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

Marcelia Soewito[1]; Linda Chiuman[1]; Setia Budi Tarigan[1]; Bungaran Sihombing[1]; Veranyca Chiuman[1]

[1]Master of Biomedical Science Study Program, Faculty of Medicine, Dentistry, and Health Sciences, Prima Indonesia University, North Sumatra.

*Email : veranycachiuman@unprimdn.ac.id

ABSTRACT

Diabetes Mellitus is one of the threats to human health. The abnormalities that occur in the kidneys of people with diabetes mellitus begin with the presence of microalbuminuria. Microalbuminuria is generally defined as albumin excretion of more than 30 mg per day and is considered important for the onset of diabetic nephropathy which if uncontrolled will then develop into clinical proteinuria and end in kidney failure.

This study aims to prove the effect of leaf extract (*Andrographis paniculata*) on kidney function and histopathology of the kidneys of male Wistar rats with diabetes mellitus. This study is an experimental study using a pre-post test control group design. In this study, 24 male Wistar rats were used as samples which were divided into 6 groups and 4 rats for each group.

The results of the study showed that administration of leaf extract (*Andrographis paniculata*) at a dose of 600 mg/KgBW was effective in significantly improving kidney function in white rats (*Rattus norvegicus*) Wistar strain with diabetes mellitus. This improvement can be seen through the levels of urea, creatinine, and histological structure of the kidneys that have improved. Leaf extract (*Andrographis paniculata*) contains secondary metabolites in the form of saponins, tannins, flavonoids, alkaloids, and steroids that help repair kidney cells that experience fatty deposits and decreased kidney function due to diabetes mellitus. Given its antihyperglycemic and anti-inflammatory properties, *Andrographis paniculata* functions as a protective agent for kidney health in patients with diabetes mellitus.

Keywords: *Kidney, Sambiloto Leaves, Diabetes Mellitus*

INTRODUCTION

One of the risks to human health is diabetes mellitus. Although this illness is not communicable, its prevalence will only rise in the coming years. Diabetes Mellitus is a spectrum of metabolic illnesses marked by hyperglycemia that arises from abnormalities in insulin production, insulin function, or both, according to the American Diabetes Association (ADA) in 2010. The kidneys are one of the organs that might develop problems, long – term damage, malfunction, and failure as a result of chronic hyperglycemia in diabetes mellitus. Diabetic nephropathy, the leading cause of mortality for people with diabetes mellitus, is one of the causes of kidney damage (kidney failure) brought on by uncontrolled diabetes mellitus. Microalbuminuria is the first sign of renal problems in individuals with diabetes mellitus. More than 30 mg of albumin excretion per day is commonly referred to as microalbuminuria. This condition is thought to be crucial for the development of diabetic nephropathy which if left untreated, progresses to clinical proteinuria, a decline in glomerular filtration rate function, and kidney failure. It is expected that diabetic nephropathy, which can lead to kidney failure, will eventually affect 20 – 30% of persons with type 2 diabetes and 30 – 40% of those with type 1 diabetes. Aminoglycoside antibiotics are known to produce harmful kidney side effects, particularly ototoxic and nephrotoxic ones (Purnasari et al., 2019). Therefore, the majority of people worldwide use traditional medicine to cure a variety of illnesses. Plants are regarded by many researchers as a valuable resource for creating novel treatments. Herbal medicines are used extensively nowadays to prevent or treat illnesses, and several plants are still being studied for their pharmacological qualities, including their anti-inflammatory, anti-apoptotic, antioxidant, and antibacterial qualities (Nurhamidin S, 2022).

The bitter plant is one of the herbal or active chemical substances that may be used to make the medications. Growing in tropical or subtropical climates like Thailand, Vietnam, and Indonesia, *Andrographis paniculata* also known as the "king of bitter," is a herbal plant with numerous health benefits, including anti-inflammatory, antimicrobial, antihyperglycemic, anti-atherosclerosis, and in some studies, an antidiabetic effect (Dai Y, 2018).

Previous research conducted by Madhan Vijayanan and Weseley for 21 days on albino rats with type 1 DM induced by streptozotocin at a dose of 60 mg/KgBB, was given sambiloto leaf extract (*Andrographis paniculata*) at a dose of 25 ml/KgBB and 50 ml/KgBB orally. At a dose of 25 ml/KgBB, there was healing of the effects of kidney cell necrosis and at a dose of 50 ml/KgBB the shape and size of the kidney cells had returned to the same as the control group (Vijayanand S, 2009). Previous research has resulted in research that in female and male Charles Foster rats with type 2 DM induced by nicotinamide at a dose of 120 mg/KgBB 15 minutes later induced by streptozotocin at a dose of 65 mg/KgBB for 7 days intraperitoneally. Sambiloto leaf extract (*Andrographis paniculata*) was given at a dose of 50 mg/KgBB, 100 mg/KgBB, and 200 mg/KgBB orally for 10 days. At a dose of 50 mg/KgBB, glomerular and

tubular cell necrosis was still visible, but at a dose of 100 mg/KgBB there was improvement in glomerular and tubular cells and at a dose of 200 mg/KgBB the glomerular and tubular cells returned to normal (Thakur A, 2014).

In addition to the well-known terpenoids (entalabdane diterpene lactones), which are most frequently employed in medicine, *Andrographis paniculata* also contains additional macroelements, flavonoids, xanthones, and noriridoides. The diterpenes andrographolide, neoandrographolide, and andrograpanin are the most bioactive substances found in sambiloto leaves (*Andrographis paniculata*). *Andrographis paniculata* includes flavonoids in addition to diterpenes, with the latter being mostly present in the plant's roots.Given this context, the researcher wants to assess how giving *Andrographis paniculata* leaf extract affects the kidneys' histological characteristics and renal function in male Wistar strain white rats with diabetes mellitus.

LITERATURE REVIEW

Diabetes Mellitus, according to the American Diabetes Association (2010), is a category of metabolic illnesses marked by hyperglycemia brought on by anomalies in insulin production, insulin function, or both (Ndraha, 2014). Diabetes, a dangerous chronic illness, is brought on by either insufficient insulin production by the pancreas or inefficient insulin utilization by the body. Insulin is a hormone that controls blood sugar, or glucose. When blood glucose levels rise due to ineffective insulin production or use by the body, diabetes mellitus, a chronic illness, develops (Organization, 2019).

Blood glucose testing provides the basis for the diagnosis of diabetes mellitus. Enzymatic glucose testing using venous blood plasma material is the suggested method for measuring blood glucose levels. Capillary blood glucose testing with a glucometer can be used to track the effectiveness of therapy. Glucosuria alone cannot be used to make a diagnosis (Perkeni, 2015). By preserving fluid balance and ensuring that other organ systems operate appropriately, the renal system has an impact on every region of the body. The bladder, urethra, two ureters, and two kidneys make up the renal-urologic system. The kidneys of a typical adult are bean-shaped and situated retroperitoneally between the third lumbar and the twelfth thoracic vertebrae. Due to the liver's displacement, the right kidney is situated somewhat lower than the left.

Sambiloto leaf plant (*Andrographis paniculata*) is a plant that has medicinal properties because it contains chemical compounds such as flavonoids, glycosides, saponins and tannis (Esha, 2019). These substances exhibit a range of pharmacological properties, including antioxidant, antibacterial, analgesic, and anti-inflammatory properties (Royani, 2014). The remarkable health advantages of smabiloto leaves are crucial for maintaining a balanced and

healthy lifestyle in addition to their usage in natural medicine. The power of sambiloto leaves may be used to sustain bodily health and enhance quality of life in a safe, natural manner. Herbs have been used for centuries in Indonesia to cure a variety of illnesses, including diabetes mellitus. Although there has been no research related to reducing cholesterol levels, researchers are interested in creating a research title using this chemical compound. The effect of giving sambiloto leaf extract (*Andrographis paniculata*) on kidney function and histopathological features of the kidneys of white Wistar rats with diabetes mellitus. The conceptual framework in this study can be seen in Figure 1 below.

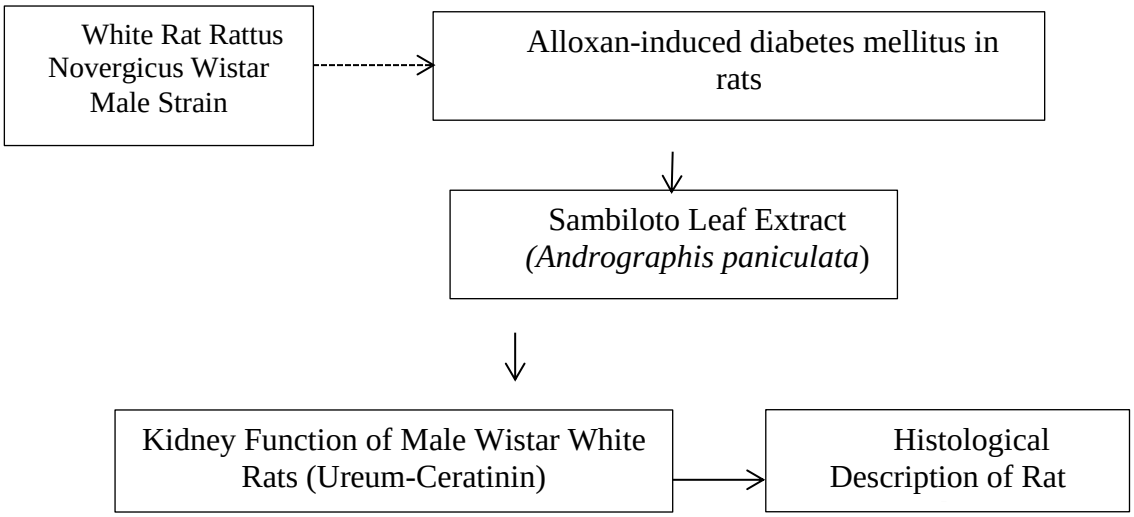

Figure 1. Conceptual Framework

METHODS

The research design employed in this study is a post-test only control group design, which is a kind of study that only looks at the control and treatment groups after they have been given an activity. This study is a true experimental study. The efficiency of sambiloto leaves (*Andrographis paniculata*) on the kidney function of male white galus wistar rats (*Rattus norvegicus*) with diabetes mellitus is examined using a post-test with control group design or controls samples depending on the treatment group. The study will be conducted in the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra, from May to August 2024. The procedure of obtaining ethical clearance is ongoing and will be submitted to Prima Indonesia University's Health Research Ethics Commission (KPEK). In order to address any ethical concerns pertaining to the treatment and care of animals, all methods adhere to animal welfare norms.

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 metformin, 4) treatment group-1, rats with diabetes mellitus and given 200 mg/KgBW, 5)Treatment group-2 mice that had diabetes mellitus and were given 400 mg/KgBW sambiloto leaf extract, 6) Treatment group-3, mice with diabetes mellitus and given 600 mg/KgBW sambiloto leaf extract.

Precondition variables, dependent variables, and independent factors make up the study's variables. The availability of leaves is the independent variable. The improvement in kidney function and its histological appearance are the dependent factors for *Andrographis paniculata* leaves, whereas rats given alloxan are the preconditioning variables. Fresh ingredients in the form of carefully chosen, cleaned, and dried *Andrographis paniculata* leaves are used to make the leaf extract. For later usage, the dried herbal ingredients can be kept in plastic bags that are well sealed. Using the right solvent, maceration is a method of processing herbal compounds. The maceration procedure uses a 96% alcohol solvent to extract the leaves of the leaves of *Andrographis paniculata* are harvested at the same time, from the same garden, at the same age, and with the same branch arrangement. 100 grams of *Andrographis paniculata* leaf powder are made by blending fresh leaves that have been boiled for two days at a temperature between 30 and 35°C. The mixture is mixed and then filtered. The dregs are macerated with 96% ethanol using the same procedure. This is carried out with a digital shaker set to 50 rpm until a clear macerate is created. A rotary evaporator was used to evaporate the liquid extract for two hours.

The process of adjusting to a new environment is where the research process starts. Ad libitum food and water were provided to mice based on their normal requirements. After a week of environmental adaptation, male white mice weighing 200 – 300 grams were given an intraperitoneal dose of alloxan (150 mg/KgBW) to induce hyperglycemia; if the mice were 200 – 300 grams, 30 grams of alloxan was administered. Alloxan monohydrate powder was weighed up to 1.2 grams and dissolved with sterile injection aquades up to 100 mL Alloxan-induced blood glucose levels were assessed three days later. The mice were considered to have diabetes mellitus if their blood sugar levels were greater than 150 mg/dL, even if they were still within the normal range of 70–140 mg/dL(Akbarzadeh, 2007). Following the alloxan-induced acclimation phase, the test animals were split into six groups, each consisting of four mice, and the mice developed diabetes mellitus. A non – wet marker was used to mark each mouse's tail. The control group of mice received just alloxan. Mice in other groups received varying dosages of leaf extract from *Andrographis paniculata*.

Using a gastric tube, *Andrographis paniculata* leaf extract was administered orally. The white mice or experimental animals were killed after two weeks so that their renal organs could be examined. Urea and creatinine levels served as the study's renal function metrics. Damage to the kidneys is indicated by elevated blood urea levels. Because glomerular filtration must drop by 50% before blood urea levels rise, if the kidneys are unable to eliminate enough urea, blood urea levels rise above normal. A common metric for assessing kidney function is serum creatinine levels. Muscle creatine phosphate, which the body continuously produces based on muscle mass, is broken down to generate creatinine. Creatinine levels describe changes in creatinine and renal function and are correlated with muscle mass. Creatinine in seru. Serum creatinine is used to measure glomerular filtration capacity and monitor the course of kidney disease.

Kidney tissue was examined histopathologically by contrasting the treatment group with the control group. The alterations will be fatty degeneration, hydropic degeneration, and necrosis. Quantitative data is obtained by grading each change. A 400x magnification light microscope is used to observe the scoring system. Kidney injury is the basis for the score system, which is as follows:

Score 0 = no histopathological damage;
Score 1 = there is focal (mild) damage;
Score 2 = there is multifocal (moderate) damage;
Score 3 = there is diffuse (severe) damage.

After that, scoring information was created using microscopic analysis of histopathological observation data. The study's data were tallied, examined for any alterations, and then given in a descriptive manner. Additionally, the Statistical Package for the Social Sciences (SPSS) 25.0 for Windows was used to analyze the research data. The Kolmogorov-Smirnov test was employed to determine whether the data was normal ($p>0.05$). Additionally, one-way analysis of variance, or one-way ANOVA, was used to evaluate for significance between the trial groups at a 95% confidence level. The Post Hoc Test and LSD methods were used for additional testing or analysis.

RESULTS

Male Wistar strain white rats (*Rattus norvegicus*) weighing 200 – 300 grams were employed as test animals in this investigation. There were 24 rats in total in this study since the sample was calculated using the Ferderer method for 6 groups and the findings showed that each group included four rats. Alloxan was used to induce the negative control group, alloxan and metformin were used to induce the positive control group, and alloxan and sambiloto leaf

extract (*Andrographis paniculata*) were used to induce the treatment group at varying doses (200 mg/KgBB, 400 mg/KgBB, and 600 mg/KgBB). The control group was given only regular feed and distilled water.

It has been shown that alloxan harms the β cells in the pancreas, which stops the organ from making enough insulin and causes diabetes mellitus. The alloxan dosage for each experimental mouse in P1, P2, and P3 was 100 mg/KgBW. Alloxan was made by adding injection aquadest since the diabetogenic substance would eventually be administered intraperitoneally. The study's mice ranged in weight from 160 to 200 grams. According to the calculation, if a mouse weighed 200 grams, the dose of alloxan would be 300 grams, or 0.3 kilograms, per mouse. This indicates that sambiloto leaf extract and 100 mg/KgBW X 0.3 kilograms = 30 mg (per mouse) were given intraperitoneally to P1, P2, and P3 for seven days.

From day 1 to day 7, mice received 30 mg of alloxan intraperitoneally. Then, on day 14, 200, 400, and 600 mg/kg BW of sambiloto leaf extract were administered. The mice's average body weight before and after alloxan induction and after receiving sambiloto leaf extract is as follows. It is evident from the above table that mice's average body weight rose following 14 days of Alloxan induction. Treatment group 3 was the one that had the most significant gain. This demonstrates how mice with diabetes mellitus respond to increasing body weight. Only on the first day is alloxan administered; subsequent blood sugar levels are measured with a blood glucose meter, often known as a blood sugar checker. A blood sugar level of 50 – 150 mg/dLis considered normal, while a level of 200 mg/dLis considered to indicate diabetes mellitus. Additionally, mice or other animals are considered to have diabetes if their blood sugar levels are greater than 200 mg/dL, according to Oktaria (2013). In this instance, researchers also came to the conclusion that, in accordance with earlier study material, blood sugar levels over 200 mg/dLare indicative of diabetes mellitus. The results of the blood sugar level test can be seen in table 1

Table 1 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 being given extract treatment (H14)	Difference in KGD (after alloxan induction-treated)
Control	97	123.25	124.25	+ 1

Negative control (K-)	105	256	258	+2
Positive control (K+)	98.75	257.75	167.75	-90
Treatment 1 (P1)	100.75	256.25	165.75	- 90.5
Treatment 2 (P2)	105.5	257.5	163.75	-93.75
Treatment 3 (P3)	105	258.5	162	-96.5

A dosage of 200 mg/kg BW, 400 mg/kg BW, and 600 mg/kg BW of sambiloto leaf extract (*Andrographis paniculata*) has been shown to lower blood sugar levels in rats with diabetes mellitus, according to the average blood sugar levels seen in Table 1. Blood sugar levels in all treatment groups significantly decreased when 600 mg/KgBW of sambiloto leaf extract (*Andrographis paniculata*) was administered.

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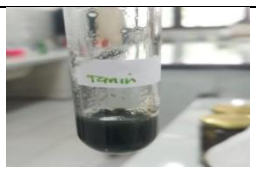
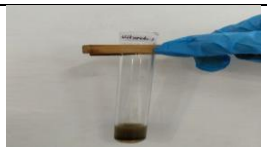
Results Description Special Review

The extract of sambiloto leaves (*Andrographis paniculata*) includes secondary metabolites in the form of flavonoids, saponins, tannins, alkaloids, and steroids, according to the findings of the phytochemical tests that were performed. The results of testing secondary metabolites of sambiloto leaves can be seen in table 2.

Table 2 Phytochemical Tests

No.	Secondary Metabolites	Extract Sambiloto leaves (Andrographis paniculata)	Results and Colors
1.	**Saponins**		+ Red
2.	**Flavonoid**		+ Yellow and foamy
3.	**Tannin**		+ turquoise

4.	**Alkaloid**		+ Chocolate
5.	**Steroid**		+ Green
6	**Glycosides**		- Purple Chocolate

Description: (+) = Contains the tested compound group

(-) = Does not contain the tested compound

Results of Observation of Urea and Creatinine Levels

Following a high-fat meal and the administration of *Andrographis paniculata* leaves, alterations in urea levels were observed. The urea levels in the treatment group changed, according to the findings of observations conducted on all groups. The control group's average urea level was 16.52 mg/dL prior to therapy, and after 14 days, it increased to 17.075 mg/dL. The mice in the control group's urea levels returned to normal, or served as a reference for the high and low urea levels in the treatment group caused by *Andrographis paniculata* leaf extract and alloxan. Treatment group 1's urea level was 24.35 mg/dL following alloxan administration and *Andrographis paniculata* leaf administration. Treatment group 2's blood sugar levels dropped from 29.15 mg/dL following a high-fat meal to 19.8 mg/dLfollowing 400 mg/KgBW of sambiloto leaf extract (*Andrographis paniculata*). Ultimately, treatment group 3 was 17.85 mg/dL after receiving moringa flower extract (*Moringa oleifera*) at a dosage of 600 mg/KgBW and after being induced by alloxan at 29 mg/dL.

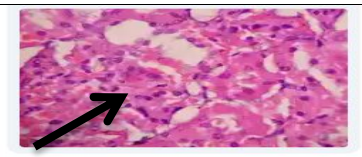
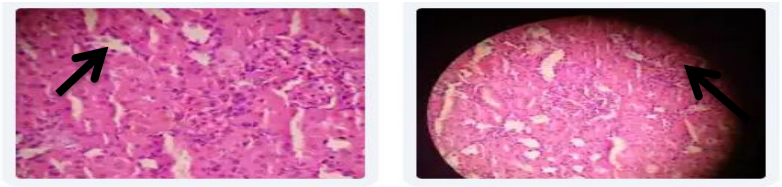
The researchers determined that treatment group 3, which consisted of obese mice administered 600 mg/KgBW of *Andrographis paniculata* leaf extract, had the largest reduction in urea levels and was comparable to the control group based on the difference in the average value of urea levels. However, treatment group 1, which consisted of obese mice administered 200 mg/KgBW of *Andrographis paniculata* leaf extract, showed the least amount of improvement or reduction.

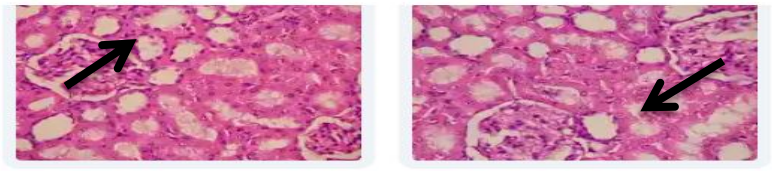
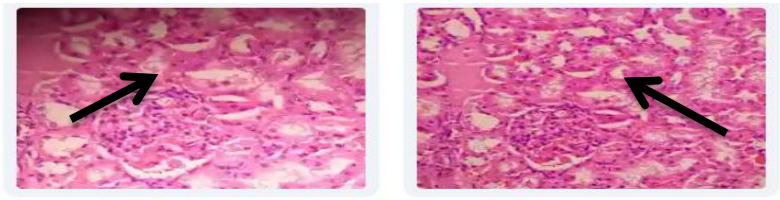
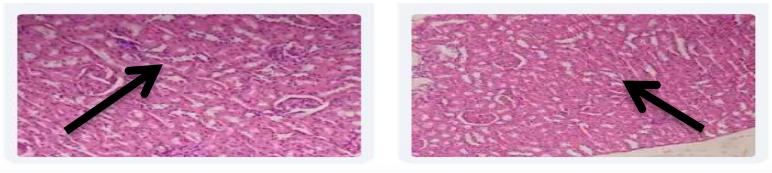
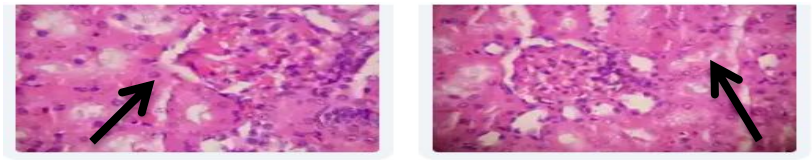
Creatinine levels in the treatment group changed, according to the findings of observations made on all groups. The control group had an average creatinine level of 3.7 mg/dL prior to

therapy and 4.25 mg/dL following 14 days, according to the average creatinine levels. In the treatment group, the results acquired in this control group were used as benchmarks for both high and low creatinine levels, as well as normal levels. Following a high-fat meal, treatment group 1's creatinine level was 9.3 mg/dl; however, after receiving 200 mg/KgBW of sambiloto leaf extract (*Andrographis paniculata*), it dropped to 6.02 mg/dL. Treatment group 2 had 10.6 mg/dL following a high-fat meal, but it dropped to 5.325 mg/dL after receiving 400 mg/KgBW of sambiloto leaf extract (*Andrographis paniculata*). Lastly, treatment group 3 decreased to 4.7 mg/dL following a high-fat meal of 9.75 mg/dL and sambiloto leaf extract (*Andrographis paniculata*) at a dosage of 600 mg/KgBW. The researchers determined that treatment group 3, which consisted of obese mice administered 600 mg/KgBW of *Andrographis paniculata* leaves, had the largest reduction in blood creatinine levels and was comparable to the control group based on the difference in the average creatinine level values. While treatment group 1, namely obese mice given *Andrographis paniculata* leaves at a dose of 200 mg/KgBW experienced the least decrease or improvement in creatinine levels.

Histological Observation Results:

Table 3 Histopathological Description of Kidney Tissue

No	Group	Histopathological Image of Kidney Tissue
1	Control (Aquades)	 Score 0 there is no histopathological damage to the kidney tissue. The kidney histopathology in the control group was in normal form because it was not induced by alloxan so it was used as a reference to describe other groups and as a comparison with the treatment group given a high-fat diet and *Andrographis paniculata* leaf extract.
2	Negative Control	 Due to the diffuse (severe) damage, the score is 3. Due to the fact that the negative control group received alloxan induction but no treatment for diabetic mellitus

3	Positive Control		Score 3 becausethere is diffuse (severe) damage. Because the negative control group has been given alloxan induction but to reduce liver damage was given metmorphine for diabetes mellitus.
4	Treatment 1 (200mg/KgBW)		Score 2 because of the multifocal (moderate) liver damage that was caused by alloxan; also, sambiloto leaf extract was administered at a dose of 200 mg/KgBW to treat diabetes mellitus.
5	Treatment 2 (400mg/KgBW)		Score 2 because there is damage to the liver organ which is multifocal (moderate); because after being induced by alloxan there is treatment by giving sambiloto leaf extract at a dose of 400 mg/KgBW to reduce diabetes mellitus.
6	Treatment 3 (600mg/KgBW)		Score 1 because there is focal (mild) liver damage; because after being induced by alloxan there is treatment by giving sambiloto leaf extract at a dose of 600 mg/KgBW to reduce diabetes mellitus.

Histopathological examinations revealed a variety of cell appearances. The renal histology of the control group, which was simply given distilled water, was normal, and they fell into score category 0, indicating that there was no histological damage to the kidney tissue. Because the control group was not fed a high-fat diet, its kidney histology was in normal form; thus, it was used to characterize other groups and to compare it to the treatment group, which was fed a high-fat diet and leaf extract from Andrographis Paniculata. In the negative control group that

was given alloxan induction but not given blood sugar lowering drugs, it was included in the score category 3 because there was diffuse (severe) damage, the positive control group that had been given alloxan induction but was given metmorphine to lower blood sugar levels was included in category 3 because metmorphine did not help repair the damage.

DISCUSSION

An energy imbalance known as diabetes mellitus is brought on by consuming too many calories in comparison to the energy needed to sustain oneself and carry out physical labor. Complex metabolic abnormalities brought on by diabetes mellitus have a broad influence on renal illnesses. According to Perkeni (2015), this syndrome raises the chance of acquiring significant risk factors for chronic kidney disease (CKD). One frequent mechanism connecting obesity and its related problems is oxidative stress. An imbalance between the generation of free radicals and antioxidant defenses is known as oxidative stress. The pathophysiology and course of chronic kidney disease are known to be significantly influenced by oxidative stress, which is a disruption in the pro-/antioxidant complex's equilibrium (Sianipar, 2021).

Antioxidants are the body's natural defensive mechanism against oxidative damage. By oxidizing themselves, antioxidants prevent some harmful oxidation events. This defensive mechanism works by preventing the first generation of free radicals and scavenging oxidants, which transform oxidants into less harmful substances and prevent the secondary synthesis of harmful metabolites. The defense system then seeks to either strengthen the endogenous antioxidant defense system, which is made up of both enzymatic and nonenzymatic antioxidants, or repair the molecular damage.

The leaves of sambiloto (*Andrographis paniculata*) are one of the medicinal herbs that have antioxidant properties. Protein, fatty acids, minerals, and polyphenol chemicals are all found in sambaloto plants. The human body is affected by sambaloto leaves (*Andrographis paniculata*) in several systems. In the neighborhood, this plant is a well-known herb. Phenolics (phenolic acids, flavonoids, coumarins, quinones, tannins, and stilbenes), nitrogen (alkaloids, amines, and B-alanine), vitamins, terpenoids (carotenoids), and other endogenous metabolites are among the free radical inhibitors found in sambiloto (Siskawadani et al., 2021). This rationale leads researchers to believe that giving sambiloto leaf extract (*Andrographis paniculata*) to male Wistar strain white rats (*Rattus norvegicus*) with diabetes mellitus may improve kidney function.

CONCLUSION

1. White rats (*Rattus norvegicus*) Wistar strains with diabetes mellitus benefit from improved kidney function when administered *Andrographis paniculata* leaf extract at a concentration of 600 mg/KgBW. The urea and creatinine levels as well as the kidneys' better histological structure demonstrate this improvement
2. Compared to the other groups, the histological findings of kidney tissue in treatment group 3, which received a dosage of 600 mg/KgBW of sambiloto leaves (*Andrographis paniculata*), showed the greatest improvement and came closest to the control group.
3. Secondary metabolites such as saponins, tannins, flavonoids, alkaloids, and steroids found in sambiloto leaf extract (*Andrographis paniculata*) aid in the repair of kidney cells that suffer from fatty liver and impaired kidney function as a result of diabetes mellitus.

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