deparafinized by xylene and rehydrated by different graded ethanol dilution (100%, 90%, and 70%). The sections were stained with hematoxylin and eosin (H&E) (Nurdiana et al., 2017). Histopathological preparations were examined under a microscope each in 5 microscopic fields. Examination with a microscope was carried out at 100x magnification followed by 400x magnification (Campbell-Thompson et al., 2012). The histopathological changes observed included fatty degeneration and necrosis.

**Calculation of the Number of Endocrine Cells**

Observation of preparations is done by observing the entire field of view. Calculation of the number of cells was carried out on cells that reacted positively and had clear nuclei at low magnification (Adnyane et al., 2001). Then the number of fibrous cells was counted. The results of these calculations were compiled and the data were analyzed using the ANOVA (Analysis of Varians) statistical test, then the percentage of the number of damaged cells to all endocrine cells was calculated.

**RESULTS**

This research was conducted at the Laboratory of the Faculty of Pharmacy, the Laboratory of the Faculty of Medicine, Halu Oleo University and the Anatomical Pathology Laboratory of Stella Maris Hospital, Makassar. Samples that have been processed into extracts are then subjected to phytochemical screening and extract characteristic tests.

**Phytochemical Screening**

Screening was carried out to identify secondary metabolites found in teak leaf extract (*Tectona grandis* L). The results of the phytochemical screening of the ethanol extract of teak leaves were flavanoids, tannins, terpenoids, saponins and alkaloids.

**Profile of Blood Glucose Rise**

Animal modeling was carried out by inducing 40 mg/Kg BW strepzotocin with the aim of increasing blood glucose levels. Before being induced by STZ, the average glucose level of the experimental animals was 90.62 mg/dL. Blood glucose measurements were observed 2-4 days after STZ induction. The mean glucose levels before and after STZ induction can be seen in Figure 1. An increase in blood glucose levels occurred after STZ induction. This increase proved that Strepzotocin 40 mg/KgBW was able to significantly increase blood glucose levels in test animals.

**Pancreas Organ Histopathology**

Histopathological examination of the pancreas organs was carried out in all treatment groups using H.E. staining, and observed under a 40× magnification microscope with the examination data shown in Figure 3. The histological picture of rats with diabetes mellitus can be seen from the reduced cell nuclei.

Examination results showed that the normal group saw Langerhans islands of normal size. In the positive control group, the pancreatic islets of

Langerhans were of various sizes, medium to large. In the negative control group, relatively small pancreatic islets of Langerhans were seen. Whereas in the treatment group 1, the pancreatic islets of Langerhans were seen which were quite large and of normal size. In the treatment group 2, the pancreatic islets of Langerhans varied in size, normal to moderate, and in the treatment group 3, the pancreatic islets of Langerhans were very large.

**Observation of Endocrine Cell Numbers**

Observation of the number of endocrine cells was carried out with a microscope (Figure 3) which was equipped with a photographic instrument and a counter. Calculation of the number of endocrine cells was carried out on cells that reacted positively (dark brown to black in color) and had clear nuclei at low magnification. Calculations were carried out on five fields taken randomly. The average number of endocrine cells in each test group can be seen in Figure 2. The average number of endocrine cells obtained showed a significant difference in each group (*p=0.000*) which was statistically analyzed using the one way ANOVA test.

**DISCUSSION**

Measurement of glucose levels after modeling the test animals can be seen in Figure 1. The average blood sugar level has increased compared to the fasting blood glucose level before modeling. STZ affects glucose oxidation and decreases insulin biosynthesis and secretion. STZ enters pancreatic β-cells via the GLUT2 glucose transporter causing decreased expression of GLUT2. This results in decreased peripheral insulin receptor sensitivity resulting in increased insulin resistance and increased blood glucose levels (Firdaus et al, 2016). This is a feature of type II DM.

Based on measurements of blood sugar levels after therapy, a significant decrease in blood glucose levels can be seen. The potential of teak leaf ethanol extract in reducing blood glucose levels can be seen between the treatment groups (1, 2 and 3) to the negative control (K-).

The effectiveness of teak leaves in reducing blood glucose levels in rats with Type II DM by reducing oxidative stress by the metabolites contained in the extract. Increased oxidative stress in pancreatic β cells that lasts a long time will cause damage to some cells and cause impaired insulin secretion or decreased insulin secretion (Lestari, 2018). Insulin is synthesized in the β cells of the pancreas, precisely in the endoplasmic reticulum. Insulin will be secreted if there is a stimulus in the form of an increase in blood glucose levels. A continuous increase in glucose levels will cause the work of pancreatic β cells to increase (Azizah et al., 2019).

In the mechanism of healing diabetes, flavonoids are thought to play a role in increasing the activity of antioxidant enzymes and being able to regenerate damaged pancreatic β-cells so that insulin deficiency can be overcome (Madihah, Alfina and Gani, 2016). Flavonoids contained in plants are also thought to improve insulin

receptor sensitivity. So that the presence of flavonoids has a beneficial effect on diabetes mellitus (Marianne et al, 2011).

The description of mice with diabetes mellitus will be characterized by reduced cell nuclei. The microscopic structure of the pancreas of the normal rat group can be seen in Figure 3 (a) showing pancreatic tissue with Langerhans islands of normal size, the number of Langerhans islands is 0-1 pcs/LPB. The large blood vessels are well visible and not hyalinized. Pancreatic cells are generally good, are still within normal limits in the ratio of the size of the nucleus to the cytoplasm and the shape of the nucleus. It looks homogeneous, not atypia. These results indicate that the pancreas is normal without certain abnormalities.

The microscopic structure of the pancreas the rats in the positive group can be seen in Figure 3(b) where the large blood vessels thicken and hyalinization occurs. These results show an improvement in the size of the islets of Langerhans which has increased slightly, with the presence of a vasculopathy in the form of a wall. Treatment in the positive control group given glibenclamide works by stimulating pancreatic β cells to secrete insulin so that they can repair β cells because they can increase insulin secretion(Liem, Yuliet and Khumaidi, 2015; Hutapea et al., 2021). This is consistent with the decrease in blood glucose levels in mice where the blood glucose levels after being induced were 246.75 mg/dL, and after being treated with glibenclamide there was a decrease of 92.5 mg/dL, this is also consistent with the improvement of the islets of Langerhans which seen from the number of endocrine cells, namely as many as 474.75 (Figure 4).

The microscopic structure of the pancreatic organs of the negative group rats can be seen in Figure 3(c) where the islets of Langerhans are relatively small, with a vasculopathy in the form of thickened blood vessel walls. Damage to pancreatic β cells by inducing STZ causes DNA alkylation which causes depletion of cellular NAD+ and ATP. The increase in ATP dephosphorylation after STZ induction produces a substrate for the catalytic reaction of xanthine oxidase which produces superoxide radicals. As a result, hydrogen peroxide and hydroxyl radicals are also formed. Furthermore, STZ released many toxic substances from nitric oxide which inhibited aconitase activity and contributed to DNA damage, which ultimately resulted in apoptosis and necrosis of ß cells (Szkuldeski 2001).

The microscopic structure of the pancreatic organs of group P1 rats (dose of 100 mg/Kg BW) can be seen in Figure 3(d) where the pancreatic beta cells are almost normal and show improvement in the size of the islets of Langerhans which increases to a greater extent, with the presence of vasculopathy. Improvement of the pancreas organ at a dose of 100 mg/kgBB was in line with a decrease in blood glucose levels in rats, namely 110.25 mg/dL where the previous glucose level was 267.5 mg/dL, this was also in accordance with an increase in the number of endocrine cells in the islets. langerhans that is as much as 450.25 (Figure 2). Based on the

results above, it can be seen that the regeneration of pancreatic β cells that occurs after therapy causes an increase in insulin secretion resulting in a decrease in glucose in the blood.

The microscopic structure of the pancreas organs of P2 group rats (dose of 200 mg/KgBB), can be seen in Figure 3(e). Based on the results of these examinations, it can be seen that the pancreas in this group is close to normal by showing an improvement in the size of the islets of Langerhans, some of which are larger, without any vasculopathy. This is in line with the decrease in the rat's blood glucose level, which is equal to 106 mg/dL, which was originally the rat's blood glucose level before being treated, which was 268.25 mg/dL. This can be seen from the increase in the number of endocrine cells in the islets of Langerhans, which is 462.5. When compared with the negative control, teak leaf therapy at a dose of 200 mg showed improvement in the islets of Langerhans as seen from the ability of the cells to regenerate again resulting in an increase in the number of pancreatic β cells and the resulting insulin secretion. An increase in insulin causes a decrease in blood glucose levels even though the decrease is not significant.

The microscopic structure of the pancreas organs of P3 group rats (dose 300 mg/KgBB), can be seen in Figure 3(f). The P3 group looked almost like normal cells, and the number of endocrine cells increased, namely 469, although it was not the same as normal cells. This indicated that administration of ethanol extract at a dose of 300 mg was able to show an improvement in endocrine cells, although not significantly. This is in line with the significant decrease in blood glucose where the glucose level before treatment was 220 mg/dL and after treatment it was 67 mg/dL. This is also consistent with the histopathological picture of the pancreas where cell regeneration occurs toward normal. The regeneration of these cells causes an increase in insulin secretion and a decrease in blood glucose levels.

Based on the one way Analysis of Variance (ANOVA) showing a significance value of <0.05, it can be assumed that there is a significant difference in the entire treatment group. The intended significant difference is that there is a significant difference in each test/treatment group in the number of endocrine cells.

## CONCLUSION

The ethanol extract of teak leaves (*Tectona grandis* Linn) has antidiabetic activity which can be seen from the histopathological picture of the pancreatic organs of Wistar strain male rats with type 2 diabetes mellitus as indicated by the repair of islets of Langerhans cells observed from the large number of endocrine cells regenerating in the islets. Langerhans for all treatment groups.

## SUGGESTION

Further research is needed regarding the isolation of metabolite compounds contained in teak leaves, in order to determine the compounds that play the most role in reducing blood

glucose levels and regenerating pancreatic beta cells to optimize type 2 diabetes mellitus therapy.

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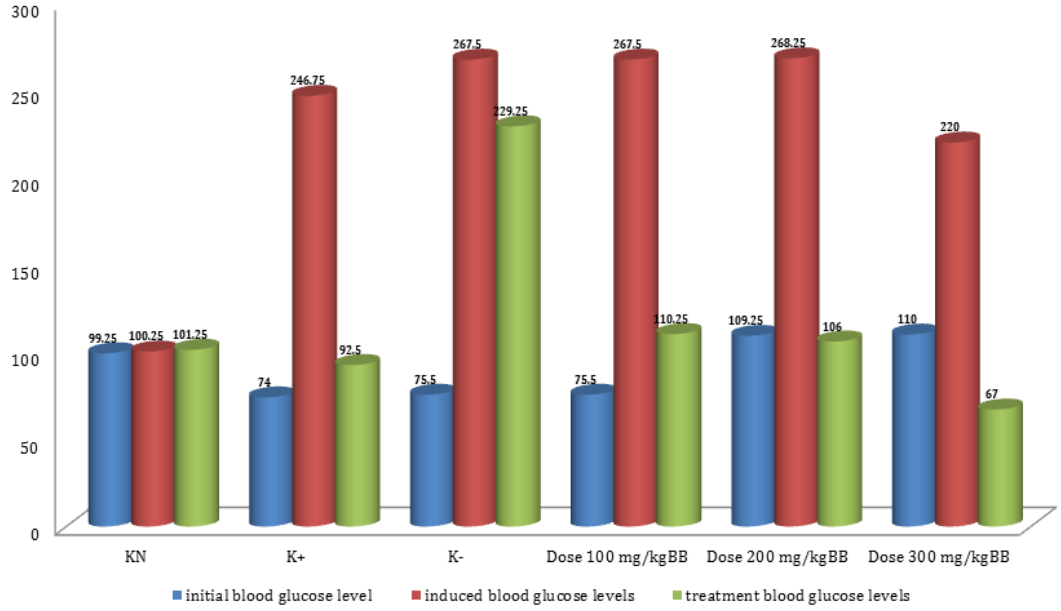


Figure 1. Graph of Mean Blood Glucose Levels for the Test Animal Group

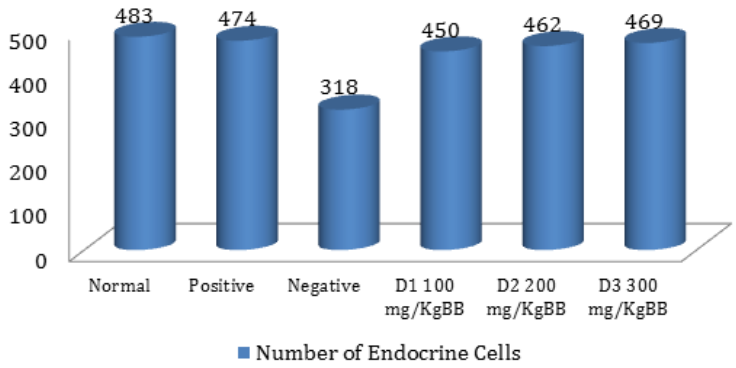


Figure 2. The average number of endocrine cells in all test groups

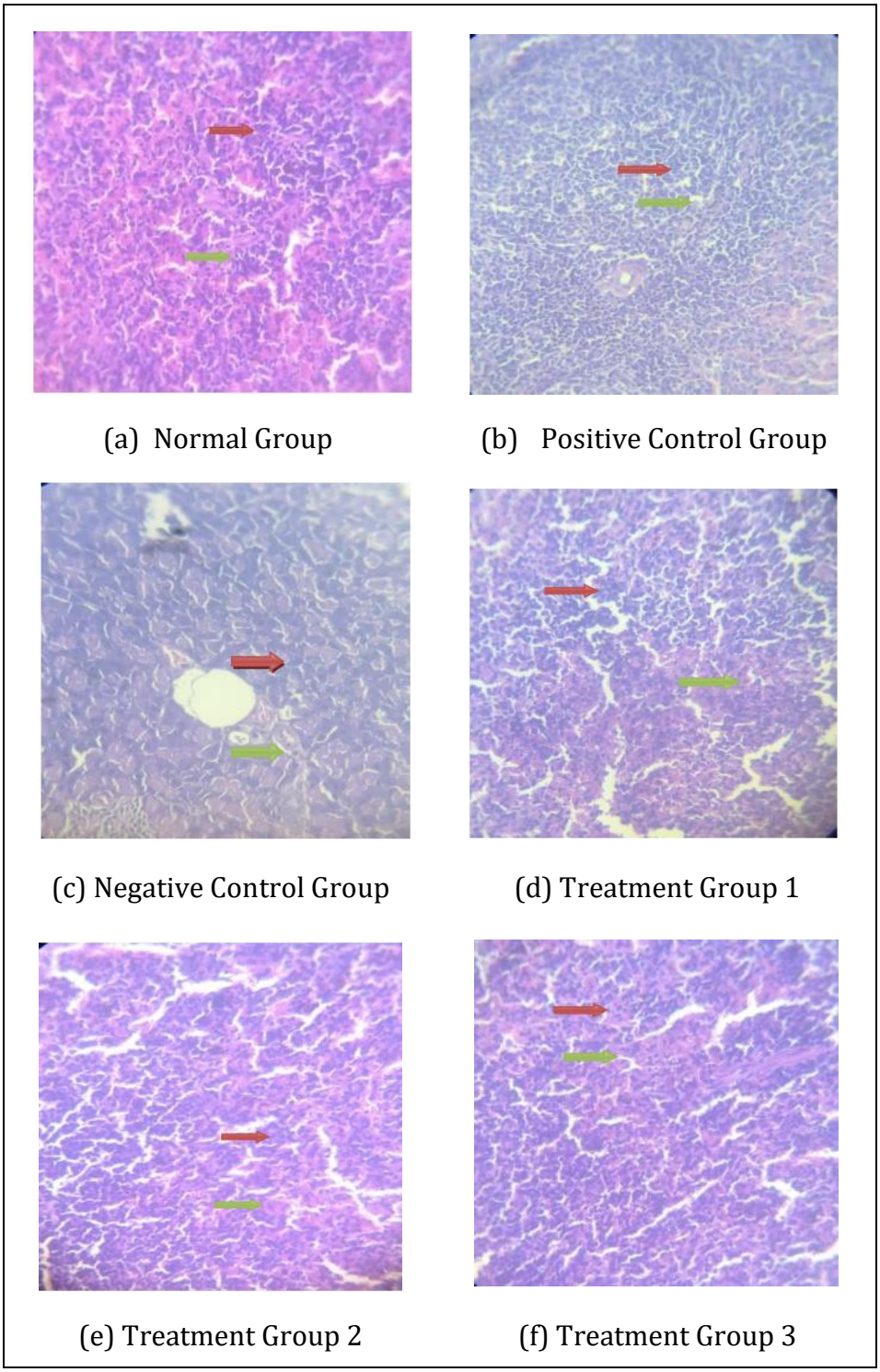


Figure 3. Histopathology of the pancreas of the rats in the test group after being treated at 40× magnification with HE staining. Pancreatic alpha cells (➡) and pancreatic beta cells (➡).