The Effect of Sambiloto Leaf Extract (Andographis Paniculatu) on Liver Function and Liver Histopathology of Male Wistar White Rats with Diabetes Mellitus

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Abstract. Diabetes Mellitus is characterized by impaired insulin secretion or impaired insulin function (insulin resistance) in the liver and muscles. The liver is one of the largest organs in the body and the center of metabolism in the body. The study aims to determine the effect of Andrographis paniculata leaf extract on liver function and liver histopathology of male white wistar rats with diabetes mellitus. This type of research is experimental using pre-post test control group design. 24 male wistar rats as samples were divided into 6 groups so that 4 rats per group. The results of the One-Way Anova statistical test showed that the significance value produced was $0.000 < 0.05$, which concluded that there was a significant difference between the control group and the treatment group. Further Post-hoc LSD tests were conducted to analyze the differences in average ALT and AST levels between groups. A significance value of $0.00 < 0.05$ means that the group has a significant difference between the control group and the other treatment groups and vice versa. Administration of sambiloto leaf extract (Andrographis Paniculata) at a dose of 600mg/KgBW is effective in improving liver function in Wistar strain rats with diabetes mellitus. Histopathological observations of liver tissue also experienced the most significant improvement and approached the control group compared to other groups. Sambiloto leaf extract (Andrographis Paniculata) contains secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids to help repair liver cells that experience fatty liver and necrosis due to diabetes mellitus.

Keywords: Liver, Diabetes Mellitus, Sambiloto Leaves

1 Introduction

A class of metabolic illnesses known as diabetes mellitus is typified by hyperglycemia, which can be brought on by anomalies in either the action or production of insulin, or both. The malfunction or failure of several bodily organs is

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directly linked to chronic hyperglycemia in diabetes mellitus. Both macrovascular and microvascular diseases can be complications of diabetes mellitus. Type 1 diabetes, type 2 diabetes, various forms of diabetes, and gestational diabetes mellitus, or pregnancy, are the four categories into which diabetes mellitus is divided [3].

Hyperglycemia in diabetes mellitus causes enhanced lipolysis by raising the activity of the lipase enzyme in adipose tissue. When the distribution and synthesis of free fatty acids are out of balance and exceed the liver's ability to oxidise or distribute them, lipid accumulation occurs in the liver, which can have harmful effects on the liver through ineffective oxidation or the activation of inflammatory pathways. Increased lipolysis results in an increase in free fatty acids in the circulation and portal. Hepatocyte cells may sustain damage as a result of increased oxidative stress brought on by elevated free fatty acids in the liver, which in turn generate more reactive oxygen species (ROS). [7]

Impaired insulin production or function (insulin resistance) in target organs, particularly the muscles and liver, is typically a hallmark of diabetes patients. The biggest organ in the body and the most intricate metabolic hub is the liver (EJ, 2001). Insulin and glucagon are crucial for the metabolism of lipids, proteins, and carbohydrates. Both of these hormones affect blood sugar regulation as well. The liver serves as both an organ for metabolism and a location to store nutrients that are taken up from the digestive system for later usage by other bodily systems [11] The plant known as sambaloto (Andrographis paniculata) is native to India and a number of other Asian nations. People in Southeast Asia, China, and India have long utilised sambaloto to aid in the healing process of a variety of medical issues. One advantage of using sambiloto leaves (Andrographis paniculatum) in traditional medicine is that, according to study findings, they contain antioxidant, antifungal, and antibacterial properties. Flavonoids are among the compounds found in sambiloto (Andrographis paniculatum) leaves that have antioxidant properties. The flavonoids found in sambiloto leaves (Andrographis paniculatum) reduce cell damage caused by free radicals (ROS) that are created as a result of fat buildup in hepatocyte cells. This has a hypoglycemic impact [8]. Researchers used sambiloto herb (Andrographis paniculata (Burm.f.) Nees) which contains diterpenes, flavonoids, and stigmasterol. The main compound contained in this plant has a basic structure of diterpene lactones [6]

Andrographolide has various pharmacological activities including hepatoprotective, immunostimulant, anti-inflammatory, antimalarial, cardiovascular, hypoglycemic. [4]. Based on research conducted by ayu Adhistania, et al. in 2018 regarding the effect of ethanol extract (Andrographis paniculatum) on the histopathological picture of the liver of 3-4 month old male white mice weighing 200-250 grams as many as 24 which were divided into 6 groups that experienced diabetes mellitus due to streptozotocin induction with a dose of 45 mg/kgBW, administration of ethanol extract (Andrographis paniculatum) was carried out for 35 days given orally with several doses of administration, namely 100, 200, 300, 400, 500 mg/kgBW/day, from the results of the study it was found that at a dose of 400 mg/kgBW/day ethanol extract (Andrographis paniculatum) max-

imally repaired liver damage due to diabetes mellitus in mice(Kumar V, 2019). Based on several previous studies, the author would like to review more deeply the effectiveness of liver function and histopathological changes in the liver of rats with alloxan-induced diabetes mellitus after being given Andrographis paniculatum leaf extract. Sambiloto is a medicinal plant with erect herbaceous plants up to 90 cm tall. It is thought to have originated in Tropical Asia and spread from India south to Siam, east to the Malay Peninsula, before being found in Java. It grows well in lowlands up to an altitude of 700 meters above sea level. Rainfall of 2,000–3,000 mm/year and air temperature of 25−32°C are ideal conditions for the growth of sambiloto.The position of the sambiloto plant (Andrographis paniculata) in plant taxonomy is as follows [9].

Kingdom: Plantae, Sub kingdom : Viridiplantae, Infra kingdom : Streptophyta, Super division : Embryophyta, Division:Tracheophyta, Sub division : Spermatophyta, Class : Magnoliopsida, Super order : Asteraceae, Order: Lamiales, Family : Acanthaceae, Genus : Andrographis Wall.ex Nees, Species: Andrographis paniculata (Burm.f.) Wall ex Nees.

2 Literature Review

LITERATURE REVIEW Alloxan, also known as 2,4,5,6-tetraoxypyrimidn or 5,6-dioxyuracil, is an unstable and hydrophilic substance. Alloxan is administered subcutaneously, intraperitoneally, and intravenously as a diabetogenic drug. Intraperitoneally and subcutaneously, the dosage is often two to three times the intravenous dose, which is typically 65 mg/kg body weight (AE, 2006). The production of reactive oxygen is the primary cause of cell damage, and it starts with the reduction of alloxan in beta Langerhans cells. The resulting diluric acid then reoxidises to alloxan, triggering the redox cycle and producing superoxide radicals. Aalloxan can enter the liver rapidly. If used, alloxan can cause diabetes mellitus, which is characterised by elevated blood sugar levels.

Diabetes Mellitus is a metabolic disease with the characteristics of hyperglycemia that occurs due to abnormalities in insulin secretion, insulin function or both. Based on the report of the results of the Basic Health Research (RISKESDAS) in 2018 by the Ministry of Health, there was an increase in the prevalence of DM to 8.5% or around 20.4 million Indonesians affected by DM(Soelistijo SA, 2019)Diabetes mellitus can cause damage to organs, especially the liver. The liver is the largest and heaviest glandular organ in the body. In men, the liver is slightly heavier than in women. The average adult weighs 1.5 kg, or about 2% of their body weight. A good liver has a smooth surface, a soft to hard consistency, and a deep burgundy color (reflecting its rich vascularity). [10] The liver is an important organ in the human body that does many things, such as supporting metabolism, immunity, digestion, detoxification, vitamin storage, and more. [5]. The liver is the largest gland in the body, so it is very good at receiving nutrients and cleaning absorbed drugs and other harmful substances. The liver is both an endocrine and exocrine organ. Its exocrine functions mainly include the conjugation of bilirubin and excretion into the intestine, as well as the synthesis

and excretion of bile salts into the common hepatic duct. The use of insulin and glucagon to control glycemic levels is one of its endocrine functions.

The liver produces amino acids such as fibrinogen, albumin, prothrombin, and other important proteins and converts proteins into enzymes and peptide hormones. (Vernon et al., 2018). The liver stores minerals and vitamins, such as iron, and is involved in the metabolism of lactic acid, synthesizing lipoproteins, cholesterol, and phospholipids, and converting ammonia to urea. In addition, the liver is involved in carbohydrate metabolism, including storing glycogen and gluconeogenesis. In short, the liver is responsible for the metabolism of macronutrients, hormones, blood plasma components, and exocrine and endocrine substances, and serves as an important mediator connecting the intestine to the blood. [15].

One of the benefits of sambiloto leaves (Andrographis paniculatum) is used as traditional medicine, from the results of research, sambiloto leaves (Andrographis paniculatum) have activity as antibiotics, antifungals and antioxidants. One of the contents of sambiloto leaves (Andrographis paniculatum) which acts as an antioxidant is Flavonoid. Flavonoids in sambiloto leaves (Andrographis paniculatum) work by suppressing free radicals (ROS) produced due to the accumulation of fat in hepatocyte cells, thereby reducing cell damage due to ROS that is formed and has a hypoglycemic effect(Lindawati NY, 2014). So the hypothesis of the researcher is that there is an effect of sambiloto leaf extract (Andrographis Paniculata) on liver function in male white rats (Rattus norvegicus) Wistar strain with diabetes mellitus. The conceptual framework in this study is as follows:

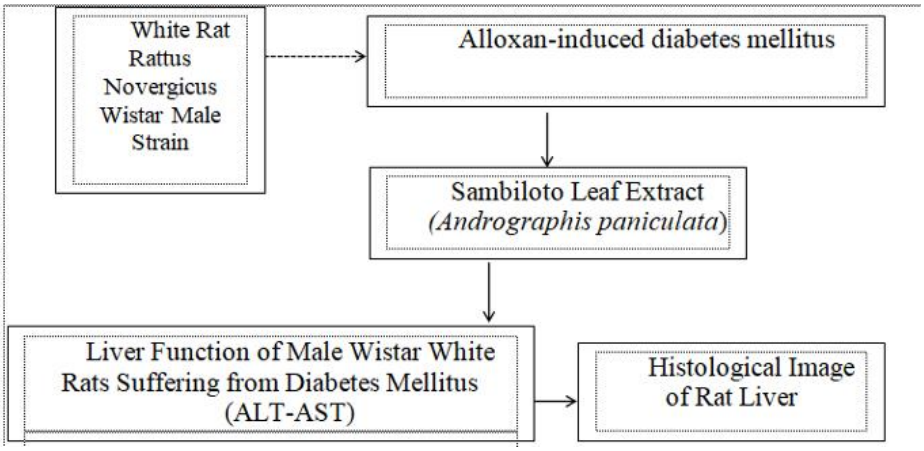


Fig. 1. Effect on Uric Acid Level

3 Method

This research is a 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 Universitas Prima Indonesia 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/kgBW sambiloto leaf extract, 6) Treatment group-3, mice with diabetes mellitus and given600 mg/kgBW sambiloto leaf extract.

The variables in this study consist of independent variables, dependent variables and precondition variables. The independent variable is the provision of leaves.Andrographis paniculata leaves, the dependent variables are pancreatic function improvement and histopathological picture and the preconditioning variables are alloxan-induced rats. The process of making Andrographis Paniculata leaf extract begins with fresh materials in the form of selected and washed and dried bitter leaves.

Andrographis paniculata leaves must be carefully selected, washed, and dried. The dried herbal material can be stored for further use in a tightly closed plastic bag. By using the right solvent, maceration can be used to produce herbal materials. Andrographis paniculata 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. The maceration method with 96% ethanol solvent is used for the extraction of bitter leaves. To make bitter leaf extract, fresh moringa flowers are cooked for two days at a temperature of 30-35°C. After that, the bitter leaves are crushed using a blender to obtain bitter leaf powder. 100 grams of bitter leaf powder is added to 100 milliliters of 96 percent ethanol solvent. Then put it in a jar and add 1 liter of 96 percent ethanol again. After that, it is closed and left protected from sunlight for 48 hours. After the mixture is filtered, a macerate is made. Then, in the same way, the dregs are macerated with 96% ethanol. During the maceration process, a digital shaker with a speed of 50 rpm is used to produce a clear macerate. For two hours, the liquid extract results are evaporated by a rotational evaporator. The extraction results used in this study used the extract of sambiloto leaves (Andrographis Paniculata) doses 200 mg/kgBW, 400 mg/kgBW, and 600 mg/kgBW 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 of 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 liver organs. Liver function can be measured by examining serum enzyme activity, one of which is serum aminotransferase or transaminase. Aminotransferase is a good indicator for assessing liver damage. If both are increased, then there has been damage to the liver. The two aminotransferases are Aspartate Aminotransferase (AST) or formerly called Serum Glutamic Oxaloacetic Transaminase (SGOT), and Alanine Aminotransferase (ALT) or formerly called Serum Glutamic Pyruvic Transaminase (SGPT). ALT and AST can indicate liver parenchymal damage, they function as markers of liver functional status.. For histological examination, the fixed liver was cut and placed in a plastic specimen pot. Then, the preparation was stained with hematoxylin-eosin (HE) and viewed under a microscope at 400x magnification. Histopathological changes in mice were assessed using the Manja Roenigk scoring model as presented in the following table:

Table 1. Scoring System for Level of Damage

No.	Score	Level of Damage
1	1	Normal
2	2	Parenchymatous Degeneration
3	3	Hydropic Degeneration
4	4	Necrosis

Microscopic analysis was used to gather data from histological findings, which were subsequently categorised. The study's data were tallied, examined for any alterations, and then presented in a descriptive manner. Additionally, the Statistical Package for Social Sciences (SPSS) 25.0 for Windows was used to analyse

the research data. The Kolmogorov-Smirnov test was used to determine whether the data were normal ($p > 0.05$). The significance between test groups was tested at a 95% confidence level ($p < 0.05$) using a one-way ANOVA. The Post Hoc Test and LSD methods were used for additional testing or analysis.

4 Results

Description of Blood Sugar Level Results Alloxan administration is only done on day 1 after that the sugar is tested using a blood sugar checker or called a blood glucose meter. Based on Wolfenshon and Lloyd, (2013) normal blood sugar levels are 50-150mg/dL and are said to have diabetes mellitus more than 200 mg/dL. There is also according to (Oktaria, 2013) mice or other animals are said to have diabetes with blood sugar levels of more than 200 mg/dL.

In this case, the researcher also concluded that blood sugar levels of more than 200 mg/dL are said to have diabetes mellitus according to the research literature that has been done previously.

Table 2. Average Blood Glucose Levels (KGD)mg/dLMice Before and After Alloxan Induction and Given Sambiloto Leaf Extract Treatment

Group	Early KGD (H0)	KGD (mg/dL) After Alloxan Induction (H7)	KGD (mg/dL) After Treatment (H14)	Difference in KGD
Control	99	121.25	122.25	+1.25
Negative control (K-)	104	254	256	+2
Positive control (K+)	95.75	245.75	165.75	-80
Treatment 1 (P1)	98.25	248.25	140.75	-107.5
Treatment 2 (P2)	102.5	252.5	143.75	-108.75
Treatment 3 (P3)	102	254.5	141.25	-113.25

From the table above, it can be seen that the average blood glucose levels in mice increased after 7 days of Alloxan induction.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.From the table 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 sambiloto leaf extract (Andrographis Paniculata) at a dose of 600 mg/KgBW with an average blood sugar level of 254.5mg/dLto 141.25mg/dLexperienced a decrease of 113.25mg/dL.

Based on the results of observations of the average blood sugar levels in table 1, it can be concluded that the extract of sambiloto leaves (Andrographis Paniculata) at a dose of 200 mg/KgBW, a dose of 400 mg/KgBW and a dose of 600 mg/KgBW has an effect on reducing blood sugar levels in mice with diabetes mellitus. The concentration of secondary metabolite chemicals in Andrographis Paniculata leaf extract is investigated using phytochemical testing. testing for

flavonoids, alkaloids, tannins, saponins, and steroids/triterpenes are examples of phytochemical testing. A flavonoid test is conducted first. After adding 1 gramme of Andrographis Paniculata leaf extract to a test tube, strong HCl is added, and the mixture is cooked in a water bath for 15 minutes. Flavonoids (flavones, chalcones, and aurones) are favourable if a reddish-yellow hue develops. When flavonoids are tested, a crimson extract is produced, indicating the presence of flavonoids.

Fig. 2. Flavonoids

The second test, known as the saponin test, involves adding 10 milliliters of hot water to a test tube containing one gram of sambiloto leaf extract (*Andrographis Paniculata*), cooling it down and shaking it vigorously for ten seconds. If a foam forms as high as 1–10 cm for at least 10 minutes and does not disappear after 1 drop of 2N HCl is applied, the result is positive for saponins. Researchers discovered that the sambiloto leaf extract (*Andrographis Paniculata*) had foam, indicating the presence of saponins.

Fig. 3. Saponin

In the third tannin test, one gram of sambiloto leaf extract (*Andrographis Paniculata*) was placed in a test tube with ten millilitres of hot water. The mixture was then boiled for five minutes, and three to four drops of $FeCl_3$ were added to the filtrate. If the filtrate was green-blue (green-black), it indicated a positive catechol tannin test, and if it was blue-black, it indicated a positive tannin test. A blackish-blue liquid observed in the tannin test findings indicates the presence of tannins.

Fig. 4. Tannin

Two grams of sambiloto leaf extract (*Andrographis Paniculata*) were placed in a test tube, dripped with five millilitres of 2N HCl, heated, cooled, and then separated into three test tubes, each holding one millilitre, for the fourth alkaloid test. Each reagent was introduced into a tube. If a white or yellow precipitate occurs after adding Mayer's reagent, it indicates the presence of alkaloids. The alkaloid test findings in this investigation were yellow, indicating a positive result for alkaloids.

Fig. 5. Tannin

The fifth test for steroids, Put as much of the sambiloto leaf (Andrographis Paniculata) extract as possible in a test tube, then shake with two milliliters of ethyl acetate. After removing the ethyl acetate layer, it is dropped onto a drop plate and allowed to dry. One drop of concentrated sulfuric acid and two drops of acetic acid hydrate are added after drying.

It indicates a favorable result for terpenoids if a red or yellow tint develops. A green tint indicates a positive result for steroids. The color that appears in the steroid/triterpenoid test is green, indicating a good result for steroids.

Fig. 6. Tannin

Based on the results of the phytochemical tests conducted, it can be concluded that the extract of sambiloto leaves (Andrographis Paniculata) contains secondary metabolites in the form of flavonoids, saponins, tannins, alkaloids, and steroids.

ALT and AST Level Observation Results

Observation of changes in ALT levels was carried out after a high-fat diet and after administration of *Andrographis Paniculata* leaves. The results of observations made on all groups showed that there were changes in ALT levels in the treatment group. Based on the average ALT level, it can be seen that the control group on day 7 had an average value of 119.95 U/L and after 14 days it became 120.6 U/L. The negative control group had an average value of 178.95 U/L after being induced by alloxan and after 14 days it became 179.25 U/L. The positive control group had an average value of 185.4 U/L after being induced by alloxan and given metmorphine; after 14 days it became 176.275 U/L.

The ALT level value of mice in this positive control group became the normal level or reference for the high and low ALT levels in the treatment group. Treatment group 1, after being induced by alloxan, had an ALT level of 189.34 U/L and, after being given sambiloto leaf extract at a dose of 200 mg/KgBW, decreased to 143.65 U/L. Treatment group 2, after being induced by alloxan, had an ALT level of 188.5 U/L and, after being given sambiloto leaf extract at a dose of 400 mg/KgBW, decreased to 133.07 U/L. Finally, treatment group 3, after being induced by alloxan, had an ALT level of 186.37 U/L and, after being given sambiloto leaf extract at a dose of 600 mg/KgBW, decreased to 120.07 U/L.

Based on the difference in the average ALT levels, the researchers concluded that treatment group 3, namely rats with diabetes mellitus and given sambiloto leaf extract at a dose of 600 mg/KgBW, had the greatest decrease in ALT levels and was close to the control group. While treatment group 1, namely rats with diabetes mellitus and given sambiloto leaf extract (*Andrographis Paniculata*) at a dose of 200 mg/KgBW, experienced the lowest decrease or improvement in ALT levels compared to treatment groups 2 and 3.

Observation of changes in AST levels was carried out after a high-fat diet and after administration of *Andrographis Paniculata* leaf extract at doses of 200 mg/KgBW, 400 mg/KgBW, and 600 mg/KgBW. The results of observations made on all groups showed that there were changes in AST levels in the treatment group. Based on the average AST levels, it can be seen that the control group on day 7 had an average value of 98.825 U/L and after 14 days it became 99.75 U/L. The negative control group had an average value of 152.4 U/L after being induced by alloxan and after 14 days it became 152.97 U/L. The positive control group had an average value of 160.22 U/L after being induced by alloxan and given metmorphine; after 14 days it became 125.87 U/L.

The AST levels of mice in the positive control group became normal levels or references for high and low AST levels in the treatment group. Treatment group 1, after being given a high-fat diet, had an AST level of 160.82 U/L and, after being given *Andrographis Paniculata* leaf extract at a dose of 200 mg/KgBW, it became 116.37 U/L. Treatment group 2, after being induced by alloxan, had an AST level of 161.15 U/L and, after being given *Andrographis Paniculata* leaf extract at a dose of 400 mg/KgBW, it became 109.87 U/L. Finally, treatment group 3, after being induced by alloxan, had an AST level of

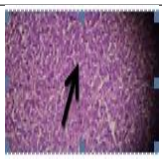
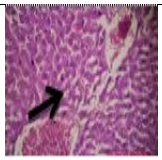
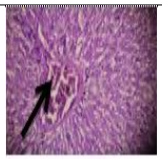
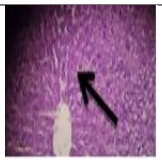
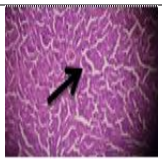
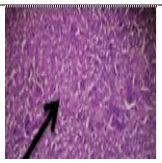
161.125 U/L and, after being given *Andrographis Paniculata* leaf extract at a dose of 600 mg/KgBW, it became 102.97 U/L.

Based on the difference in the average value of AST levels, the researchers concluded that treatment group 3, namely mice with diabetes mellitus and given sambiloto leaves (*Andrographis Paniculata*) at a dose of 600 mg/KgBW, had the greatest decrease in serum AST levels and approached the control group. While treatment group 1, namely mice with obesity and given sambiloto leaf extract (*Andrographis Paniculata*) at a dose of 200 mg/KgBW, experienced the least decrease or improvement in AST levels.

Based on the results of the statistical test, ALT and AST levels were normally distributed and had homogeneous data in each control and treatment group, namely a significance value of 0.231 and $0.230 > 0.05$. The One-Way Anova test on ALT and AST levels showed that the significance value produced was $0.000 < 0.05$. Based on these data, it can be concluded that there is a significant difference between the control group and the treatment group. Further Post-hoc LSD tests were conducted to analyze the differences in average ALT and AST levels between groups. A significance value of $(0.00 < 0.05)$ means that the group has a significant difference from the control group to the other treatment groups and vice versa.

The following is a histological image of the liver tissue of each treatment group:

Table 3. Histopathological Observation of Liver Tissue in Each Group

No	Group	Histopathological Image of Liver Tissue
1	Control (Aquades)	 There are no changes in the histological structure of the liver (normal) which falls into score category 1.
2	Negative Control	 There is necrosis in the liver cells, so it falls into the score category 4 (visible necrosis).
3	Positive Control (Methmorphine)	 There is necrosis in the liver cells but it appears to be getting smaller so it falls into score category 4 (visible necrosis).
4	Treatment 1 (200 mg/KgBW)	 There is necrosis in the liver cells but it appears to have disappeared, so it falls into score category 3 (visible necrosis).
5	Treatment 2 (400 mg/KgBW)	 Improvement of liver histological structure but still hydropic degeneration, so it is included in score category 2.
6	Treatment 3 (600 mg/KgBW)	 The histological structure of the liver is seen to be close to the control group, so it falls into the score category 1.

5 Discussion

High blood sugar and diabetes mellitus are significant risk factors for a variety of acute and chronic illnesses, from cancer to mental and metabolic disorders. Non-alcoholic fatty liver disease (NAFLD), a liver condition associated with diabetes, has dramatically increased as a result of the obesity pandemic. The liver is an intriguing organ with a lot of unique morphological and functional characteristics.

It is also the body's largest and heaviest solid glandular organ, and its abundant blood supply comes from a peculiar mix of two sources: venous and arterial. The liver performs a wide variety of functions. A healthy liver can regenerate itself rather well. If the liver is overworked because of diabetes, it might become polluted and cease to function as the body's natural filter [3].

Consuming medicinal herbs, such as the sambiloto leaf plant (*Andrographis paniculata*), is one way to cure this illness with minimal adverse effects. The findings of this study suggest that giving *Andrographis paniculata* leaf extract to male Wistar strain white rats (*Rattus norvegicus*) with diabetes mellitus can enhance the histological structure of the liver. This is evident from the findings of the liver histological observations in treatment group 3 and the control group, which show no variation. The kind and quantity of substances affect changes in the liver's histological structure. The quantity and kind of substances that enter the liver organ, such as the administration of *Andrographis paniculata* leaves, affect changes in the histological structure of the liver.

The chemicals in *Andrographis paniculata* leaf extract are inextricably linked to improvements in the histological structure of the liver of male white rats (*Rattus norvegicus*) of the Wistar strain with diabetes. *Andrographis paniculata* leaf extract includes secondary metabolites in the form of flavonoids, saponins, tannins, and triterpenoids, according to the findings of phytochemical experiments that have been conducted. As natural chemicals with a wide range of pharmacological activities and beneficial therapeutic benefits, flavonoids have been shown in previous research to have great antioxidant, anti-inflammatory, metabolic disease improvement, anti-tumor, and other qualities. They may also dramatically decrease fatty liver.

6 Conclusion

1. Administration of Andrographis Paniculata (Andrographis Paniculata) leaf extract at a dose of 600mg/KgBW is effective in improving liver function in white rats (Rattus norvegicus) Wistar strain with diabetes mellitus. This improvement can be seen through ALT, AST levels, and liver histology structure which have improved and resemble the control group. 2. The results of histopathological observations of liver tissue in treatment group 3, namely the administration of sambiloto leaf extract (Andrographis Paniculata) at a dose of 600 mg/KgBW, experienced the most significant improvement and approached the control 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 liver cells that experience fatty liver and necrosis due to diabetes mellitus.

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