The Effect Of Giving Sambiloto Leaf Extract (*Andrographis Paniculatu*) On Pancreatic Function And Pancreatic Histopathology In White Male Wistar Rats With Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels caused by impaired insulin secretion from pancreatic β cells.

This study aims to evaluate the effect of *Andrographis paniculata* leaf extract on pancreatic function and histopathological features of the pancreas of male Wistar white rats with diabetes mellitus. This study is an experimental study using a pre-post test control group design. The research sample of 24 Wistar rats was divided into 6 groups.

The results of observations conducted on all groups showed changes in amylase and lipase levels in the treatment group. The results of the normality test of amylase and lipase levels were said to be normally distributed because the p values were > 0.05, namely 0.100 and 0.436. Based on the differences in the average serum amylase levels, the researchers concluded that the treatment group given *Andrographis paniculata* leaf extract (*Andrographis paniculata*). dose of 600mg/KgBW had the highest decrease in serum amylase and lipase levels. Histopathology of pancreatic tissue showed that the treatment group given *Andrographis paniculata* leaf extract (*Andrographis paniculata*) dose of 600mg/KgBW) category score 1 because the number of degenerative cells with a degree of damage (<1-25%), the number of necrotic cells <25% and the number of inflammatory cells <10 in the entire pancreatic interstitial space experienced the most significant improvement. Sambiloto leaf extract (*Andrographis paniculata*) contains secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids which help repair pancreatic cells damaged by diabetes mellitus.

Keywords: *Pancreas, Sambiloto Leaves, Diabetes Mellitus*

INTRODUCTION

Alloxan is a compound that has diabetogenic and toxic properties, especially to pancreatic beta cells and when given to experimental animals, namely mice, it will cause the mice to become diabetic. The mechanism of action of alloxan that causes damage to pancreatic beta cells is to enter the pancreatic beta cells first and then be absorbed by the pancreatic beta cells. The ability of alloxan to absorb substances by pancreatic beta cells will determine the level of toxicity and diabetogenic properties. After absorption of the substance, pancreatic beta cells will be damaged through several processes simultaneously, namely through oxidation of sulfhydryl groups and the formation of free radicals (Prameswari and Widjanarko, 2014). One of the typical and frequently found pathological features in patients and animal models of Diabetes Mellitus is changes in the histological structure of the pancreas.

The pancreas is closely related to diabetes. Diabetes is a disorder of carbohydrate metabolism, characterized by the body's inability to produce enough insulin, or respond appropriately to it. In addition, dysregulated glucagon secretion by alpha cells is a major feature of both type 1 and type 2 diabetes. Therefore, the importance of the endocrine pancreas lies in the fact that it secretes two major hormones, glucagon and insulin, which play a central role in regulating energy metabolism (Chioma, 2021).

Diabetes can be treated by taking antidiabetic drugs. However, the available antidiabetic drugs are expensive, ineffective, and have serious side effects. Biguanides, sulfonylureas, and thiazolidinediones, which are often used as oral antidiabetic drugs, are also not recommended for diabetic patients with kidney, liver, or heart failure. Thus, the use of bioactive compounds derived from plants that are effective, easily accessible, safe, and cheaper is an option.

Nowadays, people prefer alternative medicine using herbal medicine from plants or plant extracts to treat diseases. The use of herbal medicine is one of the effective and relatively safe treatment options, can be used to treat various diseases and is also often used to prevent disease and increase the body's resistance to a disease.

Sambiloto or *Andrographis paniculata*, is a traditional medicine known to have antioxidant effects that lower blood glucose levels. It is also known as an antibacterial, anti-inflammatory, immune system reaction, analgesic, antipyretic, eliminates internal heat, and detoxification. Previous studies have shown that ethanol extract of sambiloto herb lowers blood glucose in streptozotocin-induced diabetic rats. This is due to the antioxidant activity contained in it, namely by capturing or neutralizing free radicals associated with phenolic OH groups. Thus, flavonoid compounds can help repair damaged tissue conditions (Hossain MS, 2014).

Previous studies have reported the pharmacological properties of *Andrographis paniculata*, including antiplatelet aggregation, vasodilation, antidiabetic, and antioxidant activities. It was recently reported that bitter leaf extract inhibited carbohydrate digestive enzymes such as

intestinal α-glucosidase and pancreatic α-amylase in vitro. To improve bioaccessibility, microencapsulation of bitter leaf extract (*Andrographis paniculata*) increased the ability to inhibit pancreatic α-amylase and antioxidant activity after simulated gastrointestinal digestion (Lau SHA, 2019). Research on *Andrographis paniculata* leaf extract on pancreatic regeneration has been conducted previously. However, evaluation was conducted in this study to determine the antidiabetic and antihyperlipidemic effects on diabetic rats given alloxan and to see the differences in pancreatic histopathology before and after being given *Andrographis paniculata* leaf extract. According to (Paramitha MD, 2016), *Andrographis paniculata* leaf extract can stimulate the regeneration of damaged pancreatic beta cells.

Based on the above phenomenon, researchers are interested in analyzing the effect of giving sambiloto leaf extract (*Andrographis paniculata*) on pancreatic function and histopathological features of the pancreas of male Wistar white rats with diabetes mellitus. Although Andrographis paniculata has been shown to show antidiabetic effects in previous studies, its specific impact on pancreatic histopathology, especially in the alloxan-induced diabetes model, has not been explored. This study aims to fill this gap. This study is also important to study further considering that herbal medicine is believed to have fewer side effects and is more affordable compared to drugs (Widayati, 2017).

LITERATURE REVIEW

The human pancreas is a multifunctional organ. The exocrine compartment consists of acinar cells that produce and secrete digestive enzymes into the pancreatic duct system which then drains into the intestine. The endocrine compartment synthesizes and secretes glucose homeostasis hormones that are secreted into the circulation in response to blood glucose. The exocrine compartment comprises approximately 98% of the mass of the pancreas, with the endocrine comprising only 2%. The endocrine cells of the pancreas are grouped into discrete "islets" known as islets of Langerhan, which are scattered throughout the pancreas (Zheng, 2018) Pancreatic ß cells secrete insulin and are found in the islets of Langerhans. These islets are specialized clusters of several hundred to several thousand endocrine cells that are anatomically and functionally distinct from the exocrine tissue of the pancreas, their primary function being to secrete pancreatic enzymes into the duodenum.

The pancreas is divided into the head, body, and tail. The pancreatic parenchyma has a lobular structure and contains numerous secretory vesicles, which make up 80–85% of the organ's mass. The excretory ducts are very important for the functioning of the pancreas. Each bubble has an outlet cord that connects to the others and connects to the main duct. The main duct is the pancreatic duct, which begins in the tail of the pancreas, runs along the entire length of the organ, and finally enters the duodenum through the greater papilla (Vatera). In addition, there

is also an accessory pancreatic duct, which in about 70% of people is connected to the pancreatic duct, and finally, substances secreted by the pancreas, transported through both ducts, go to the so-called greater duodenal papilla. In the histological structure of the pancreas, two basic elements are distinguished: pancreatic islets (or islets of Langerhans - their number can even reach 2 million and they produce pancreatic hormones) and secretory cells, which are the rest of the organ and are responsible for the secretion of pancreatic juice and pancreatic enzymes (Karpinska, 2022.)

The pancreas is a glandular organ that affects the function of the entire body. Pancreatic insufficiency that occurs is the inability of the pancreas to biosynthesize and/or secrete digestive enzymes in sufficient quantities to digest and absorb food components in the intestine. Insufficiency usually occurs due to pancreatic damage, which can be caused by various clinical conditions, such as recurrent acute pancreatitis, chronic pancreatitis, diabetes, autoimmune diseases, after pancreatectomy surgery. Pancreatic insufficiency is usually manifested by malabsorption, malnutrition, vitamin deficiencies, and weight loss (or failure to gain weight in children (Karpinska, 2022.)

Diabetes mellitus or diabetes is a chronic disease that can be suffered throughout life (Sihotang, 2017). Diabetes mellitus (DM) is caused by metabolic disorders that occur in the pancreas which are characterized by increased blood sugar or often referred to as hyperglycemia caused by decreased insulin from the pancreas. DM can cause various complications, both macrovascular and microvascular. DM can cause cardiovascular disorders which are quite serious diseases if not treated immediately so that they can increase hypertension and heart infarction (Sharma, 2021).

Diabetes is often caused by genetic factors and a person's behavior or lifestyle. In addition, social environmental factors and the use of health services also cause diabetes and its complications. Diabetes can affect various organ systems in the human body over a period, which are called complications. Diabetes complications can be divided into microvascular and macrovascular blood vessels. Microvascular complications include damage to the nervous system (neuropathy), damage to the kidney system (nephropathy) and eye damage (retinopathies) (Rachdaoui, 2020).

Sambiloto is a medicinal plant up to 90 cm tall. It was originally thought to originate from Tropical Asia and spread from India south to Siam, east to the Malay Peninsula, before being found in Java.This plant has a wide range of pharmacological activities and most of its many activities and health benefits have been attributed to its phytochemical constituents. Phytochemical analysis shows that this plant is rich in potassium, calcium, phosphorus, iron, vitamins A and D, essential amino acids, carbohydrates, and powerful antioxidant compounds such as ß-carotene, vitamin C, and flavonoids (Rani, 2018).

Andrographolide, an active compound in sambiloto leaves that is useful as a medicine, is the main component of its active compound. In addition, sambiloto leaves contain saponins, flavonoids, phenols, alkaloids, and tannins. One of the chemical compounds found in sambiloto leaves is flavonoids, which function as growth hormones and enzyme inhibitors by forming complexes with proteins (Rani, 2018). Flavonoid components found in sambiloto leaves (*Andrographis paniculata*) could prevent damage to beta cells in the pancreas that are damaged by diabetes mellitus. Andrographolide, the main bioactive component of sambiloto leaves consisting of diterpenoids and flavonoids, is a very bitter diterpenoid that can increase appetite because it can increase salivary gland secretion, increase antibody production, and improve the immune system (Singh, 2020).

So, the researcher's hypothesis is that there is an effect of *Andrographis paniculata* leaf extract on pancreatic function in male Wistar strain white rats (Rattus norvegicus) with diabetes mellitus.

METHODS

This research is true experimental research, with a post test only control group design. This is a type of research that only looks at the control group and its treatment after being given the action. pThe research was conducted from May to August 2024 at the Department of Pharmaceutical Pharmacology, Faculty of Medicine, University of North Sumatra and the Anatomical Pathology Laboratory, University of North Sumatra. Ethical Clearance will be submitted to the Health Research Ethics Commission (KPEK) of Prima Indonesia University and is still in process.

Based on the sample calculation above, each group must have at least 4 test animals, so a total of 24 were used in this study. The animals tested were randomly assigned to 6 test groups. The groups in this study were 1) standard group, rats were not induced by alloxan and were not given sambiloto leaf extract. 2) negative control group, rats were only induced by alloxan, 3) positive control group, rats were induced by alloxan and given metmorphine, 4) treatment group-1, rats with diabetes mellitus and given 200mg/kgBW, 5) Treatment group-2 mice that had diabetes mellitus and were given 400mg/kgBWsambiloto leaf extract, 6) Treatment group-3, mice with diabetes mellitus and given600 mg/kgBWsambiloto leaf extract. The conceptual framework are shown in Figure 1.

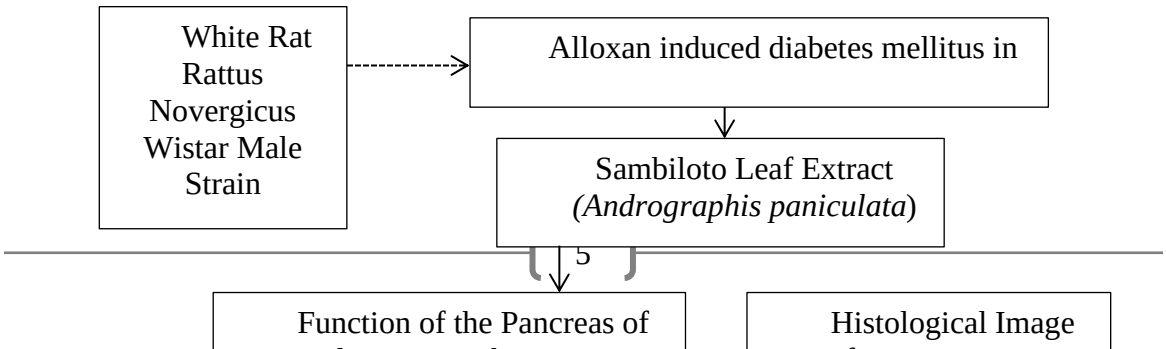


Figure 1. Conceptual Framework

The variables in this study consist of independent variables, dependent variables and precondition variables. The independent variable is the provision of leaves. Sambiloto leaves (*Andrographis paniculatu*), the dependent variable is the improvement of pancreatic function and its histopathological picture, and the preconditioning variable is alloxan-induced rats. The tools used to make ethanol extract of sambiloto leaves include a set of maceration tools, filters, rotary evaporators, evaporating cups, water baths. Tools for in vitro tests include 10 ml, 25 ml, 100 ml measuring flasks, test tubes, test tube racks, 1000µL BioHit micropipettes, measuring pipettes, spatulas, vials, incubators, pH meters, cuvettes, centrifuges, centrifuge tubes, UV-Vis spectrophotometers, beaker glasses, The materials used are simplicia of sambiloto leaf extract (*Andrographis paniculatu*). The chemicals used include trichloroacetic acid (TCA), Ethanol pa (Brataco), Aquades.

The process of making bitter leaf extract (*Andrographis paniculata*) begins with fresh ingredients in the form of bitter leaves that have been selected, washed and dried. The dried herbal ingredients can be stored in tightly closed plastic bags for further use. Herbal ingredients can be processed by maceration using an appropriate solvent. To extract bitter leaves, 96% alcohol solvent is used in the maceration process. The bitter leaves are taken from the same location and garden, at the age of 3 years, with the same branch order, and at the same time. Fresh bitter leaves are cooked for two days at a temperature of 30-35°C, and then crushed using a blender to obtain 100 grams of bitter leaf powder. After mixing, the mixture is filtered. Using the same method, the dregs are macerated with 96% ethanol. This is done until a clear macerate is produced with a digital shaker at a speed of 50 rpm. For two hours, the liquid extract is evaporated by a rotational evaporator.The research procedure begins withthe process of adapting to a new environment. Mice were given food and drink ad libitum according to their standard needs. Male white mice weighing 200 to 300 grams were adapted to the environment for one week, then given a dose of alloxan to make the mice hyperglycemic, namely 150 mg / kgBW intraperitoneally, if the weight of the mouse is 200-300 grams, then the alloxan given is 30 grams, alloxan monohydrate powder was weighed as

much as 1.2 grams then dissolved with sterile injection aquades up to 100 mL. Three days after being induced by alloxan, blood glucose levels were measured. The blood sugar levels of the mice were still in the normal range, namely 70-140 mg / dL and were said to have diabetes mellitus more than 150 mg / dL (Akbarzadeh, 2007). The test animals were divided into six groups, each with four mice, after they passed the acclimation period and were induced by alloxan and the mice experienced diabetes mellitus. Each mouse was labeled on its tail with a non-wet marker. Mice in the control group were only given alloxan. In other groups, mice were given different doses of *Andrographis paniculata* leaf extract. The administration of *Andrographis Paniculata* leaf extract was done orally using a gastric tube. After two weeks, the white mice or experimental animals were sacrificed to observe their pancreas.

Parameters for pancreatic function examination are amylase and lipase enzymes. Amylase works by hydrolyzing carbohydrates and forming simple sugars, while lipase works by hydrolyzing fats to form fatty acids. Amylase and lipase are enzymes secreted by the exocrine part of the pancreas. Amylase and lipase levels are used as biochemical markers of pancreatic dysfunction.

The results obtained from histopathological observations through microscopic examination were collected and then scored. Analysis was carried out to identify the changes found, and then presented descriptively. Furthermore, the research data were analyzed using the Statistical Package for the Social Sciences (SPSS) 25.0 for Windows. To assess the normality of the data, the Kolmogorov-Smirnov test was used ($p > 0.05$). In addition, the significance between the trial groups was tested by One Way ANOVA or one-way analysis of variance at a 95% confidence level. Post Hoc tests or follow-up tests were carried out using the LSD method. In this study, phytochemical screening was also carried out with the aim of seeing the content of compounds that can affect pancreatic function in male Wistar white rats (*Rattus norvegicus*) with diabetes mellitus.

RESULTS

Results Description Overview

Alloxan has been proven to cause diabetes mellitus by damaging pancreatic β cells so that the pancreas cannot produce enough insulin. The dose of Alloxan given to each experimental mouse from P1, P2 and P3 was given a dose of 100 mg/kgBW. Alloxan was made by adding injection aquadest because later the diabetogenic substance would be injected intraperitoneally. The weight of the mice used in the study was 200gr to 300gr, below is an example of calculating the dose of alloxan, if the weight of the mouse is 300g then the dose per mouse is 300 g = 0.3 kg, then 100 mg/kgBW X 0.3kg = 30 mg (per mouse) in P1, P2 and P3 were given alloxan for seven days intraperitoneally and sambiloto leaf extract was given

orally. Mice were given alloxan 100 mg/kgBW per mouse peritoneally on day 1 to day 7. Then on day 14, sambiloto leaf extract was given at a dose of 200 mg/kgBW, 400 mg/kgBW and 600 mg/kgBW.

From the results of the average body weight of the mice, the results showed that the body weight of the mice increased after 14 days of Alloxan induction. The group that experienced the most drastic increase was the control group (K) with an average of 303.7 gr. This shows a reaction to increased body weight in mice that have experienced diabetes mellitus. Then after being given the treatment of extract *Andrographis paniculata* leaves are seen in groupscontrol (K) experienced an average increase in body weight with a difference of 20.5 grams, while the K-, K+, P1, P2, and P3 groups experienced a decrease in body weight.

Table 1. Average Blood Glucose Levels (KGD)mg/dLMice Before and After Alloxan Induction and Given Sambiloto Leaf Extract Treatment

Group	**KGDBeginning (H0)**	**KGD (mg/dL) AfterAlloxan Induced(H7)**	**KGD (mg/dL) After being given extract treatment (H14)**	**KGD Difference (afteralloxan-treated induction)**
Control	105.75	110	112.5	+ 2.5
Negative control (K-)	87.5	268.75	283	+14.25
Positive control (K+)	93.25	330.75	197.75	-133
Treatment 1 (P1)	98.25	326.75	163.75	- 163
Treatment 2 (P2)	114.75	323.75	141.25	-182
Treatment 3 (P3)	98	300.25	115.75	-184.5

The average blood glucose levels (KG) mg/dL mice before and after alloxan induction and given sambiloto leaf extract treatment are shown in Table 1. From the results of the average blood glucose levels that increased throughout the group, it can be concluded that the control group, negative control group, positive control group, treatments 1, 2 and 3 experienced diabetes mellitus because they had blood sugar levels ≥ 200 mg/dL.This shows a reaction to increased glucose levels in mice that have been induced by alloxan so that the mice experience diabetes mellitus. Then the mice were given treatment to each group to lower blood sugar levels after being induced by alloxan. The average sugar levels of mice after being treated can be observed on the 14th day. The control group was only given regular feed and distilled water, the negative control group was induced by alloxan, the positive control group was

induced by alloxan and metformin, the treatment group was induced by alloxan and *Andrographis paniculata* leaf extract with different doses, namely treatment 1 dose 200mg/KgBB, treatment 2 dose 400mg/KgBB, and treatment 3 dose 600mg/KgBB. From table 1 we can conclude that the average blood sugar levels of mice that experienced a significant decrease were in treatment group 3 with the administration of *Andrographis paniculata* leaf extract at a dose of 600mg/KgBB with an average blood sugar level of300.25mg/dLto 115.75mg/dL experienced a decrease of 184.5mg/dL.

Results Description Overview

The results of phytochemical testing of sambiloto leaf extract (*Andrographis paniculata*) showed that it contains metabolite compounds including flavonoids, saponins, tannins, alkaloids, and steroids/triterpenoids. The results of phytochecimal tests are shown in Table 2.

Table 2. Phytochemical Tests

Secondary Metabolites	Testing	Color	Results
Flavonoid	Wilstater	Red	+
Saponins	Forth	Blue and foamy	+
Tannin	FeCl3	Blackish green	+
Alkaloid	Wagner	Yellow	+
Triterpenoid	Lieberman – Burchard	Red	+

Description: (+) = Contains the tested compound group

(-) = Does not contain the tested compound

Based on the results of observations made on all groups showed that there was a change in amylase levels in the treatment group. Based on the average value of amylase levels, the control group had an average value of 59.92 U / L before treatment and 58.95 U / L after being given distilled water for 14 days, the negative control group had an average value of 63.92 U / L after being induced by alloxan and no treatment increased to 64.575 U / L. The increase in amylase levels experienced by the negative control group was due to the absence of treatment given to mice with diabetes mellitus.

The positive control group had an average amylase value of 68.05 U/L after being induced by alloxan and given metmorphine to decrease to 66.82 U/L. The amylase level of rats in the positive control group became a reference for the high and low levels in the treatment group. Treatment group 1 after being induced by alloxan had an amylase level of 68.75 U/L and after being given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 200mg/KgBW it

became 65.82 U/L. Treatment group 2 after being induced by alloxan was 68.24 U/L and after being given sambiloto leaf extract (*Andrographis paniculata*). at a dose of 400mg/KgBW it became 60.25 U/L. Finally, treatment group 3 after being induced by alloxan was 68.72 U/L and after being given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 600mg/KgBW it became 59.15U/L. Based on the difference in the average serum amylase levels, the researchers concluded that treatment group 3, namely rats with diabetes mellitus and given *Andrographis paniculata* leaf extract. dose of 600mg/KgBW had the greatest decrease in serum amylase levels. While the positive control group, namely rats with diabetes mellitus and given metmorphine but not given *Andrographis paniculata* leaf extract. experienced the least decrease or improvement in lipase levels.

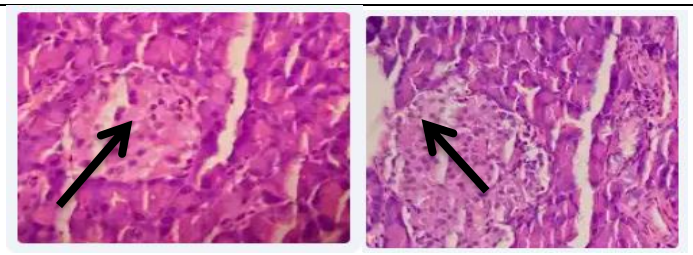
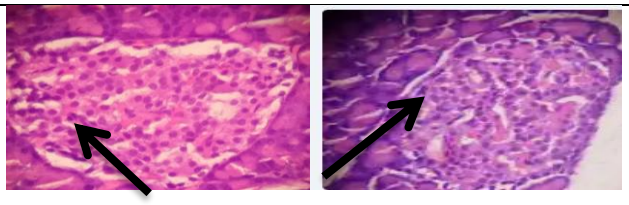
The results of observations made on all groups showed that there was a change in lipase levels in the treatment group. Based on the average lipase levels, the control group had an average value of 32.05 U/L before treatment and 14 days to 32 U/L, the negative control group had an average value of 34.05 U/L before treatment and 14 days to 33.5 U/L and the positive control group had an average value of 33.8 U/L before treatment and 14 days to 32.6 U/L. The lipase levels of mice in the negative and positive control groups are used as a reference for the high and low lipase levels in the treatment group.

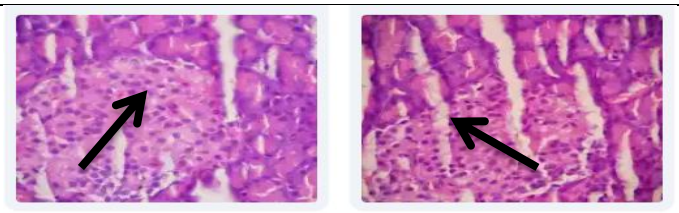
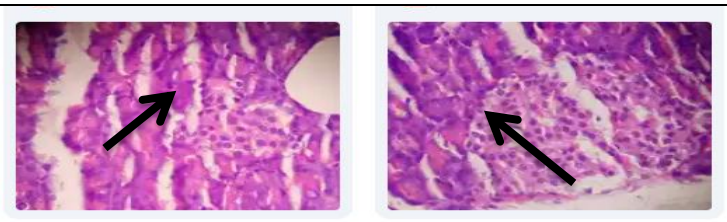
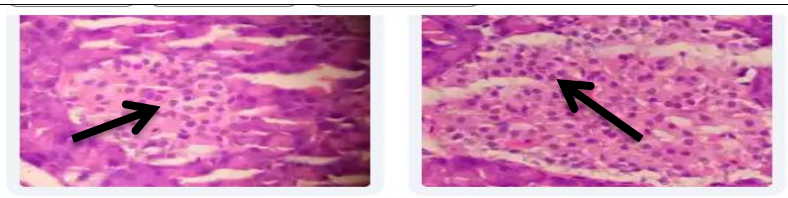
Treatment group 1 after being induced by alloxan had a lipase level of 42.6 U/L and after being given sambiloto leaves (*Andrographis paniculata*) at a dose of 200mg/KgBW it became 31.975U/L. Treatment group 2 after being induced by alloxan was 42.02U/L and after being given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 400mg/KgBW it became 24.02U/L. Finally, treatment group 3 after being induced by alloxan had a fat level of 42.15U/L and after being given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 600mg/KgBW it became 22.8U/L. Based on the difference in the average lipase levels, the researchers concluded that treatment group 3, namely obese mice and given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 600mg/KgBW had the greatest decrease in lipase levels. Meanwhile, the negative control treatment group, namely mice that were only induced by alloxan, experienced the lowest decrease or improvement in lipase levels compared to the positive control group, treatments 1 and 2.

Histopathological observations were carried out using a light microscope with 400x magnification. The purpose of this observation was to see the structure and morphology of the cells in each pancreatic tissue specimen in the control group and the treatment group given sambiloto leaf extract at a dose of 200mg/KgBB, 400mg/KgBB, and 600mg/KgBB. The administration of sambiloto leaf extract was carried out every day in the morning. The scoring method observed in histopathological changes was seen from the degree of damage to the

number of all types of lesions that occurred, the damage was given a score from 0 to 10. The histopathological description of pancreatic tissue are shown in Table 3.

Table 3. Histopathological Description of Pancreatic Tissue

No	Group	Histopathological Image of Pancreatic Tissue
11	Control (Aquades)	 Score 0 because tno degenerative changes were found, Nonecroti changes occur and no inflammatory cells were found in the entir pancreatic interstitial space. This group was not induced and was no given extract treatment.
2	Negative Control (alloxan induction)	 Score4because the number of cells dgenerative > 76 of all LPnumber o necrotic cellsbetween 26%-50% of all LP and number of inflammatory cells > 100 in the entire pancreatic interstitial space. This group wa induced by alloxan alone, so there was no treatment to reduce KGD i mice.
3	Positive Control (alloxan + metmorphine induction)	 Score 3 because the number of inflammatory cells is between 51-100 i the entire pancreatic interstitial space, the number of cells with a degre of damage (51% - 75%) of the entire LP (Visual Field).

4	Treatment 1 (dose200mg/KgBW)	 Score 3 because the number of inflammatory cells is between 51-100 i the entire interstitial space of the pancreas, number of cells with degre of damage (51% - 75%) of the entire LP (Visual Field).
5	Treatment 2 (dose400mg/KgBW)	 Score 2: if the number of degenerative cells with a degree of damag (26-50%) of the entire LP (Visual Field), number of cellsnecrotic < 25% of the entire LP and the number of inflammatory cells is between 11-5 in the entire interstitial space of the pancreas.
	Treatment 3 (dose600mg/KgBW)	 Score 1 due to the number of degenerative cells with a degree of damag (< 1-25%) of the entire LP (Visual Field), the number of necrotic cells < 25% of the entire LP. and the number of inflammatory cells < 10 in th entire pancreatic interstitial space.

DISCUSSION

The pancreas is closely related to diabetes. Diabetes is a disorder of carbohydrate metabolism, characterized by the body's inability to produce enough insulin, or respond appropriately. Type 2 diabetes mellitus often occurs in people who are overweight or obese. Excessive dietary lipids cause obesity, and this extra fat is transported to other tissues such as the liver and pancreas where it has toxic effects and causes organ dysfunction (Li et al., 2020). This damage can be overcome by consuming plants that contain antidiabetic properties.

Alloxan has been proven to cause diabetes mellitus by damaging pancreatic β cells so that the pancreas cannot produce enough insulin. The dose of Alloxan given to each experimental mouse from P1, P2 and P3 was given a dose of 100 mg/kgBW. Alloxan was made by adding

injection aquadest because later the diabetogenic substance would be injected intraperitoneally. The weight of the mice used in the study was 200gr to 300gr, below is an example of calculating the dose of alloxan, if the weight of the mouse is 300g then the dose per mouse is 300 g = 0.3 kg, then 100 mg/kgBW X 0.3 kg = 30 mg (per mouse) in P1, P2 and P3 were given alloxan for seven days intraperitoneally and sambiloto leaf extract was given orally. From the results of observations of the average blood sugar levels in table 3, it can be concluded that the extract of sambiloto leaves (*Andrographis paniculata*) at a dose of 200mg/KgBB, a dose of 400mg/KgBB and a dose of 600mg/KgBB influences reducing blood sugar levels in rats with diabetes mellitus. Of all treatment groups, a significant decrease in blood sugar levels was found by giving sambiloto leaf extract (*Andrographis paniculata*) at a dose of 600mg/KgBB.

Sambiloto leaf extraction (*Andrographis paniculata)* In the sambiloto leaf screening results table, there are flavonoid, saponin, and tannin compounds. According to Chon et al (2000), flavonoids have an antidiabetic or antihyperglycemic role in the content of sambiloto leaf extract (*Andrographis paniculata*). The function of flavonoids themselves is known to play a significant role in increasing the activity of antioxidant enzymes and can regenerate damaged pancreatic β cells so that insulin deficiency can be overcome. Flavonoids contained in plants are also thought to be able to improve the work of insulin receptors, thus providing a beneficial effect on diabetes mellitus (Eryuda, et al., 2016)

CONCLUSION

1. Administration of sambiloto leaf extract (*Andrographis paniculata*) at a dose of 600 mg/kgBW is effective in improving pancreatic function in white rats (*Rattus norvegicus*) Wistar strain with diabetes mellitus.
2. The results of histopathological observations of pancreatic tissue in treatment group 3 (600mg/KgBW) experienced the most significant improvement and approached the control group (reference group) compared to the other groups.
3. Sambiloto leaf extract (*Andrographis paniculata*) contains secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids which help repair pancreatic cells damaged by diabetes mellitus.

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