The Effects of Salak Fruit Skin Extract (Salacca Zalacca) on Kidney Function and Histopathology in Male Wistar Rats with Diabetes Mellitus

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ABSTRACT

This study was conducted to determine the effect of Salak fruit skin extract (*Salacca Zalacca*) on kidney function and histopathology of the kidneys of rats with diabetes mellitus. This study used 20 white rats (Rattus norvegicus) into 5 groups, namely K-, K+, P1, P2 and P3 with different doses. The results of phytochemical testing of Salak fruit skin extract contain saponins, tannins, flavonoids, alkaloids, and steroids. The initial stage uses alloxan induction to induce diabetes mellitus in rats. The results After 14 days, the treatment groups (P1, P2 and P3) had experienced DM and were then given Salak fruit skin extract treatment of 200 mg/kgBW, 400 mg/kgBW, 600 mg/kgBW, and were seen to be normal in terms of urea and keratin levels. Based on the results of histopathology of the rat kidneys, which illustrated damage to the kidneys due to diabetes mellitus, it looked better and normal in treatments P2 and P3. data analysis In the One-Sample Kolmogorov Smirnov normality test, the significance results of Keratinin 0.079 > 0.05 and Ureum 0.109> 0.05 so that they are normally distributed.

***Keywords**: Salak Skin, Kidney, Diabetes Mellitus*

INTRODUCTION

The kidneys themselves are part of the urinary system that filters incoming waste, especially urea..The function of this organ is to filter blood before returning it to the heart. Some of its functions include maintaining the body's fluid balance, controlling and filtering minerals from the blood, filtering waste from food, drugs, and toxic substances, producing hormones that help form red blood cells and improve bone health, and regulating blood pressure. One of the most dangerous diseases for human health is diabetes mellitus (DM). Although this disease is not contagious, the number of people suffering from it will increase in the

future.Chronic hypoglycemic diabetes mellitus will cause various complications such as long-term damage, dysfunction, and failure of various organs, one of which is the kidney organ. Herbal products are now widely used to control or prevent disease, and some plants are still being studied for their pharmacological properties, such as antibiotics, anti-apoptosis, antioxidants, and anti-inflammatory.Salak fruit skin (*Salacca Zalacca*) is a plant originating from India and several countries in Asia that has been used for a long time to help cure various health problems of people in India, China, and Southeast Asia. The results of the study showed that Salak fruit skin (*Salacca Zalacca*) is used as a traditional medicine because of its properties as an antibiotic, antifungal, and antioxidant. Previous studies have found that Salak fruit skin has many benefits for body health, and its diverse and potential pharmacological properties due to its high antioxidant content show many benefits. Phytochemical studies on this fruit have shown the presence of glycosides, flavonoids, phenolics, and several volatile and aromatic compounds. These include ß-carotene, lycopene, epicatechin, proanthocyanidins, chlorogenic acid, gallic acid, and quercetin.

LITERATURE REVIEW

The kidneys perform their primary functions to balance the transport of solutes and water, excrete metabolic waste products, maintain nutritional balance, and maintain acid-base balance in the body to provide a stable environment for tissue and cell metabolism. Almost two-thirds of the human body is water (Rahayu, 2024). Each part of the kidney does its job, but they work together to filter and remove waste and toxins through urine. The kidneys also remove metabolic waste products (e.g., urea, creatinine, and uric acid) and foreign chemicals (Oktaria, 2017). Kidney function tests usually examine urea, creatinine, and glomerular filtration rates. Typical results for both tests indicate that the kidneys are working well.

Diabetes mellitus is a type of metabolic disease that causes hyperglycemia due to abnormalities in insulin secretion, insulin action, or both (Ndraha, 2014). Diabetes is a severe chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar or glucose) or when the body cannot use the insulin it produces effectively (WHO, 2022). Diabetes mellitus is a chronic condition that occurs when there is an increase in blood glucose levels due to the body being unable to produce or use enough insulin hormone or insulin hormone effectively. (Staff, 2014). Each person with diabetes mellitus in this health will show different symptoms. Therefore, this condition will differ depending on the type and severity of the patient's sugar disease. However, people with

type 1 or type 2 usually show some symptoms (Banday et al., 2020), such as increased thirst, increased urination, fatigue, visual disturbances, etc. By checking blood glucose levels, it will be possible to determine whether someone has diabetes mellitus or not from the results of the examination whether someone has high blood sugar or not.

Salak fruit, or Salacca Zalacca, is an oval or spindle-shaped fruit approximately six centimeters long and has sweet, pale yellow flesh with elongated tips and reddish brown scales resembling salaks. Although the fruit's skin is scaly like a salak and is reddish brown, the taste of the fruit's flesh is sweet. Salak fruit is an extraordinary source of antioxidants (Ismail, NA, & Abu Bakar, 2018). The antioxidant content of plants can be used to ward off free radicals and strengthen the body to ward off other disease viruses.(Syaputri, Girsang and Chiuman, 2022). Free radicals are not harmful to the body in small amounts. However, in large amounts, they can increase the risk of heart disease, diabetes, premature aging, and heart disease (Ginting et al., 2020). The fiber in the skin of the Salak fruit helps the body control blood sugar. This is good news for those who have diabetes or want to prevent it. The skin of the Salak fruit also has phytochemicals that have anti-inflammatory properties, which can help reduce inflammation (Alice Erza, 2023).

METHODS

This study is a True experiment by controlling all external variables that can affect the experimental activities. The research was conducted in the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra in May - July 2024. Ethical Clearance will be approved by the Health Research Ethics Commission (KPEK) Universitas Prima Indonesia Committees (Approval No. [070/(KPEK-FKKGIK/2023]). This study uses a post-test-only group design to determine and analyze the effect of giving Salak fruit skin extract (Salacca Zalacca) on kidney function and kidney histopathology in male Wistar rats (Rattus norvegicus) with diabetes mellitus. Researchers used the 3R Principle (Replacement, Reduction, and Refinement), namely Reduction, in determining the number of research samples (Kendall et al., 2018). The research sample, namely 20 male rats, will be divided into 5 groups. Negative control group (K-) alloxan induction without treatment, positive control (K+) alloxan induction and given the antidiabetic drug metmorphine 9 mg treatment 1,2,3 (P1, P2, P3) induced by alloxan and each given Salak fruit skin extract with a dose of 200mg/kgBW, 400mg/kgBW and 600mg/kgBW. Three days after being induced with naloxone, blood glucose levels were measured. Normal

blood glucose levels in mice are 50-135 mg/dL; when blood glucose levels are >300 mg/dl, new mice are declared diabetic mellitus (Andi Emelda, 2022). The Salak fruit skin extract treatment was administered in the second week after the acclimatization process and preparation of test animals after being declared diabetic mellitus. Kidney function can be measured by measuring keratin and serum levels in rats. Blood is taken on days 0, 7, and 14. Blood was taken as much as ± 2 ml from the rat's tail vein. Normal ketamine levels in rats are in the range of 0.2 to 0.8 mg/dL. Normal serum levels in rats range from 15 to 21 mg/dL. After treatment for 14 days, the rats were then terminated under anesthesia, and then a laparotomy was performed to remove the kidney organs. After the kidney organs were taken, the rats were buried. Data from the histopathological examination of the kidneys were analyzed descriptively by comparing the description of changes in histopathological structures between Leptospira-positive and harmful rats based on the kidney glomerulus. Score 0 if there is no change in the histology structure of the Kidney (standard), score 1 if there is a change in the form of Inflammatory Cell Infection, score 2 if there is Edema Spatium Bowman or bleeding, and score 3 if there is necrosis in the Kidney cells. The data will be presented descriptively with data normality test analyzed using the Kolmogorov Smirnov approach ($p > 0.05$), then one-way variance analysis or one-way ANOVA at a 95% confidence level ($p < 0.05$) (Ghozali, 2018).

RESULTS

This study used male rats (Rattus norvegicus) with Wistar strains weighing 160-200 grams and aged 2-3 months. The research samples were 20 male rats divided into 5 groups. Then, the rats were adapted to the environment for one week and given a dose of alloxan to make the rats hyperglycemic, namely 150 mg/kg BW intraperitoneally. Three days after alloxan induction, blood glucose levels were measured. Mice showed hyperglycemic glucose levels if the levels were ≥ 300 mg/DL and were declared diabetes mellitus.

The entire group has experienced diabetes mellitus. It can be seen that the entire group has experienced diabetes mellitus. The group that experienced the most drastic increase was in treatment group 1 (P1), with an average of 381 mg/DL. This indicates a reaction to increased glucose levels in mice induced by alloxan so that the mice experienced diabetes mellitus. Then, while observing the blood glucose levels of the mice, the researchers also monitored the weight of the mice before and after being induced by alloxan and after being given treatment with Salak fruit skin extract (Salacca Zalacca). The group that experienced the

highest average increase was group (K-), with an average weight of 219 gr. This indicates a reaction to increased weight in mice that had experienced diabetes mellitus. Before giving treatment, secondary metabolite testing was carried out using a phytochemical test with the results of the extract of Salak fruit skin (Salacca Zalacca) positive for containing active compounds such as alkaloids, flavonoids, and saponins. So, this extract has many benefits for the skin because it has antioxidant content.

In all groups of mice (K-, K+, P1, P2, P3), urea levels were seen to increase from normal limits, and maximum results were seen in the K- group with an average value of urea levels (mg/dl) and standard deviation of 44.26±0.36. After 14 days of treatment with the K- group, the urea levels increased to 43.89±0.55. For the K+ group, the average result was 27.63±0.51 and was still above the normal urea levels in mice. For the treatment groups (P1, P2, and P3) where the rats were induced by alloxan and given Salak fruit skin extract (Salacca Zalacca) treatment of 200 mg/kgBW, 400 mg/kgBW, 600 mg/kgBW, the urea levels were seen to be expected, namely P1 with a value of 20.35±0.39, P2 with a value of 17.07±0.29 and P3 with a value of 17.20±0.45. At the level of keratinin, the K- group increased to 1.54 ± 0.25. The average result for the K + group was 0.84 ± 0.49, approaching the normal keratinin level in mice. For the treatment group (P1, P2, and P3), it was seen that the keratin level was normal, namely P1 with a value of 0.76 ± 0.27, P2 with a value of 0.60 ± 0.01 and P3 with a value of 0.68 ± 0.107.

Reporting Research Results

The conceptual framework of this research is as follows:

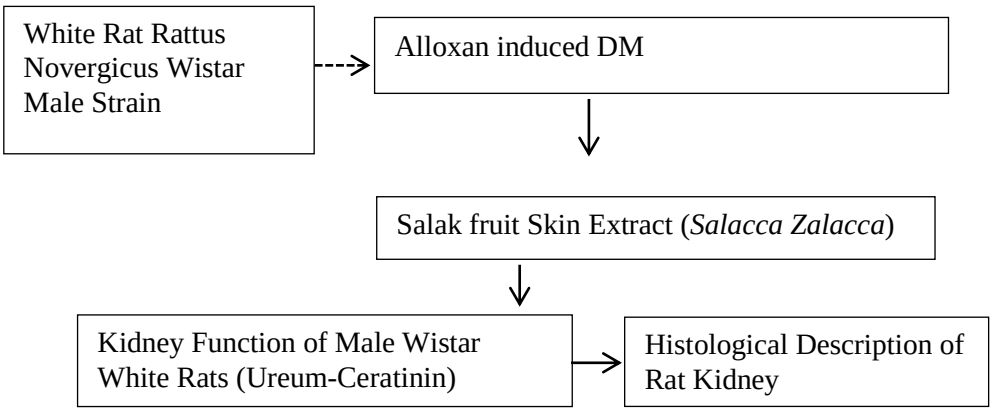


Figure 1. Conceptual Framework

The hypothesis in this study is that Salak fruit skin extract has an effect on kidney function and kidney histopathology in male Wistar strain white rats (Rattus norvegicus) with diabetes mellitus.

Table 1. Average SGOT and SGPT

	Mean ±SD			
	H0		**H14**	
Group	**Urea**	**Keratin**	**Urea**	**Keratin**
K-	44.26±0.36	1.43±0.306	43.89±0.55	1.54±0.25
K+	43.25±0.43	1.26±0.613	27.63±0.51	0.84±0.49
P1	43.4±0.44	1.24±0.275	20.35±0.39	0.76±0.27
P2	43.07±0.29	1.24±0.01	17.07±0.29	0.60±0.01
P3	42.7±0.38	1.31±0.04	17.20±0.45	0.68±0.107

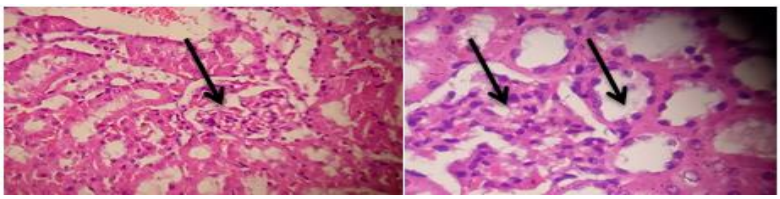
Kidney function can be measured by measuring creatinine and urea levels in mice. Normal ketamine levels in mice range from 0.2 to 0.8 mg/dL. Normal urea levels in mice range from 15 to 21 mg/dL. If seen from the results of the table above, it can be seen that after alloxan induction, urea levels in all groups of mice (K-, K+, P1, P2, P3) were seen to increase from normal limits, and maximum results were seen in the K- group with an average urea level

(mg/dl) and its standard deviation of 44.26±0.36. After 14 days of treatment with the K- group without treatment or salak skin extract (Salacca Zalacca) only induced by alloxan, the urea levels increased to 43.89±0.55. For the K+ group without treatment of Salak fruit skin extract (Salacca Zalacca) only induced by alloxan and receiving antidiabetic treatment (metformin) obtained an average result of 27.63 ± 0.51 and was still above the standard urea level limit in mice. For the treatment group (P1, P2, and P3) where mice induced by alloxan and given Salak fruit skin extract treatment (Salacca Zalacca) of 200 mg / kgBW, 400 mg / kgBW, 600 mg / kgBW were seen to be expected in urea levels, namely P1 with a value of 20.35 ± 0.39, P2 with a value of 17.07 ± 0.29 and P3 with a value of 17.20 ± 0.45. This indicates that administering Salak fruit skin extract (Salacca Zalacca) reduces urea levels in mice with diabetes mellitus.

If seen from the results of the table above, it can be seen that after the administration of alloxan induction, keratin levels in all groups of mice (K-, K+, P1, P2, P3) were seen to increase from normal limits and the maximum results were seen in the K- group with an average value of keratin levels (mg/dl) and its standard deviation of 1.43±0.306. After 14 days of treatment with the K- -group without treatment or salak skin extract (Salacca Zalacca) only induced by alloxan, keratin levels increased to 1.54±0.25. For the K+ group without treatment of salak skin extract (Salacca Zalacca) only induced by alloxan and receiving antidiabetic treatment (metformin) obtained an average result of 0.84±0.49 which approached normal keratin levels in mice. For the treatment group (P1, P2, and P3), where the rats were induced by alloxan and given Salak fruit skin extract (Salacca Zalacca) of 200 mg/kgBW, 400 mg/kgBW, 600 mg/kgBW, it was seen that the keratin levels were normal, namely P1 with a value of 0.76±0.27, P2 with a value of 0.60±0.01 and P3 with a value of 0.68±0.107. This indicates that the description of Salak fruit skin extract (Salacca Zalacca) reduces the keratinin levels of rats with diabetes mellitus.

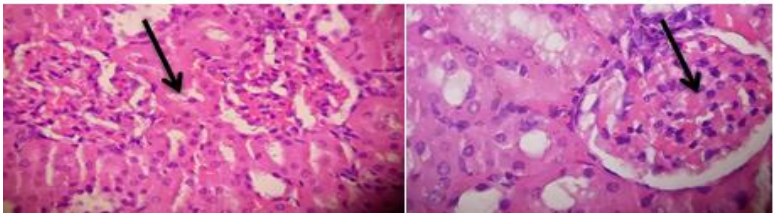
Then, in histopathological examination of the rat kidneys, it was seen:

K-



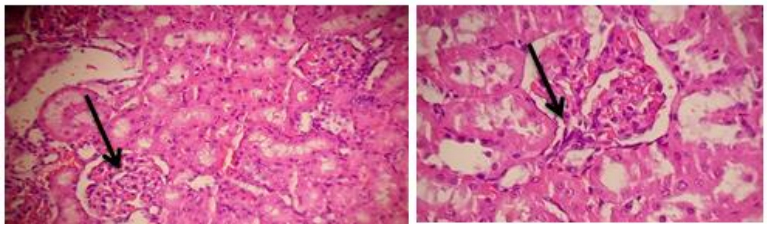
In the control group - mice were induced with alloxan and had diabetes mellitus but were not given any treatment so this group was given a score of 3 in its histological picture.there was severe necrosis and also severe inflammation in the kidneys of the rats.

K+



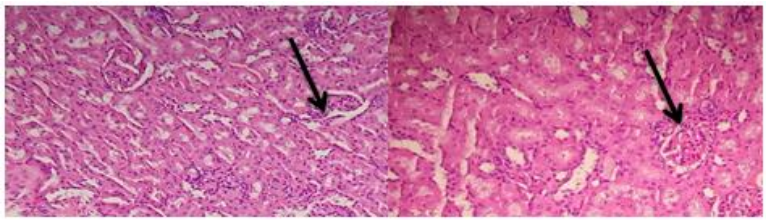
In the control group + mice induced by alloxan and experiencing diabetes mellitus and given the diabetes drug metformin. So in the pictureif there is moderate necrosis and bleeding (there is Bowman's Space Edema or bleeding) then this group gets a score of 2.

P1



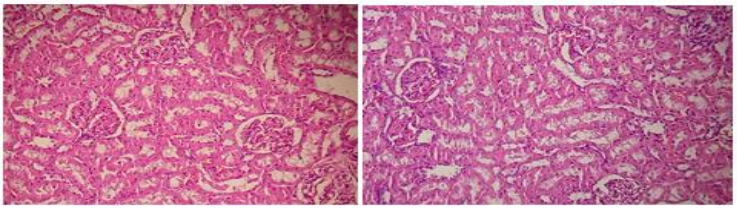
In treatment group 1, mice were induced with alloxan and experienced diabetes mellitus and Salak fruit skin extract at a dose of200 mg/kgBW. So that the picture shows moderate necrosis and bleeding (there is Bowman's Space Edema or bleeding), so this group gets a score of 2.

P2



In the treatment group 2 mice were induced by alloxan and experienced diabetes mellitus and salak skin extract at a dose of400 mg/kgBW. There is an inflammatory cell infection, so that treatment group 3 gets a score of 1 because there is still an infection in the kidney organs of the mice.

P3



In the treatment group 3 mice were induced by alloxan and experienced diabetes mellitus and salak skin extract at a dose of600 mg/kgBW and the kidney image is focal (mild) tending to be normal so it is given a score of 0 with normal results.

After conducting histopathological descriptions, the researchers then analyzed the results of liver function data by testing the data on the SPSS for Windows application for data analysis.

Table 3. Normality Test

One-Sample Kolmogorov-Smirnov Test			
		Keratin	Urea
N		20	20
Normal Parametersa,b	Mean	.8870	25.2305
	Std. Deviation	.36355	10.35855
Most Extreme Differences	Absolute	.297	.270
	Positive	.297	.270
	Negative	-.207	-.203
Kolmogorov-Smirnov Z		1,327	1.206
Asymp. Sig. (2-tailed)		.079	.109

Normality testing using the One-Sample Kolmogorov Smirnov Test technique with the following criteria:Data is said to be normal if the significance value is greater than 0.05**and** the data is said to be abnormal if the significance value is less than 0.05. So from the table above the 2-tailed significance results in the examination of Keratinin 0.079> 0.05 and Ureum 0.109> 0.05 so the data is normally distributed.

Table 4. Results*ANOVA test*

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
Keratin	Between Groups	2.274	4	.569	35,976	.000
	Within Groups	.237	15	.016		
	Total	2,511	19			
Urea	Between Groups	2035.608	4	508.902	2475.947	.000
	Within Groups	3,083	15	.206		
	Total	2038.691	19			

From the test results above, the significance value at a 95% confidence level (p <0.05) is 0.00 for kidney function-creatinine and a significant value of 0.00 for kidney-Ureum. So that there is a significant difference in each average value between sample groups. so that the conclusion obtained is that there is a significant difference in the average (mean) percentage of kidney function from the three groups. Next, see the results of the homogeneity test whether the group comes from a population that has the same variance

Table 5. Homogeneity Test

	Levene Statistics	df1	df2	Sig.
Keratin	5.284	4	15	.097
Urea	.989	4	15	.443

The results showed that the variance of the research data for the variables of the K-K+ group, groups P1, P2 and P3 were homogeneous or came from a population that had the same variance, namely 0.097 (p>0.05) for the analysis of kidney function data (Keratinin) on the 14th day during the treatment of Salak fruit skin extract, and the significance of Ureum 0.443

($p>0.05$) for the analysis of liver function Ureum on the 14th day during the treatment of Salak fruit skin extract (*Salacca Zalacca*).

DISCUSSION

The kidneys themselves are part of the urinary system that filters incoming waste, especially urea. Waste that comes from the blood and removes it in the urine along with water.(Rahayu, 2024). The kidneys also excrete metabolic waste products (e.g. urea, creatinine, and uric acid) and foreign chemicals. (Oktaria, 2017). Kidney function tests usually examine urea, creatinine, and glomerular filtration rates. Typical results for both tests indicate that the kidneys are working well.

Diabetes mellitus is a chronic condition that occurs when blood glucose levels increase due to the body's inability to produce or use enough insulin or insulin hormone effectively (Staff, 2014). If the condition is allowed to continue, it will cause several complications of disorders in the body's organs, one of which is kidney disorders.

Salak has been widely used as a traditional medicinal product for benefits such as lowering cholesterol.(Basuki Rachmad, 2023). Fruit flesh, salak seeds, and salak skin are some of the parts used in medicine in Indonesia. Previous studies conducted by(Girsang, 2020) found that salak skin has many benefits for body health, and its diverse and potential pharmacological properties due to its high antioxidant content show many benefits. Before conducting further research, the extract of salak skin (Salacca Zalacca) was first tested for its content by testing phytochemicals on its extract. Phytochemical tests are carried out to determine whether metabolite compounds are contained in the salak skin extract (Salacca Zalacca). The test results show that the extract of salak skin (Salacca Zalacca) positively contains active compounds such as alkaloids, flavonoids, and saponins. As is known, alkaloids are efficacious as antimicrobials, antidiabetics, and anti-diarrhea. Plants' flavonoid and saponin content can function as antibacterials, anti-inflammatories, and antifungals. The tannin content can function as an antiradical and antioxidant for the body. So, when testing the secondary metabolites, it is known that the salak plant has many medicinal benefits and properties.

Kidney dysfunction can cause kidney failure. Kidney failure is characterized by a functioning glomerular filtration rate of only 10–20%, high urea and creatinine levels, anemia, azotemia, metabolic acidosis, polyuria, and nocturia (K, 2014). Urea and creatinine are compounds that

can describe normal kidney function. Normal creatinine levels in rats range from 0.2 to 0.8 mg/dL.

In this study, alloxan induction caused diabetes mellitus in mice. The extract treatment was given after the mice were declared DM with glucose levels > 300 mg / DL. After 14 days of treatment with the K- -group without treatment or salak skin extract (Salacca Zalacca) only induced by alloxan, the urea levels increased to 43.89 ± 0.55. For the K + group without treatment of salak skin extract (Salacca Zalacca) only induced by alloxan and receiving antidiabetic treatment (metformin) obtained an average result of 27.63 ± 0.51 and was still above the standard urea level limit in mice. For the treatment groups (P1, P2, and P3) where rats induced by alloxan and given Salak fruit skin extract (Salacca Zalacca), treatment of 200 mg/kgBW, 400 mg/kgBW, 600 mg/kgBW were seen to be expected in urea levels, namely P1 with a value of 20.35±0.39, P2 with a value of 17.07±0.29 and P3 with a value of 17.20±0.45. Moreover, the group with the best urea levels was in group P2, with an average of 17.07±0.29.

For the testing of keratin levels, in the K+ group without treatment of Salak fruit skin extract (Salacca Zalacca) only induced by alloxan and receiving antidiabetic treatment (metformin) obtained an average result of 0.84 ± 0.49, which has approached normal keratin levels in mice. For the treatment groups (P1, P2, and P3) where mice induced by alloxan and given Salak fruit skin extract treatment (Salacca Zalacca) of 200 mg/kg BW, 400 mg/kg BW, 600 mg/kg BW were seen to be expected in keratin levels, namely P1 with a value of 0.76 ± 0.27, P2 with a value of 0.60 ± 0.01 and P3 with a value of 0.68 ± 0.107. The group with the best keratinin levels was in group P2, with an average of 0.60 ± 0.01.

Thus, it can be concluded that this indicates that the administration of Salak fruit skin extract (Salacca Zalacca) as much as 200 mg/kgBW, 400 mg/kgBW, or 600 mg/kgBW reduces urea and keratin levels in mice with diabetes mellitus. The administration of the extract with the best results is at 400 mg/kgBW of Salak fruit skin extract (Salacca Zalacca).

Then, the histopathology results showed that in the control group - rats were induced with alloxan and had diabetes mellitus but were not given any treatment, so this group was given a score of 3 in its histological picture. There was severe necrosis and also severe inflammation in the rat kidneys. In the control group, rats were induced with alloxan and diabetes mellitus and were given the diabetes drug metformin. The picture showed moderate necrosis and bleeding (Bowman's Spatium Edema or bleeding), so this group got a score of 2. In treatment

group 1, rats were induced with alloxan and had diabetes mellitus and salak skin extract with a dose of 200 mg / kgBW. The picture showed moderate necrosis and bleeding (Bowman's Spatium Edema or bleeding), so this group got a score of 2. In treatment group 2, rats were induced with alloxan and had diabetes mellitus and salak skin extract with a dose of 400 mg / kgBW. There was an inflammatory cell infection, so treatment group 3 scored 1 because there was still an infection in the rat kidney. In the treatment group, three rats were induced by alloxan and experienced diabetes mellitus and Salak fruit skin extract with a dose of 600 mg/kgBW. The kidney picture was focal (mild), tending to be expected, giving it a score of 0 with typical results.

Based on the histopathology results of rat kidneys, which describe damage to the kidney organ due to diabetes mellitus, it appears to have improved and become customary in the P2 and P3 treatments. This is also due to the secondary metabolite content found in the Salak fruit skin extract (Salaca Zalacca), which can repair damaged cell tissue due to induction and the condition of diabetes mellitus experienced by white rats (Rattus norvegicus) Wistar strain.

This is in line with previous research (Muharli Qadri Kanon, Fatimawali, 2019), which successfully tested the effectiveness of salak skin in reducing blood sugar in sucrose-induced mice. Thus, salak skin extract is indeed effective in reducing blood sugar levels in mice with diabetes mellitus.

CONCLUSION

1. In this study, it was found that there was an effect of administering Salak fruit skin extract (*Salacca Zalacca*) on kidney function and histopathological features of the kidneys of male Wistar strain white rats with diabetes mellitus, with the results of improving the kidney function of rats as measured by urea and creatinine levels.
2. Salak fruit skin extract (*Salacca Zalacca*) contains secondary metabolites in the form of saponins, tannins, flavonoids, alkaloids, and steroids which help repair kidney cells that experience fatty deposits and decreased kidney function due to diabetes mellitus.
3. Administration of Salak fruit skin extract (*Salacca Zalacca*) at a dose of 600 mg/kgBW is effective in 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 the histological structure of the kidneys which have improved.
4. The results of histopathological observations of kidney tissue in treatment group 3, namely Salak fruit skin extract (*Salacca Zalacca*) with a dose of 600 mg/KgBW,

experienced the most significant improvement and approached the control group compared to the other groups.

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