Effectiveness Test of Mangrove Leaf (*Rhizophora Apiculata*) on Decreasing Blood Glucose Levels and Pancreas Histopatology Streptozotocin Induced Male White Rats

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Abstract: Hyperglycemia, a symptom of diabetes mellitus, can lead to oxidative stress, which is indicated by elevated malondialdehyde levels. Mangrove (Rhizophora apiculata) contains secondary metabolites of alkaloids, flavonoids, saponins and tanins, this can lessen how much oxidative stress there is in DM. This study intends to demonstrate the efficacy of mangrove extracts in lowering blood glucose levels and detecting pancreatic damage. The study used 30 male Wistar rats which were divided into 6 groups (group I: normal control, group II: negative and group III: positive control given glibenclamide 0.45 mg) and the test group (trial group). group IV: level 25 mg/kg BW, group V: level 50 mg/kg BW and VI: level 75 mg/kg BW) The DM model was made by streptozotocin induction. Pancreatic damage seen at 700 magnification saw pancreatic β cells as well as the islets of Langerhans' endocrine cells. The results of research on ethanol from mangrove leaves at levels of 75 mg/kg BW are substances that are effective at lowering blood sugar levels, which on average were 105 mg/dL with a hazard value of 1.2. When compared with glibenclamide mangrove extract is not equivalent to glibenclamide but has lowered glucose levels.

Keywords: Blood Glucose; Mangrove Leaf; Diabetes; Male White Rats; Pancreas Histopatology; *Rhizophora apiculate;* Streptozotocin Induced

Introduction

Diabetes mellitus (DM) is a collection of symptoms and warning signs that occur in the body as a result of an increase in blood sugar levels and a steady decrease in insulin secretory function (Park et al., 2021). A collection of metabolic illnesses known as diabetes mellitus (DM) are defined by hyperglycemia, which is brought on by abnormalities in insulin secretion, insulin action, or both (Kamaruddin et al., 2023). Hyperglycemia can induce an inflammatory immune response and oxidative stress (Luc et al., 2019), which can increase the number of free radicals, especially reactive oxygen species (ROS) (Rajlic et al., 2023). Conditions of oxidative stress will trigger oxidative damage to cell components such as DNA, protein, and fat. Free radicals have high reactivity and stability, making them difficult to measure directly.

Hyperglycemia or high blood sugar levels are conditions when blood sugar levels exceed normal limits resulting in insulin deficiency, decreased insulin action, or both (Rodríguez-Rodríguez et al., 2019). Chronic hyperglycemic state for an extended period of time can harm, disrupt, or damage the pancreatic islets of Langerhans, particularly the beta cells. Reactive oxygen species is one type of free radical (ROS). Excess ROS can cause oxidative stress in beta cells. This situation results in pancreatic beta cells being damaged, decreased function, and decreased insulin secretion produced which can cause pancreatic histopathological conditions (Eguchi et al., 2021; Lodato et al., 2023; Semwal et al., 2021).

The results of examining the tissue that is considered to be disturbed are one of the factors in reaching a diagnosis, hence histopathology is crucial in relation to the diagnosis of disease. The condition of

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organs or tissues by observing modifications to morphology, structure, and other signs of injury, infection, or mutation brought on by illness, toxic chemicals, or other mutagenic processes (Carter et al., 2015; Tandi et al., 2020). Pancreas is an important glandular organ in the body that consists of exocrine and endocrine tissues. Pancreatic endocrine glands (Islands of Langerhans) are scattered throughout the pancreas. Histopathological changes in the islets of Langerhans can be qualitative, like necrosis, or quantitative, such a decrease in number or size, atrophy (shrinkage of cells) (Motshakeri et al., 2014).

One of the plants that can be used as an antidiabetic is the mangrove plant (Das et al., 2016; Kathiresan, 2020; Sarkar et al., 2019; Vinoth et al., 2019) because these plants contain chemical compounds such as alkaloids, steroids, triterpenes, phenolic compounds, flavonoids, stilbenes, carotenoids, anthocyanins, anthocyanidins, inositols, saponins, long-chain alcohols, fatty acids, amino acids, benzoquinones, coumarins, and tannins which are thought to have anti-diabetic properties. One of the mangrove species that have some of these ingredients is the *Rhizophora apiculata* mangrove. The chemical constituents of this type include alkaloids, flavonoids, saponins, and tannins. The content of these compounds makes this type of mangrove also have the potential as an antidiabetic (Amir et al., 2019; Sain et al., 2020; Usman et al., 2022)

In connection with the above, experts are interested in researching the impact of further mangrove leaf ethanol concentrate on reducing blood glucose levels and pancreatic tissue damage scores by looking at the histopathological features of male white rats induced by streptozotocin.

Method

Tools and materials

Mesh size 40 sieve, stir bar, a porcelain cup and a maceration vessel, beaker (Pyrex), measuring cup (Pyrex), glucotest strip test (Accu-Chek R), test animal cages, measuring flask (Pyrex), mortar and stamper, water bath (Thermostatic Wather Bath), dropper pipette, tube rack, rotary vaccum evaporator (Hedolph), injectable syringe, oral probe (One Health Med Care) (One Med Health Care), organ tubes, test tubes (Pyrex), analytical balance (Ohaus) and gram scales.

Material

Distilled water, Hydrochloric acid, ammonia, concentrated sulfuric acid, and P-hydrochloric acid, iron (III) chloride, magrove leaf extract, 96% ethanol, ethyl acetate, chloroform, Liebermann-Burchard reagent, methanol, n-hexane, sodium chloride, sodium Carboxymethyle Cellulose, Dragendorff reagent,

magnesium P powder, 0.9% NaCl, Glibenclamide tablets, and streptozotocin.

Making Magrove Ethanol Leaf Extract

Maceration is used to create magrove leaf extract. Magrove leaf powder was weighed up to 1000 grams, placed in two 500-gram-each maceration jars with up to 6 liters (2.5 liters) of 96% ethanol solvent each, closed, and left to stand for three consecutive days while being kept out of the light and sometimes stirred. A thick extract of mangrove leaves was created by filtering the extract using filter paper, collecting the filtrate, and then evaporating it using a rotary evaporator at 40 to 60 degrees Celsius and a water bath with (500).

Suspension Preparation Na CMC 0.5%

As much as 0.5 grams of sodium carboxymethyl cellulose (Na CMC) were used, which was dusted into a mortar with 10 milliliters of warm distilled water, left to stand for 15 minutes, until a translucent mass was created, and then blended thoroughly. Into a volumetric flask of 100 ml was put the CMC Na suspension. With up to 100 ml of pure water, the capacity is adequate.

Preparation of Glibenclamide Suspension 0.45 mg/kg BW

Rats weighing 200 grams are used as a substitute for adult humans, the dose of glibenclamide becomes 0.45 mg/kg BW when 200 grams is multiplied by a conversion ratio of 0.018. The glibenclamide tablet powder was weighed out to be 3.6 mg, then was added to 25 ml of 0.5% Na CMC and agitated until homogenous.

Streptozotocin Induction Solution Preparation (STZ)

Rats were given intraperitoneal injections of streptozotocin that weighed up to 0.32 grams and was dissolved in citrate-buffer saline with a pH of 4.5. (ip). The streptozotocin dosage is 40 mg/kg BW.

Test Animal Treatment

This study was carried out from June to August 2022 at the Faculty of Pharmacy's Physiology and Anatomy Laboratory, College of Pharmacy, Pelita Mas (No 1181/UN 28.1.30/KL/2022). This study employed a modified pretest-posttest randomized controlled group design together with a laboratory experimental methodology. 30 male white rats were used, and they were split into six study groups: normal control, negative control, positive control, and extract dose group at 25 mg/kg BW. The 50 mg/kg BW extract dose group and the 75 mg/kg BW extract dose group.

Analysis of Data

To compare the effects of different therapies on blood glucose levels, blood glucose data were

statistically evaluated using one-way ANOVA analysis at a 95% confidence level (Egi et al., 2006). Blood Streptzotocin-induced male white rats, then Duncan's test was carried out to determine the effective effect of mangrove leaves in reducing blood glucose levels of male white rats. Data processing was carried out using the SPSS 25 software program (Nakanishi et al., 2003).

Result and Discussion

This study used the ethanol extract of mangrove leaves (*Rhizophora apiculata*) by maceration method. The maceration method was chosen because it does not use heating during extraction so as to prevent possible damage to the bioactive compounds present in the sample. The solvent used in the maceration process is 96% ethanol. The reason for using 96% ethanol as a solvent is that ethanol is a polar compound that evaporates easily, so it is good to use as an extraction solvent. Ethanol has a high polarity so it can extract more materials than other types of organic solvents (Jie, 2018).

The purpose of the phytochemical screening test was to identify the kinds of chemicals that were present in the ethanol extract of mangrove leaves (*Rhizophora apiculata*). The ethanol extract of mangrove leaves (*Rhizophora apiculata*) included secondary metabolites, including alkaloids, flavonoids, saponins, and tannins, according to the results of the phytochemical test in Table 1.

Thirty male white rats were used in this study (Rattus norvegicus) as test animals. White rats (Rattus norvegicus) are one of the experimental animals in the laboratory which provides since they are not impacted by the estrous cycle and pregnancy as in female rats, they produce more consistent findings (Gómez-Baena et al., 2023; Salisu et al., 2021). Male white rats are easy to maintain in large quantities so that they support experimental research, one of which is research on anti-diabetic activity (Rahayu et al., 2021).

Table 1. Test results for mangrove leaf extract (Rhizophora apiculata) in terms of phytochemistry)

Chemical content	Reactor	Observation result	Note
Alkaloid Test	Dragendorf LP	Formed brick red color	+
Flavonoid Test	Concentrated HCl and magnesium metal	An orange yellow precipitate was formed	+
Tannin Test	NaCl 10% + FeCl3	Formed a dark blue color	+
Saponin Test	Shake + HCl 2N	Formation of foam / froth	+

Note : (+) : Contains the tested compound class.

The study began by measuring initial blood glucose levels (day 0) as seen in Table 2 before the study using an Accu-check glucometer, the results obtained were 59 mg/dL – 92 mg/dL, indicating that the blood glucose levels were not significantly different among all of the therapy groups. The value of p = 0.630 (P> 0.05) indicates this. demonstrates that all test animals have normal glucose levels before treatment because they are between 50 and 135 mg/dL (Munjiati, 2021; Nurmawati, 2017).

The findings of the one-way ANOVA statistical test on the blood glucose levels on day seven revealed differed significantly in each treatment group with a value (P <0.05), so continued with Duncan's further test. Duncan's additional test findings revealed that the 25 mg/kg BW dose, 50 mg/kg BW dose, and 75 mg/kg BW group, the positive control, and negative control groups were significantly different from the normal control, this showed that all test animals were in all groups except the normal control group was sick because of the effects of streptozotocin administration. Giving streptozotocin can trigger an increase in excess free radical production and cause oxidative stress which has a high role in pancreatic β-cell damage, so the rat's blood glucose level increases (Li et al., 2022; Yousef et al., 2021).

Following the one-way ANOVA statistical test, which revealed a significant difference in blood glucose levels on day 14 (P 0.05), Duncan's test was used to determine the differences between all treatment groups. The 25 mg/kg BW dose group and the positive group significantly differed from the normal group, the negative group, the 50 mg/kg BW group, and the 75 mg/kg BW group, according to the results of Duncan's test. The 25 mg/kg BW dose had a decreasing effect on blood glucose levels there's close to the positive control but not yet close to the normal group, as evidenced by the fact that there was no appreciable difference between the 25 mg/kg BW dose group and the positive group. It differed noticeably from the positive control dose of 25 mg/kg BW at doses of 50 mg/kg BW and 75 mg/kg BW.

On day 21, the one-way ANOVA statistical test revealed a significant difference in blood glucose levels across all treatment groups (P 0.05), so the Duncan test was performed. According to the results of Duncan's test, the positive group did not differ substantially from the 25 mg/kg BW treated groups or the 50 mg/kg BW treatment group, indicating that both doses had an equal impact on lowering blood glucose levels. with the favourable grouping. The 25 mg/kg BW group, the negative group, the positive group, the 75 mg/kg BW group, and the normal group were all significantly different from each other. This indicates that at a dose of 75 mg/kg BW, it has a lowering effect on blood glucose

levels that was better than the positive group but did not achieve normal control blood glucose levels.

The Duncan test was used in place of the one-way ANOVA statistical test on the 28th day since the results of blood glucose levels were substantially different from the values (P 0.05) for all treatment groups. Duncan's test findings showed that the positive group's blood glucose levels were not substantially different from those of the

25 mg/kg BW group, indicating that the 25 mg/kg BW medication had a similar decreasing effect on blood glucose levels as the positive group. The 50 mg/kg dose group and the 75 mg/kg BW dose group had a better effect on reducing blood glucose levels than the positive group, which differed considerably from them. However, they did not reach a decrease in normal group glucose levels, but had entered the normal range of rats.

Table 2. Outcomes of Mean Levels of Blood Glucose

| Days to-	Normal Control	Negative Control	Positive Control	Dosage 25 mg/kg body weight	Dosage of 50 mg/kg body weight	Dosage 75 mg/kgBB	P
0	81±8.41	77±4.38	78±4.30	76±3.36	74±4.00	76±10.00	0.630
7	86±7.05	244±22.61	246±16.01	245±15.67	247±14.76	245±17.47	0.00
14	84±6.98	247±18.43	215±12.02	218±10.23	197±10.30	186±11.57	0.00
21	85±4.95	238±10.97	177±10.21	185±11.68	169±10.83	153±8.97	0.00
28	86±3.21	249±9.07	136±5.97	139±12.29	121±8.53	105±2.74	0.00

Note : P value < 0.05 = Significantly different and P value > 0.05 = Not significantly different

The results of histopathological observations of the pancreas of male white rats induced by streptozotocin and administration adsorption of ethanol of mangrove leaves (*Rhizophora apiculata*) doses of 25, 50 and 75 mg/kg BW were carried out using an Olympus Cx-21 microscope with 400x magnification. From the pancreatic damage scoring data in Table 2, it was obtained that the average pancreatic damage score of male white rats was normal to control 0.4, negative control 3, positive control 1.6, Treatment group at a dose of 75 mg/kg BW 2.8, dose treatment group at 25 mg/kg BW 2.5, and dose treatment group at 50 mg/kg BW 1.2. In Table 3 it can be seen that the negative control experienced the highest level of damage among all treatments.

Figure 2. it can be seen that the results of scoring 1 are obtained: the size of the islets of Langhans is slightly smaller, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and basophilic round nucleus (blue circle). In the results of scoring 1 are obtained: a picture of the islets of Langhans with normal size is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal with eosinophilic cytoplasm and round nuclei that are basophilic (blue circle).

The results of scoring 0: a description of the Langhas islands with reduced size and irregular shapes, and the endocrine cells in the Langhans islands are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and

round nuclei. basophilic (green circle). In figure A4, the result of scoring is 0: a picture of Langhas islands with normal size but somewhat irregular shape is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei. basophilic (green circle). The result of scoring 0 is obtained: a picture of Langhas islands with normal size is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (green circle).
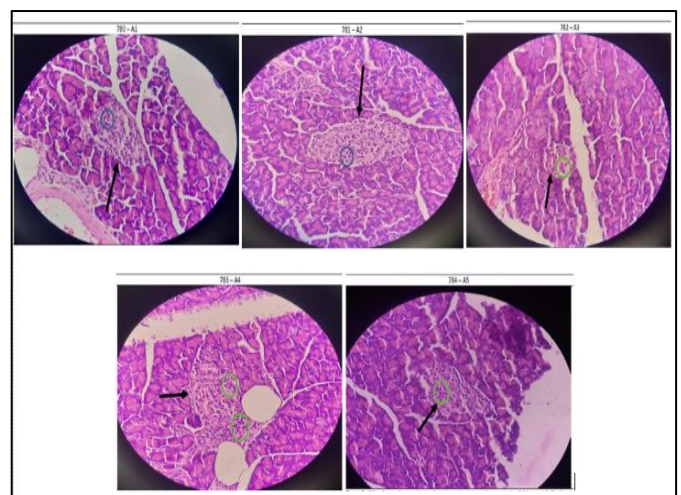
Figure 2. Obtained description of the island of langhas in the normal group, with an average damage score of 0, with normal size at langhas

**Table 3.** Results of Mean Pancreatic Damage Score

Treatment Group	Damage Score					Average	SD
	1	2	3	4	5		
Normal Control	1	1	0	0	0	0.4	0.548
Negative Control	4	3	3	2	-	3	0.816
Positive Control	2	1	0	4	1	1.6	1.517
Dosage 25 mg/kgBB	2	3	3	4	1	2.6	1.140
Dosage 50 mg/kgBB	2	1	1	1	1	1.2	0.447
Dosage 75 mg/kgBB	1	3	3	4	3	2.8	1.095
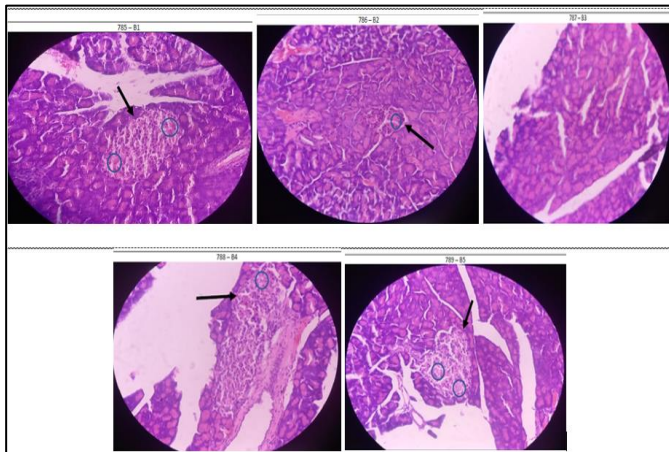
Figure 3. Langerhans island description was obtained in the negatif group, with an average damage score of 3, with normal size at Langerhans

Figure 3, it can be the results of scoring 4 are obtained: a picture of Langhans islands is obtained with a slightly smaller size but a regular shape (arrows), and the endocrine cells in the islands of Langhans experience degeneration and necrosis, namely the morphology is polygonal with cytoplasm pale and the core condenses, shrinks and disappears (blue circle).
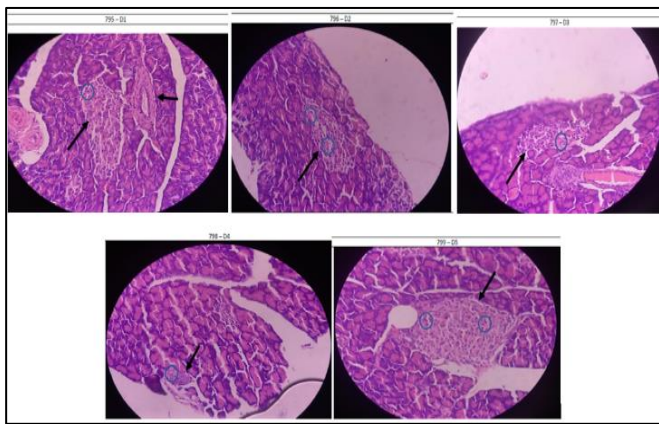
The result of scoring 3 is obtained: an overview of Langhans islands with reduced size but regular shape and some are irregular (arrows), and the endocrine cells in Langhans islands are experiencing degeneration and necrosis, namely the morphology is polygonal in shape with pale cytoplasm and the condensed nucleus partially shrinks and disappears (blue circle).
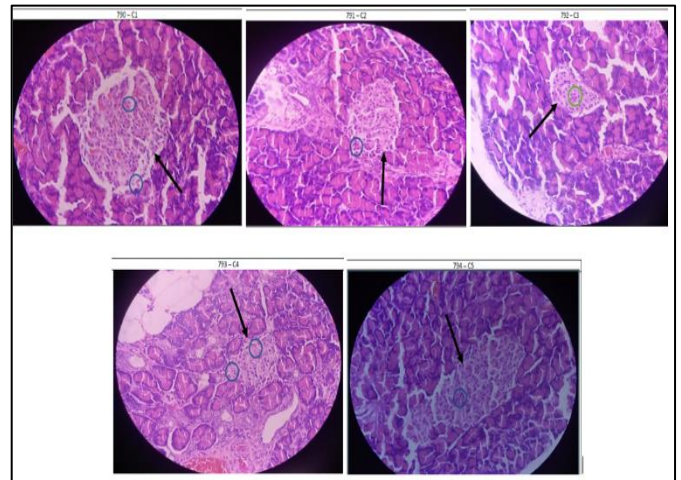
Figure 4. Langerhans islands were found in the positive group. with normal Langerhans size with a slightly irregular shape, and the endocrine cells in the Langhans islands are still within normal limits. with an average damage of 1.6

The results are inconclusive: there is no pancreatic islet. The result of scoring 3 is obtained: a picture of the islets of Langhans with normal size but irregular shape (arrows), and the endocrine cells in the islets of Langhans experience degeneration and necrosis, namely the morphology is polygonal in shape with the cytoplasm blanching and the nucleus condensing, some shrinking and disappear (blue circle). The result of scoring is 2: a slightly smaller size of the islets of Langhans is obtained, and many of the endocrine cells in the islets of Langhans are degenerate, characterized by unclear cell boundaries and pale nuclei (blue circle).

Figure 4, it can be seen that the results are obtained Score 2: a slightly smaller size of the islets of Langhans is obtained, and many endocrine cells in the islets of Langhans are degenerate, characterized by unclear cell boundaries and pale nuclei (blue circles). Spots of bleeding are also visible, the results of scoring 1: the normal size of the islets of Langhans with regular shapes but there are also irregular ones, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and a round, basophilic nucleus (blue circle).

Figure 5. Obtained description of the Langhans islands in the 25 mg dose group with slightly smaller Langhans size and somewhat irregular shape with an average damage score of 2.6

The results of the pancreas are obtained. Score 0: the Langhas islands are slightly smaller in size and there is also an irregular shape, and the endocrine cells in the Langhans islands are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and basophilic round nucleus (green circle). The result of scoring 4 is obtained: an overview of Langhans islands with slightly smaller size and somewhat irregular shape (arrows), and the endocrine cells in the Langhans islands experience degeneration and necrosis, namely the morphology is polygonal in shape with pale cytoplasm and condensed nucleus. shrink and disappear (blue circle). In Figure C5, the results of scoring 1: the normal size of the islets of Langhans with a slightly irregular shape, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei. basophilic (blue circle).

Figure 5, the results are obtained Score 2: obtained an image of the islets of Langhans with a slightly smaller size with a somewhat irregular shape and many endocrine cells in the islets of Langhans are experiencing degeneration, marked by unclear cell boundaries and pale nuclei (blue circle. The results of scoring 3: an overview of the islands of Langhans is obtained with a slightly smaller size and somewhat irregular shape (arrows), and the endocrine cells in the islands of Langhans experience degeneration and necrosis, namely the morphology is polygonal in shape with the cytoplasm turning pale and the nucleus condensed, some shrinking and disappearing (blue circle).

The results of scoring 3: an overview of the islands of Langhans is obtained with a slightly smaller size and somewhat irregular shape (arrows), and the endocrine cells in the islands of Langhans experience degeneration and necrosis, namely the morphology is polygonal in shape with the cytoplasm turning pale and the nucleus

condensed, some shrinking and disappearing (blue circle). The results of scoring 4: a reduced size and somewhat irregular shape of the islets of Langhans is obtained (arrows), and the endocrine cells in the islets of Langhans undergo degeneration and necrosis, namely the morphology is polygonal in shape with pale cytoplasm and the nucleus condenses, shrinks and disappears. (blue circle). The results of scoring 1: an overview of the islets of Langhans with normal size and somewhat irregular shape is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue circles).
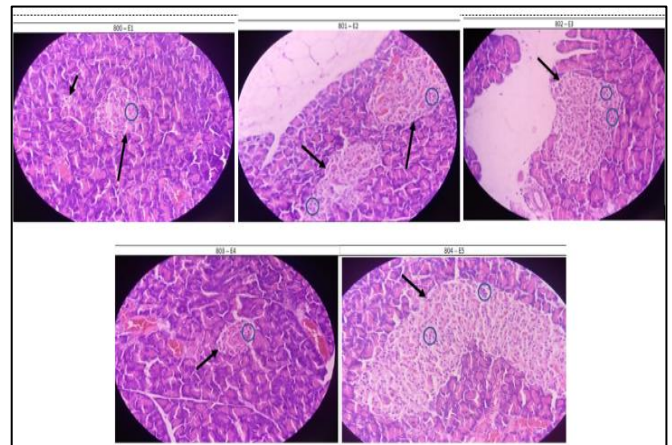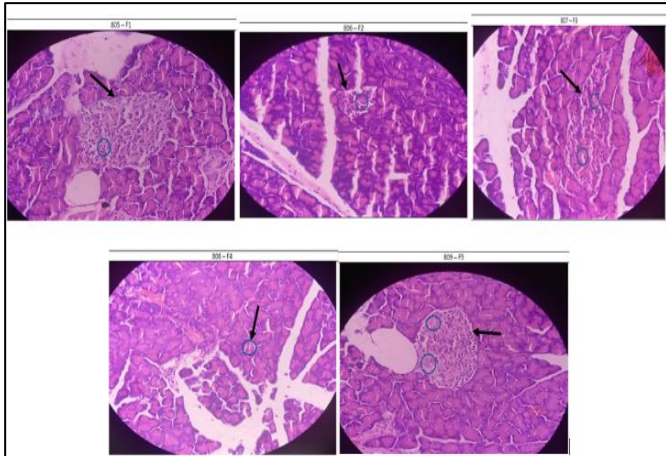

Figure 6. in the 50 mg dose group, the islets of Langhans with normal size and somewhat irregular shape with an average total damage of 1.2

Figure 6, that the results are obtained Score 2: obtained a picture of the islands of Langhans with a slightly smaller size, and there are also irregular ones and many endocrine cells in the islets of Langhans are degenerating, marked by unclear cell boundaries and pale nuclei (blue circle). The results of scoring 1: an overview of the islets of Langhans with normal size and somewhat irregular shape is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue circles).

The results of scoring 1: the normal size of the islets of Langhans is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue circles). In figure E4, the results of scoring 1: a reduced size of the islets of Langhans is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue

circles). In figure E5, the results of scoring 1: an overview of the islets of Langhans with normal size and somewhat irregular shape is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue circles).

Figure 7. In the 75 mg dose group, Langhans islands with very small sizes and irregular shapes with a total damage of 2.8

Figure 7. it can be seen the results of scoring 1: an overview of the islets of Langhans with normal size and regular shape is obtained, and the endocrine cells in the islets of Langhans are still within normal limits (arrows), that is, the morphology is polygonal in shape with eosinophilic cytoplasm and round nuclei that are basophilic (blue circles). The results of scoring 3: : obtained a description of the islands of Langhans with reduced size and irregular shape (arrows), and the endocrine cells in the islands of Langhans experienced degeneration and necrosis, namely the morphology of the polygonal shape with the cytoplasm blanching and the nucleus condensed, some of which decreased and disappeared (blue circle), the results of scoring 3: an overview of the islands of Langhans is obtained with a slightly smaller size and somewhat irregular shape (arrows), and the endocrine cells in the islands of Langhans experience degeneration and necrosis, namely the morphology is polygonal in shape with the cytoplasm turning pale and the nucleus condensed, some shrinking and disappearing (blue circle).

The results of scoring 4: obtained a description of the islets of Langhans with a very small size and irregular shape (arrows), and the endocrine cells in the islets of Langhans experience degeneration and necrosis, that is, the morphology is polygonal in shape with pale cytoplasm and the nucleus condenses, shrinks and disappears (blue circle), the results of scoring 3: the appearance of the islets of Langhans is obtained with a slightly smaller size but a regular shape (arrows), and

the endocrine cells in the islets of Langhans experience degeneration and necrosis, namely the morphology is polygonal in shape with the cytoplasm is pale and the nucleus is condensed, some are smaller and disappear (blue circle).

Based on the results of pancreatic tissue damage scores in the 6 sample groups, it was found that the normal control group had a damage score of 0.4 and can be seen in the picture where there is no cell damage in the islets of Langerhans or exocrine. This was because Streptozotocin was not administered to the usual controls which could damage the pancreas and wase only suspended with Na-CMC which functioned as a solution stabilizer and had no effect on pancreatic tissue damage. The negative control group had the highest damage score with average damage (3) and it can be seen in the picture that there was moderate damage where cells in the islets of Langerhans were 51% -75% necrotic. This is due to the administration of streptozotocin which can damage pancreatic tissue and is only suspended by Na-CMC which functions to stabilize the solution and has no impact on pancreatic tissue damage. The positive control group has a damage score (1.6). This looks better than the negative control due to the therapeutic effect of the drug glibenclamide. The statistical results of Kruskal-Wallis histopathological scoring showed a value of $p = 0.010$, namely ($p < 0.05$) for pancreatic histopathology scoring which showed that there was a significant difference between the 3 treatment groups given mangrove leaf ethanol extract (*Rhizophora apiculata*) dose of 25 mg/kg BW, dose 50 mg/kg BW and a dose of 75 mg/kg BW with normal control and negative control and positive control. So theMann-Whiteyy test was carried out to see significant differences between treatment groups.

The Mann-Withney test's findings analysis in table 3 show that there was a significant difference in the histopathological scoring of the pancreas of each treatment group, namely the treatment groupwas givenn mangrove leaf extract (*Rhizophora apiculata*) There were significant differences between the levels of 25 mg/kg BW, 50 mg/kg BW, and 75 mg/kg BW (p0.05) from the normal control group which indicated that the level of improvement had not reached the normal control. This is because doses of 25 mg/kg BW, doses of 50 mg/kg BW and doses of 75 mg/kg BW have low active substances so the therapeutic effect is not maximized. The 50 mg/kg BW and 75 mg/kg BW levels were substantially different from the negative controls in the 25 mg/kg BW treatment group.

Conclusion

Alkaloids, flavonoids, saponins, and tannins belong to the secondary metabolites included in the ethanol

extract of mangrove (*Rhizophora apiculata*) leaf material. If streptozotocin was used to induce blood glucose levels in male white rats (Rattus novergicus), mangrove leaf extract (*Rhizophora apiculata*) levels of 25 mg/kg BW, 50 mg/kg BW, and 75 mg/kg BW had a negative effect on blood glucose levels. A dose of 75 mg/kg BW of the mangrove extract (*Rhizophora apiculata*) is most successful in lowering blood glucose levels in male white rats (Rattus novergicus). Male white rats given ethanol formulations of mangrove leaves (*Rhizophora apiculata*) in doses of 25 mg/kg BW, 50 mg/kg BW, and 75 mg/kg BW showed a reduction in the pancreatic tissue damage score (*Rattus norvegicus*)

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